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# Hepatitis C virus infection: Epidemiology in Egypt, Pathophysiology and Daclatasvir-based therapy

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## ABSTRACT

Hepatitis C virus (HCV) was first identified in 1989. The situation in Egypt is dire. The prevalence of HCV genotype 4 (GT-4) is 14.7 percent. About 10% of the middle-aged population (ages 15 to 59) is infected with HCV. As a result, the Hepatitis C virus is considered extremely contagious. The introduction of the directly acting antiviral medications (DAAs), sofosbuvir or simeprevir, in GT-4 patients with PEGylated interferon (PEG-IFN) and ribavirin (RBV) in a 12-week regimen substantially increased sustained virological response (SVR) rates for HCV GT-4 in 2014. Daclatasvir (DCV) is the first DAA identified in the family of HCV NS5A inhibitors with antiviral activity against a variety of HCV genotypes. It is well-tolerated and safe, with a low risk of drug-drug interactions and resistance. Many investigations have discovered a rapid initial viral decline followed by a gradual decline in viral RNA, demonstrating DCV's inhibitory effect on viral reproduction, assembly, and secretion. DCV is a CYP3A4 substrate as well as a substrate for P-glycoprotein (P-GP), the most common drug efflux transporter, which are both expressed in hepatocytes and enterocytes, however, it is not a BCRP substrate (Breast Cancer Resistance Protein). Concomitant treatment of DCV with other medications targeting CYP3A4 or P glycoprotein may change its pharmacokinetic characteristics.

**Keywords:** *Hepatitis C; DAAs; Daclatasvir; P-glycoprotein; CYP3A4.*

## 1. Introduction

Hepatitis C virus (HCV) is a blood-borne virus that is quite prevalent. HCV infects about 200 million individuals worldwide, with the majority of cases occurring in Asia and Northern Africa [1]. Around 80% of infected patients acquire chronic HCV infection [2], with approximately 20% developing liver consequences such as fibrosis, hepatocellular carcinoma, cirrhosis, and end-stage liver disease [3].

More than half of all HCV infections are detected before severe liver fibrosis develops [4]. As a result, in Europe and America, HCV is the most common reason for liver transplantation [3, 5]. In chronic patients, early diagnosis of HCV and effective therapeutic therapy can prevent these consequences, improve their health, and lower their morbidity and mortality [6].

In HIV-positive individuals on antiretroviral treatment, HCV is currently the leading cause of death [7]. It has been proven that during the next 20 years, fatalities from liver disease caused by

HCV infection would continue to rise [8]. HCV comes at tenth to seventh place as a cause of death globally between 1990 and 2013, surpassing HIV infection, malaria, and TB [9].

There are geographical variations in HCV prevalence, with Egypt and Mongolia having the highest rates of infection (15%). Contamination was mostly nosocomial in those nations, either to a lack of hemovigilance in Mongolia or the systematic treatment of schistosomiasis without single-use equipment in Egypt [10]. Other regions, such as West Africa and Central Africa, are heavily infested, with 5–8% of the population infected, not just as a result of nosocomial infection but also as a result of specific "folkloric" behaviors (scarification, excision, and cupping in Japan or barber in Sicily) [10].

## 2. HCV Epidemiology in Egypt

HCV is now infecting around 2% of the world's population [11]. The situation in Egypt is quite precarious. The highly contagious blood-borne virus affects at least one out of every ten people aged 15 to 59 years old [12]. When HCV antibody testing became widely accessible in 1992, 10.8% of first-time blood donors in Egypt tested positive for the virus [13]. Many estimates of HCV prevalence have been published since then, including the Egyptian Demographic Health Survey (EDHS) [14, 15]. The rural lower and upper Egypt governorates had the highest prevalence (19.5% and 28.4%, respectively), whereas the border and urban governorates had the lowest incidence (5.9% and 8.2%, respectively) [16].

HCV has seven main genotypes, which are numbered one through seven [17]. Type 4 (73 percent) is the most common genotype in Egypt, followed by genotype 1 (26 percent). Mixed HCV genotype infection was detected in 15.7 percent of patients in Egypt [18]. In Central and West Africa, as well as the Middle East, genotype 4 is the most common. Due to variations in population structure, immigration, and transmission pathways, HCV 4 infection has recently expanded in Africa, the Middle East, and numerous western nations, notably in Europe [19].

## 3. Risk Factors and Transmission

### 3.1 History of Anti Schistosoma Injection

Schistosomiasis was a prevalent parasite illness in Egypt [20], and it was spread by swimming or strolling in filthy water channels. Egypt's hepatitis C pandemic began decades ago when glass syringes used in large schistosomiasis immunization programs were not adequately sanitized [21]. Despite the reduction in schistosomiasis-related morbidity, Egypt had a widespread HCV infection, which had replaced schistosomiasis as the leading cause of liver disease [22]. When compared to those who had not gotten a schistosomiasis injection, active infection rates are notably high among those who had had at least one [15].

### 3.2 Age

Different studies have shown a significant increase in HCV prevalence with age [23].

### 3.3 Gender

Males have a higher prevalence of HCV infection than females. These differences might be attributed in part to parenteral anti-schistosomiasis programs (PAT), which targeted males who were more infected with schistosomiasis and so were the major focus of these efforts [24].

### 3.4. Geographical Differences

The prevalence of the disease was found to be higher in rural regions than in metropolitan areas. These differences might be attributed in part to the PAT efforts, as schistosomiasis was more prevalent in rural regions [25].

### 3.5. Injection Therapy

For any other indication, like hemorrhoids or urinary incontinence [24].

### 3.6. Hospital-based Procedures

### 3.6.1. Blood transfusion

Blood transfusion was the most prevalent method for HCV transmission in Egypt before 1994 [26]. Blood and blood products were tested for HCV after 1994, removing the possibility of HCV transmission through this method [21].

### 3.6.2. Other procedures

HCV vulnerability is increased by exposure to certain facility-based medical treatments [15]. Many studies have linked surgical treatments, prenatal care, and dental therapy to HCV transmission [27].

### 3.6.3. Occupational hazards

Transmission among health care workers through needle sticks and sharp injuries is very common in Egypt [28].

### 3.7. Community-based Risk Factors (Intrafamilial and sexual transmission)

The risk of HCV infection was higher among HCV patients' household contacts [29]. El-Bendary et al. [30] conducted a pilot investigation of the epidemiological features of HCV virus transmission among families in the Egyptian community in 2014. They revealed that intrafamilial interaction has a significant role in HCV transmission in Egypt. Family interaction, sexual conduct, and the shared use of personal utensils are all potential sources of transmission.

### 3.8. Intravenous Drug Using (IDU)

In many countries, intravenous drug use is the leading cause of HCV prevalence [31]. IDU, on the other hand, may account for around 1% of HCV prevalence in Egypt [32].

### 4. HCV Pathophysiology in liver

HCV is an enveloped ribonucleic acid (RNA) virus that targets liver cells and has ten protein-coding genes. The viral proteins induce an immunological response, which causes cytotoxic CD4 T cells to become activated. To prevent future infection, these cytotoxic T cells go out and lyse infected hepatocytes with viral proteins on their surface. This inflammatory reaction in the host is thought to cause liver cirrhosis and, eventually, hepatocellular cancer [33]. HCV belongs to the Flaviviridae family and the Hepacivirus genus [34]. HCV virions have a diameter of 45–65 nm and are encased in a lipid bilayer containing two envelope glycoproteins (E1 and E2). The envelope encases the non-icosahedral nucleocapsid, which includes a positive-strand RNA genome of about 9.6 kb and an open reading frame encoding a single polyprotein of around 3,000 amino acids. The non-structural proteins are coded for in the remaining section (p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B) [35].

HCV virions produce lipoviroparticles when they combine with low-density lipoproteins (LDLs) and very-low-density lipoproteins (VLDLs) in the host. Apolipoprotein B (APOB) and other exchangeable apolipoproteins, such as APOC and APOE, are also present in the lipoviroparticles [36]. The two envelope glycoproteins, E1 and E2, as well as apolipoproteins on the lipoviroparticles' surface and many cell surface components, are involved in viral attachment. Low-affinity initial cell-binding might be mediated by glycosaminoglycan and the LDL receptor. Then E1–E2 interacts with CD81 and scavenger receptor class B member 1, whereas claudin 1, occludin, and perhaps additional molecules like claudin 6 or claudin 9, epidermal growth factor receptor, or ephrin receptor type A2 are required for cell entry [37].

## 5. Complications

HCV infection typically results in an asymptomatic chronic condition that can develop into active liver disease and severe compilations later on. One of the most striking characteristics of HCV infection is that most patients are unaware of their disease status until they develop a severe hepatic infection that can last for years In Egypt, chronic HCV infection is the primary cause of liver cirrhosis and cancer, as well as one of the top five reasons of death [20]. Every year, HCV kills around 40,000 Egyptians [12].

## 6. HCV Comorbidities

Understanding the most common comorbidities associated with HCV is critical for improving the efficacy of existing and future HCV treatment regimens. Successfully managing these comorbidities might result in enhanced treatment eligibility and better results. Up to 30% of HCV patients had comorbidity that would exclude them from receiving antiviral HCV therapy. This indicates that if comorbidities are adequately controlled, many HCV patients may be treated well [38]. The following are the seven broad categories of comorbidities identified by a study [38].

Digestive system disorders like diseases of the liver [rank 1], disorders of the gastrointestinal tract [rank 13], and disorders of the esophagus [rank 16].

Musculoskeletal system and connective tissue disorders like diseases of connective tissue [rank 2], disorders of the back [rank 7], and disorders of the joint (non-traumatic) [rank 8].

Respiratory system disorders like infections of the upper respiratory tract [rank 4], diseases of the upper respiratory tract [rank 17], and lower respiratory disease [rank 5].

Circulatory system disorders like essential hypertension [rank 6] and any non-specific chest pain [rank 10].

Endocrine, nutritional, metabolic, and immunity diseases like lipid metabolism disorders [rank 11] and uncomplicated diabetes mellitus [rank 23].

Mental disorders like alcohol and substance-related mental disorders [rank 20], depression [rank 22]) and disorders of the nervous systems and sense organs (blindness and vision defects [rank 21], eye diseases [rank 25]).

Symptoms influencing the overall health status like malaise [rank 12] and allergic reactions [rank 18] were also common in HCV patients.

## 7. Treatment of HCV

Since the virus' discovery in 1989, a close collaboration between fundamental, translational, and clinical research has resulted in the development of new diagnostic tools and management techniques [39]. For years, patients with HCV were treated with PEGylated interferon (PEG-IFN) and ribavirin (RBV), until the introduction of numerous direct-acting antivirals (DAAs) [40]. Most patients can be cured of chronic HCV infection with DAA-based therapy, including those who were previously difficult to treat (for example, patients with HCV and HIV co-infection), decompensated liver disease patients, and renal impairment patients) [41].

### 7.1. Interferon

Patients with non-A, non-B hepatitis (a designation used for hepatitis C before the hepatitis C virus (HCV) was identified in 1989) were given recombinant interferon (IFN) injections three times a week [42].

### 7.2. Interferon & Ribavirin

IFN was used in conjunction with ribavirin, a non-specific antiviral medication. Between 2001

and 2011, ribavirin and long-acting PEGylated (PEG)-IFNs, such as PEG IFN2a or PEG IFN2b, was the gold standard of treatment [43]. Treatment for chronic hepatitis C with this combination for 12 to 72 weeks resulted in sustained virological response (SVR) rates of 40% for HCV genotype 1 patients and 80% for HCV genotype 2 patients, albeit with some adverse effects. SVR is defined as undetectable HCV RNA levels in the blood for 12 or 24 weeks following therapy completion) [39].

## 7.3. Direct-acting antiviral agents (DAAs)

### 7.3.1. Background

BILL 2061, an inhibitor of the NS3/4A protease, was the first DAA to show a significant reduction of viral replication in humans, but its clinical development was halted owing to safety concerns. DAAs against three separate targets of the HCV life cycle was authorized as a result [44]. Boceprevir and telaprevir, two HCV protease inhibitors, were authorized in 2011, however, due to side effects; therapy had to be supplemented with PEG-IFN and ribavirin. Between 2013 and 2016, many NS3/4A and NS5A inhibitors, as well as one nucleotide and one non-nucleotide NS5B polymerase inhibitor, were authorized. Cure rates of 90 percent to 100 percent are reached when two or three DAAs are combined. These novels' all-oral, IFN-free DAA regimens have great tolerability and safety when used for 8–24 weeks [45].

NS3/4A inhibitors [e.g. boceprevir (BOC), telaprevir (TPV), simeprevir, asunaprevir (ASV), and paritaprevir (ASV) enhanced by ritonavir], NS5A inhibitors [e.g. daclatasvir (DCV), ledipasvir, and ombitasvir], and NS5B nucleoside [sofosbuvir SOF] are the three main classes of DAAs [40]. These DAAs have been approved in various areas of the world as PEG-IFN with RBV, RBV, or numerous all-oral DAAs with or without RBV [40]. In Chronic Hepatitis C

patients, the risk of morbidity and death associated with SOF/DCV RBV treatment is low, but it is substantially connected to advanced cirrhosis [46].

For the treatment of HCV in older individuals, direct-acting antiviral medication therapy is extremely effective and safe [47]. Inherited blood disorders (IBLD) patients are at a higher risk of contracting the hepatitis C virus (HCV). In the actual world, DAA-based regimens are well tolerated and very effective in individuals with chronic hepatitis C and IBLD [48].

A sustained virological response (SVR) is defined as undetectable HCV RNA levels in the blood after 24 weeks or, more recently, 12 weeks following the completion of therapy. Patients' quality of life (QOL) increased considerably with DAA treatment, in contrast to IFN-based regimens [49]. For accurate diagnosis and treatment of HCV patients, diagnostic techniques such as anti-HCV antibody testing, serum HCV RNA measurement, genotyping, and analysis of resistance-associated substitutions (RASs) are utilized. RASs are HCV RNA amino acid alterations that cause the virus to become resistant to DAA-based therapy regimens [50].

Comorbidities and co-medications, as well as drug-drug interactions, are prevalent in hepatitis C patients. Even when second-generation medicines are taken, the possibility of drug-drug interactions remains a serious concern [51].

### 7.3.2. Mechanism of Actions of DAAs:

Three structural proteins are located off the N-terminus of the HCV genome, while seven nonstructural (NS) proteins are found off the C-terminus. NS3/4A, NS5A, and NS5B are three non-structural proteins that are critical for HCV replication and so are candidates for suppression [52]. The serine protease NS3/4A is required for viral replication. NS3/4A inhibitors including

TPV, BOC, simeprevir, paritaprevir, and grazoprevir have high efficacy and a low barrier to resistance **[52]**.

NS5B is an RNA polymerase that is reliant on HCV RNA and is required for HCV replication. Because the catalytic region of NS5B is substantially similar across all HCV GTs, nucleotide inhibitors like SOF have pan-genotypic action and are known for their high potency and low resistance **[53]**. Dasabuvir and beclabuvir (BCV, previously BMS-791325) are non-nucleoside NS5B polymerase inhibitors that target allosteric regions on NS5B and have a low barrier to resistance, moderate efficacy, and limited activity across all HCV GTs **[53]**.

NS5A is a zinc-binding phosphoprotein with 447 amino acids that performs a critical yet unclear role in HCV replication. Although NS5A inhibitors appear to have a low barrier to resistance, they are thought to have strong antiviral action **[54]**.

## 8. Daclatasvir

The first-in-class HCV NS5A inhibitor, daclatasvir (DCV), has shown considerable efficacy in clinical studies **[52]**. Other NS5A inhibitors, such as ledipasvir and ombitasvir, have since been authorized, while GS-5816 and elbasvir are currently in clinical trials.

In some parts of the world, DCV has been authorized for the treatment of HCV genotype 1 patient in combination with PEG-IFN and RBV. Furthermore, the European Association for the Study of the Liver (EASL) has recently recommended the use of DCV-based regimens for all HCV GTs, including treatment-naive, treatment-experienced, compensated, and decompensated cirrhosis, chronic kidney disease, post-liver transplantation (LT), and HIV co-infection **[40]**.

For patients with all genotypes of hepatitis C who have significant renal impairment, including those on hemodialysis, the combination of sofosbuvir and daclatasvir is an effective and safe therapy **[55]**. SOF in conjunction with DCV demonstrated great effectiveness in Chronic Hepatitis C GT-2 patients, regardless of cirrhosis, treatment history, or chronic kidney disease status. As a result, in these groups, the introduction of DAA treatment to eliminate HCV should not be postponed **[56]**.

Patients with HCV/HIV co-infection were effectively treated with sofosbuvir and daclatasvir, and HRQoL (health-related quality of life) improved 12 weeks following treatment completion **[57]**. For individuals who are co-infected with HIV and HCV, a single-tablet combination of DCV and SOF is a successful and safe therapy. The combination is effective in individuals on antiretroviral treatment who require dosage adjustments. Cirrhotic patients, those who have had past treatment failures, and people of diverse genotypes all respond in the same way **[58]**.

In patients with HCV genotypes, 1 and 3 who are on maintenance hemodialysis, direct-acting antiviral treatment with sofosbuvir and daclatasvir is very efficacious and tolerated, especially when administered daily **[59].** For genotype 1b Acute Hepatitis C virus infection patients with overt hepatic decompensation, a combination of sofosbuvir and daclatasvir with ribavirin can be utilized **[60]**.

### 8.1. DCV Pharmacodynamics

The imino-thiazolidinedione BMS-858, DCV precursor, was discovered as a weak inhibitor of HCV replication after screening hundreds of chemicals from the Bristol-Myers Squibb (BMS) proprietary library. Many chemical changes were made to this molecule to increase potency, broaden the spectrum of GTs impacted, and improve the pharmacokinetics and oral

bioavailability of DCV **[61]**. The method by which DCV prevents viral replication is unknown. Small structural distortions caused by DCV are thought to limit NS5A activity directly or allosterically. DCV may also be able to stop viral replication by blocking two or more NS5A activities that operate together **[52]**. A mathematical model of viral kinetics during therapy revealed an early, fast viral decline followed by a gradual reduction in HCV-RNA, demonstrating that DCV inhibits viral reproduction as well as viral assembly and secretion **[62]**.

### 8.2. DCV Preclinical Pharmacokinetics

DCV is prescribed at a dose of sixty milligrams (mg) once a day (QD) **[63]**. The properties of DCV absorption, distribution, metabolism, and excretion have been investigated in a variety of cell lines and animal species.

### 8.2.1. Absorption

According to US Food and Drug Administration guidelines, daclatasvir is classed as a Biopharmaceutical Classification System Class II chemical (low solubility/high permeability) and a Biopharmaceutical Drug Disposition Classification System Class II molecule (low solubility/extensive metabolism) **[64]**. The efflux ratios were >24 and decreased to 1.6 and 0.8, respectively, in bi-directional experiments employing Caco-2 monolayers and DCV (0.3 lM) at pH 7.4 in the presence of P-glycoprotein (P-GP) inhibitors, ketoconazole, and cyclosporine. DCV is a substrate for efflux transporters such as P-GP, according to these findings **[64]**.

Due to its wide specificity and impact on drug pharmacokinetic (PK) characteristics, P-glycoprotein (Pgp) is an excellent example of a clinically relevant drug transporter **[65]**. Pgp is a member of the ATP-binding cassette (ABC) superfamily, and multidrug resistance (MDR)

genes encode it. PGP is found in numerous organs and physical barriers, including the GI tract, the blood-brain barrier (BBB), the kidney, liver, endothelium, and the placenta **[66]**. Pop acts as a unidirectional efflux pump that extrudes its substrate from within to outside of cells, limiting cellular uptake, distribution, excretion, and toxicity of a wide range of hydrophobic chemicals, pollutants, and medicines **[65]**. In research utilizing normal and P-GP knockout mice, DCV bioavailability was enhanced by 41 and 56 percent following oral and intravenous dosages, respectively, in the knockout mice compared to the normal mice. The efflux ratios in human breast cancer resistance protein (BCRP)-transfected MDCK cells were identical to those in wildtype MDCK cells, indicating that DCV is not a BCRP substrate **[64]**.

Animal species (rats, dogs, monkeys, and mice) have varying oral bioavailability (ranging from 38 to 100 percent), indicating that DCV is effectively absorbed in these animals. Increasing stomach pH by pretreating dogs with famotidine lowered DCV absolute bioavailability from 89 to 48 percent in a crossover trial in dogs, showing that DCV oral absorption is pH-dependent **[64]**.

### 8.2.2. Distribution

All animal species examined (rats, rabbits, dogs, and cynomolgus monkeys) had high levels of daclatasvir binding (95.1–99.5%), which was equivalent to human levels (98.0 percent ). The steady-state volume of distribution in animal species was more than the stated total body water volume, indicating extravascular distribution. DCV concentrates in the livers of mice, rats, dogs, and monkeys, with liver-to-plasma area under the concentration-time curve (AUC) ratios ranging from 1.9 to 17 in the various animal species examined, but has little penetration in the brain, according to in-vivo animal research (mice and rats) **[64]**.

Passive permeability and active transport are both modes of DCV liver absorption in rats, according to the results of an uptake investigation in rat hepatocytes. The results of DCV liver absorption in people by both active transport and passive diffusion were similar to these findings. Organic cation transporter (OCT1) and unidentified transporters are involved in the active liver absorption of DCV, but not organic anion transporter (OAT2), Sodium taurocholate-transporting peptide (NTCP), or organic transporting polypeptides (OATPs), according to in vitro investigations [64].

### 8.2.3. Metabolism

DCV metabolism was characterized by the synthesis of many metabolites, the majority of which were oxidation products. Oxidative pyrrolidine ring-opening was followed by intramolecular cyclization to produce M2, descarboxymethylation to form M4, and hydroxylation to form a variety of additional metabolites. In monkeys (17.5 percent of the dosage) and bile duct cannulated rats, M2 (pharmacologically active) is the major metabolite (10.5 percent of the dose). In any species, other metabolites contributed to less than 10% of the dosage [67].

### 8.2.4. Elimination

Many routes were implicated in the elimination of DCV in animals, including metabolic clearance, biliary clearance, and direct intestinal excretion, all of which resulted in DCV and its metabolites being excreted in the feces. Renal clearance was a minor route of DCV elimination in intact animals (>1% of the dosage) [67]. Daclatasvir dosage accumulation is not caused by a low eGFR (30-60 mL/min) [68].

### 8.3 Drug-drug Interactions (Mechanisms of Daclatasvir Drug Interactions)

DCV-based DDIs may be linked to the suppression or activation of CYP3A4 metabolism and/or P-GP-mediated efflux, according to several in-vitro and in-vivo investigations. DCV is a substrate for both CYP3A4 and the drug efflux pump P-GP, which are both expressed in liver and intestinal cells, according to in vitro research [64].

DCV is a modest, time-dependent inhibitor/inducer of CYP3A4, according to in-vivo findings. Multiple oral doses of 60 mg DCV and a single oral dosage of 5 mg midazolam did not result in a significant pharmacokinetic interaction, indicating that DCV is unlikely to affect the PK of CYP3A4 substrates. This finding is similar to many other DDI studies that looked at the PK of CYP3A4 substrates (e.g., ethinylestradiol, tacrolimus, cyclosporine, simeprevir, and methadone) and found that DCV did not affect the PK of the medications given together [64]. Co-administration of repeated oral doses of 60 mg DCV and 0.125 mg digoxin, on the other hand, increased the AUC and Cmax of digoxin by 27% and 65%, respectively, demonstrating that DCV is a weak-to-moderate inhibitor of P-GP in vivo. DCV has been shown to block a variety of uptake and efflux transporters in vitro, including OATP1B1, OATP1B3, and BCRP [69].

Furthermore, inhibitors or inducers of CYP3A4 are frequently coupled with comparable suppression or induction of P-GP; hence, DDI via CYP3A4 inhibition or induction may cause changes in DCV clearance for the two major routes. Because DCV is cleared by both CYP3A and P-GP, co-administered medications with inhibitory effects on P-GP but no contemporaneous inhibition of CYP3A are unlikely to produce significant changes in DCV bioavailability [64]. The use of cyclosporine (a strong P-GP inhibitor and a moderate CYP3A inhibitor) in a pharmacological interaction study resulted in a 40% rise in DCV AUC, indicating

that inhibiting P-GP alone without or with minimal inhibition of CYP3A cannot considerably enhance DCV BAV. CYP3A4 and P-GP modulators have been shown in several trials to enhance DCV AUC. Co-administration of ketoconazole (a potent CYP3A4 and P-GP inhibitor) increased AUC and Cmax by thrice and 57 percent, respectively [70]. Co-administration of ritonavir (a strong CYP3A4 and P-GP inhibitor) with boosted atazanavir (a moderate CYP3A4 inhibitor) resulted in a 2.1-fold and 35% rise in AUC and Cmax, respectively, in another research. Furthermore, adding telaprevir (a powerful CYP3A4 inhibitor) to the mix resulted in a 2-fold increase in DCV exposure. According to prior research, the greatest increase in DCV exposure after co-administration of a strong CYP3A4 inhibitor appears to be 2- to 3-fold, whereas the maximum impact of a moderate inhibitor appears to be less than 2-fold [70]. To compensate for the increased exposure, the DCV dosage can be reduced to 30 mg once a day for strong CYP3A4 inhibitors, and no dose change is required for moderate inhibitors [64].

CYP3A4 inducers, like CYP3A4 inhibitors, appear to alter DCV PK. Two investigations were conducted to assess the potential of inducers to alter DCV PK: one with rifampin, a strong CYP3A4 inducer, and the other with efavirenz, a moderate CYP3A4 inducer [71]. Rifampin co-administration reduced DCV AUC and Cmax by 79 and 56 percent, respectively, whereas efavirenz co-administration reduced DCV AUC and Cmax by 32 and 17 percent, respectively. To compensate for the decrease in exposure, the DCV dosage can be raised to 90 mg daily in the presence of a moderate CYP3A4 inducer, while powerful CYP3A4 inducers are contraindicated, according to prior studies [71].

DCV has a minimal risk of influencing the bioavailability of medicines that are CYP450 substrates when they are co-administered. Many transporters, including P-GP, OCT1, OATP1B1, OATP1B3, and BCRP, are weak to moderately inhibited by DCV in vitro. Except for rosuvastatin, DCV did not affect the pharmacokinetics of co-administered medications that are substrates of these transporters in clinical trials [64].

## 8.4. Safety and Tolerability (Side effects and adverse events)

In combination with other antivirals and DAAs such as PEG-IFN/RBV, ASV, BCV, and SOF, daclatasvir is safe and well-tolerated [50]. When DCV is used with PEG-IFN/RBV, the most common adverse effects are fatigue (43–45%) and headache (33–41%), with incidence rates similar to those of PEG-IFN/RBV alone. When ASV is added to DCV, diarrhea becomes more prevalent [72]. Headache, tiredness, diarrhea, nausea, and asthenia occurred in 24–25 percent, 21–22 percent, 12–22 percent, 11–12 percent, and 2–11 percent of participants in a Phase III study of an all-oral DCV/ASV combination [73]. In Phase II and III studies, DCV/ASV was also linked to a self-limiting increase in serum alanine aminotransferase (ALT) levels in about 5–29 percent of patients (with higher rates at doses >200 mg b.d. or when co-administered with PEG-IFN/ RBV) [74].

## Conclusion

HCV is well-known for causing liver cirrhosis, hepatocellular carcinoma (HCC), and liver-related death all over the world. For years, patients with HCV were treated with PEGylated interferon (PEG-IFN) and ribavirin (RBV), until the introduction of numerous direct-acting antivirals (DAAs). By blocking two or more activities of NS5A that work in concert, DCV may be able to stop viral propagation. When coupled with SOF or ASV/BCV, DCV, an HCV NS5A-selective inhibitor, is one of the most effective and well-tolerated oral HCV therapy

regimens. Future research on specific categories of HCV patients is strongly encouraged. All efforts should be made to eradicate HCV infection.

## Abbreviations

ABC, ATP-binding cassette; AHC, Acute Hepatitis C; ALT, Alanine aminotransferase; APO, Apolipoprotein; ASV, asunaprevir; AUC, Area under the concentration-time curve; BAV, Bioavailability; BBB, Blood brain barrier; BCRP, Breast Cancer Resistence Protein; BCV, beclabuvir; b.d., Twice daily; BOC, boceprevir; BMS, Bristol-Myers Squibb; CHC, Chronic hepatitis C; Cmax, Peak plasma Concentration; CYP, Cytochrome P450 enzymes; DAA, Direct acting antiviral drug; DCV, Daclatasvir; DDI, Drug-Drug Interactions; EASL, European Association of the Study of the Liver; EDHS, Egyptian Demographic Health Survey; eGFR, Estimated Glomerular filtration rate; GI, Gastrointestinal; GT, Genotype; HCC, Hepatocellular Carcinoma; HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus; HRQOL, Health-related quality of life**;** IBLD, inherited blood disorders; IDU, Intravenous drug use; IM, Intramuscular; IV, Intravenous; LDL, low-density lipoproteins; LT, Liver transplantation; MDCK, Madin-Darby Canine Kidney cells; mdr, multidrug resistance; NS Proteins, Non Structural proteins; NTCP, Sodium taurocholate-cotransporting peptide; OAT, organic anion transporter; OATP, organic transporting polypeptides; OCT, organic cation transporter; PAT, parenteral anti schistosomiasis campaigns; PEG-IFN, pegylated interferon; P-gp, P-glycoprotein; PK, Pharmacokinetics; PXR, Pregnane X receptor; QD, Once daily; QOL, Quality of life; RASs, Resistance-associated substitutions; RBV, Ribavarin; RNA, Ribonucleic acid; SOF, sofosbuvir; SVR, Sustained Virological response; TPV, telaprevir; T1/2, Half life; VLDL, very-low-density lipoproteins.

## Declarations

### Ethics approval and consent to participate

Not applicable

### Consent to publish

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

### Availability of data and materials

Data analyzed during this study are all included in the main manuscript.

### Competing interests

No competing interests were declared by the authors.

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## 9. References

1. Lauer, G. M.; Walker, B. D. Hepatitis C Virus Infection. *N. Engl. J. Med.* 2001, *345*, 41–52. DOI: 10.1056/NEJM200107053450107

2. World Health Organization. Hepatitis C. http://www.who.int/csr/disease/hepatitis/whocdscsrlyo2003/en/index7.html (accessed Dec 6, 2014).

3. Ghany, M. G.; Strader, D. B.; Thomas, D. L.; et al. Diagnosis, Management, and Treatment of Hepatitis C: An Update. *Hepatology*. 2009, *49*, 1335–1374. DOI: 10.1002/hep.22759

4. Zeremski, M.; Dimova, R.; Brown, Q.; et al. Peripheral CXCR3-Associated Chemokines as Biomarkers of Fibrosis in Chronic Hepatitis C Virus Infection. *J. Infect. Dis*. 2009, *200*, 1774–1780. DOI: 10.1086/646614

5. Reiser, M.; Marousis, C. G.; Nelson, D. R.; et al. Serum Interleukin 4 and Interleukin 10 Levels in Patients with Chronic Hepatitis C Virus Infection. *J. Hepatol*. 1997, *26*, 471–

478. DOI: 10.1016/s0168-8278(97)80409-6

6. Mohd Hanafiah, K.; Groeger, J.; Flaxman, A. D.; et al. Global epidemiology of hepatitis C virus infection: New estimates of age-specific antibody to HCV seroprevalence. *Hepatology*. 2013, *57*, 1333–1342. DOI: 10.1002/hep.26141

7. [52 Collaborators.] Causes of death in HIV-1-infected patients treated with antiretroviral therapy, 1996-2006: collaborative analysis of 13 HIV cohort studies. Clin Infect Dis 2010;50:1387-1396. DOI: 10.1086/652283

8. Razavi H, ElKhoury AC, Elbasha E, Estes C, Pasini K, Poynard T, et al. Chronic hepatitis C virus (HCV) disease burden and cost in the United States. HEPATOLOGY 2013;57:2164-2170. DOI: 10.1002/hep.26218

9. Stanaway JD, Flaxman AD, Naghavi M, Fitzmaurice C, Vos T, Abubakar I, et al. The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. Lancet. 2016;388:1081–88. doi: 10.1016/S0140-6736(16)30579-7.

10. Thursz M, Fontanet A. HCV transmission in industrialized countries and resource-constrained areas. Nat Rev Gastroenterol Hepatol. 2014;11:28–35. DOI: 10.1038/nrgastro.2013.179

11. Alter MJ. Epidemiology of hepatitis C virus infection. World J Gastroenterol. 2007; 13(17):2436–2441. DOI: 10.3748/wjg.v13.i17.2436

12. Egypt steps up efforts against hepatitis C; 2014. (Accessed 23 September 2014).

13. Kamel MA, Ghaffar YA, Wasef MA, Wright M, Clark LC, Miller FD. High HCV prevalence in Egyptian blood donors. Lancet. 1992;340(8816):427. DOI: 10.1016/0140-6736(92)91508-6

14. Saleh DA, Shebl F, Abdel-Hamid M, Narooz S, Mikhail N, El-Batanony M, et al. Incidence and risk factors for hepatitis C infection in a cohort of women in rural Egypt. Trans R Soc Trop Med Hyg. 2008; 102(9):921-928. doi: 10.1016/j.trstmh.2008.04.011.

15. El-Zanaty F, Way A. Egypt demographic and health survey 2008. (Egyptian: Ministry of Health and Associates and Macro International, Cairo); 2009.

16. Available:http://www.hcvegypt. net/encyclopdeia/transmission/index. htm (Accessed 5 September, 2014).

17. Nakano T. An updated analysis of hepatitis C virus genotypes and subtypes based on the complete coding region. living. 2011; 32(2):339–45. DOI: 10.1111/j.1478-3231.2011.02684.x

18. Zekri AR, Bahnassy AA, Shaarawy SM, Mansour OA, Madura MA, Khaled HM, El-Ahmadi O. Hepatitis C virus genotyping in relation to neu-oncoprotein overexpression and the development of Hepatocellular carcinoma. J Med Microbiol. 2000;49(1):89-95. DOI: 10.1099/0022-1317-49-1-89

19. Kamal SM, Nasser AI. Hepatitis C genotype 4: What we know and what we don't yet know. Hepatology. 2008;47(4): 1371–1383. DOI: 10.1002/hep.22127

20. Available:http://www.freerepublic.com/focus/f-news/3136777/posts (Accessed 20 September 2014).

21. Millera FD, Abu-Raddad LJ. Evidence of intense ongoing endemic transmission of hepatitis C virus in Egypt. Natl Acad Sci U S A. 2010;107(33):14757–14762. DOI: 10.1073/pnas.1008877107

22. Darwish NM, Abbas MO, Abdelfattah FM, Darwish MA. Hepatitis C virus infection in blood donors in Egypt. J Egypt Public Health

Assoc. 1992;13(3–4):223–236.

23. DossW, Mohamed MK, Esmat G, El Sayed M, Fontanet A, Cooper S, El Sayed N. Egyptian national control strategy for viral hepatitis; 2008-2012.

24. Mahamoud YA, Mumtaz GR, Riome S, Miller DW, Abu-Raddad LJ. The epidemiology of hepatitis C virus in Egypt: A systematic review and data synthesis. BMC Infect Dis. 2013;(13):288. DOI: 10.1186/1471-2334-13-288

25. Mostafa A, Taylor SM, El-Daly M, El Hoseiny M, Bakr I, Arafa N, et al. Is the hepatitis C virus epidemic over in Egypt? Incidence and risk factors of new hepatitis C virus infections. living. 2010;30(4):560–566. DOI: 10.1111/j.1478-3231.2009.02204.x

26. Habib M, Mohamed MK, Abdel-Aziz F, Magder LS, Abdel-Hamid M, Gamil F, et al. Hepatitis C virus infection in a community in the Nile Delta: Risk factors for seropositivity. Hepatology. 2001;33(1): 248–25. DOI: 10.1053/jhep.2001.20797

27. Kalil KA, Farghally HS, Hassanein KM, Abd-Elsayed AA, Hassanein FE. Hepatitis C virus infection among pediatric patients attending the University of Assiut Hospital, Egypt. Eastern Mediterranean Health Journal. 2010;16(4):356-361.

28. El Katsha S, Labeeb S, Watts S, Younis A. Informal health providers and the transmission of hepatitis C virus: Pilot study in two Egyptian villages. East Mediterr Health J. 2006;12(6):758 767.

29. Minola E, Baldo V, Baldovin T, Trivello R, Floreani A. Intrafamilial Transmission of Hepatitis C Virus Infection. European Journal of Epidemiology. 2006;21(4):293-927]. DOI: 10.1007/s10654-006-0016-8

30. El-Bendary M, Esmat G, Neamatallah M, Kamel E, Besheer T, Elalfy H, El-Setouhy M, Omran D. Epidemiological Aspects of Intrafamilial Spread of HCV Infection in Egyptian Population: A Pilot Study. Open Journal of Gastroenterology. 2014;4(5):228-236.

31. Aceijas C, Rhodes T. Global estimates of the prevalence of HCV infection among injecting drug users. Int J Drug Policy.2007;18(5):352-8. DOI: 10.1016/j.drugpo.2007.04.004

32. Elkareh S. HCV screening of donors in Governmental Blood Transfusion Centers at Menoufia Governorate (from Jan. 2008 to Oct. 2008).Vox Sang. 2009;13:89–90.

33. Koziel, M. The Role of Immune Responses in the Pathogenesis of Hepatitis C Virus Infection. *J. Viral Hepat.* 1997, *4* (2), 31–41. DOI: 10.1111/j.1365-2893.1997.tb00178.x

34. Simmonds, P. The origin of hepatitis C virus. *Curr. Top. Microbiol. Immunol.* 369, 1–15 (2013). DOI: 10.1007/978-3-642-27340-7_1

35. Penin, F., Dubuisson, J., Rey, F. A., Moradpour, D. & Pawlotsky, J. M. Structural biology of hepatitis C virus. *Hepatology* 39, 5–19 (2004). DOI: 10.1002/hep.20032

36. Andre, P. *et al.* Characterization of low- and very-low-density hepatitis C virus RNA-containing particles. *J. Virol.* 76, 6919–6928 (2002). DOI: 10.1128/jvi.76.14.6919-6928.2002

37. Zeisel, M. B., Felmlee, D. J. & Baumert, T. F. Hepatitis C virus entry. *Curr. Top. Microbiol. Immunol.* 369, 87–112 (2013). DOI: 10.1007/978-3-642-27340-7_4

38. Karly S Louie, Samantha St Laurent, Ulla M Forssen, et al. The high comorbidity burden of the hepatitis C virus-infected population in the United States. Louie et al. BMC Infectious Diseases 2012, 12:86 DOI: 10.1186/1471-2334-12-86

39. Lohmann, V. *et al.* Replication of subgenomic hepatitis C virus RNAs in a hepatoma cell line. *Science* 285, 110–113 (1999). This paper establishes the HCV replicon system, which is a methodological breakthrough for drug development in HCV infection. DOI: 10.1126/science.285.5424.110

40. Lok AS. HCV NS5A inhibitors in development. Clin Liver Dis 2013; 17: 111–21 DOI: 10.1016/j.cld.2012.09.006

41. Manns, M. P. & von Hahn, T. Novel therapies for hepatitis C — one pill fits all? *Nat. Rev. Drug Discov.* 12, 595–610 (2013). DOI: 10.1038/nrd4050

42. Hoofnagle, J. H. Toward universal vaccination against hepatitis B virus. *N. Engl. J. Med.* 321, 1333–1334 (1989). DOI: 10.1056/NEJM198911093211910

43. Fried, M. W. *et al.* Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N. Engl. J. Med.* 347, 975–982 (2002). DOI: 10.1056/NEJMoa020047

44. Manns, M. P. & Cornberg, M. Sofosbuvir: the final nail in the coffin for hepatitis C? *Lancet Infect. Dis.* 13, 378–379 2013. DOI: 10.1016/S1473-3099(13)70074-4

45. Manns, M. P. *et al.* Hepatitis C virus infection, NATURE REVIEWS | DISEASE PRIMERS VOLUME 3 ARTICLE NUMBER 17006.2017 DOI: 10.1038/nrdp.2017.6

46. Elsadek HM, Abdelbaser ES, Emara MH, Soliman HH, Farag AA. Morbidity and mortality during hepatitis C treatment using sofosbuvir and daclatasvir with or without ribavirin, in a cohort of Egyptian patients. Eur J Gastroenterol Hepatol. 2020 Aug;32(8):1046-1053. doi: 10.1097/MEG.0000000000001695. PMID: 33216478.

47. Ahmad M, Mahmud Y, Irfan M, Nadeem MA, Mohsin A. Response And Tolerability Of Sofosbuvir Plus Daclatasvir In Elderly Patients With Chronic Hepatitis-C. J Ayub Med Coll Abbottabad. 2019 Oct-Dec;31(4):527-529. PMID: 31933304.

48. Ruiz I, Fourati S, Ahmed-Belkacem A, Rodriguez C, Scoazec G, Donati F, Soulier A, Demontant V, Poiteau L, N'Debi M, François M, Chevaliez S, Pawlotsky JM. Real-world efficacy and safety of direct-acting antiviral drugs in patients with chronic hepatitis C and inherited blood disorders. Eur J Gastroenterol Hepatol. 2020 Nov 17. doi: 10.1097/MEG.0000000000002003. Epub ahead of print. PMID: 33208686.

49. Younossi, Z. M. *et al.* Effects of sofosbuvir-based treatment, with and without interferon, on outcome and productivity of patients with chronic hepatitis C. *Clin. Gastroenterol. Hepatol.* 12, 1349–1359.e13 2014. DOI: 10.1016/j.cgh.2013.11.032

50. Pawlotsky, J. M. Hepatitis C virus resistance to direct-acting antiviral drugs in interferon-free regimens. *Gastroenterology* 151, 70–86 2016. This review defines and explains the relevance, diagnosis, and management of drug resistance and RASs of DAAs. DOI: 10.1053/j.gastro.2016.04.003

51. Boff da Costa R, Boff Costa M, Longo L, Miotto DE, Hirata Bellavia G, Trucollo Michalczuk M, Reis Álvares-da-Silva M. Direct antiviral agents for hepatitis C and drug interaction risk: A retrospective cohort study with real and simulated data on medication interaction, the prevalence of comorbidities and comedications. PLoS One. 2021 Feb 12;16(2):e0245767. doi: 10.1371/journal.pone.0245767. PMID: 33577593; PMCID: PMC7880426.

52. Herbst DA, Reddy KR. NS5A inhibitor, daclatasvir, for the treatment of chronic

hepatitis C virus infection. Expert Opin Investig Drugs 2013; 22: 1337–46. DOI: 10.1517/13543784.2013.826189

53. Asselah T, Marcellin P. Direct-acting antivirals for the treatment of chronic hepatitis C: one pill a day for tomorrow. Liver Int 2012; 32(Suppl. 1): 88–102. DOI: 10.1111/j.1478-3231.2011.02699.x

54. Fridell RA, Qiu D, Wang C, Valera L, Gao M. Resistance analysis of the hepatitis C virus NS5A inhibitor BMS- 790052 in an in vitro replicon system. Antimicrob Agents Chemother 2010; 54: 3641–50. DOI: 10.1128/AAC.00556-10

55. Poustchi H, Majd Jabbari S, Merat S, Sharifi AH, Shayesteh AA, Shayesteh E, Minakari M, Fattahi MR, Moini M, Roozbeh F, Mansour-Ghanaei F, Afshar B, Mokhtar M, Amiriani T, Sofian M, Somi MH, Agah S, Maleki I, Latifnia M, Fattahi Abdizadeh M, Hormati A, Khoshnia M, Sohrabi M, Malekzadeh Z, Merat D, Malekzadeh R. The combination of sofosbuvir and daclatasvir is effective and safe in treating patients with hepatitis C and severe renal impairment. J Gastroenterol Hepatol. 2020 Sep;35(9):1590-1594. doi: 10.1111/jgh.14994. Epub 2020 Feb 5. PMID: 31994788.

56. Cheng TS, Liang PC, Huang CF, Yeh ML, Huang CI, Lin ZY, Chen SC, Huang JF, Dai CY, Hsieh PH, Chuang WL, Yu ML. Real-world effectiveness of direct-acting antiviral agents for chronic hepatitis C patients with genotype-2 infection after completed treatment. Kaohsiung J Med Sci. 2021 Apr;37(4):334-345. doi: 10.1002/kjm2.12315. Epub 2020 Nov 5. PMID: 33151016.

57. Yunihastuti E, Amelia F, Hapsari AI, Wicaksana B, Natali V, Widhani A, Sulaiman AS, Karjadi TH. Impact of sofosbuvir and daclatasvir on health-related quality of life in patients co-infected with hepatitis C and human immunodeficiency virus. Health Qual Life Outcomes. 2021 May 26;19(1):154. doi: 10.1186/s12955-021-01777-x. PMID: 34039353; PMCID: PMC8152304.

58. Dehghan Manshadi SA, Merat S, Mohr M, Rasoolinejad M, Sali S, Mardani M, Tabarsi P, Somi MH, Sedghi R, Tayeri K, Nikbin M, Karimi J, Sharifi AH, Kalantari S, Norouzi A, Merat D, Malekzadeh Z, Mirminachi B, Poustchi H, Malekzadeh R. Single-pill sofosbuvir and daclatasvir for treating hepatitis C in patients co-infected with human immunodeficiency virus. Int J Clin Pract. 2021 Aug;75(8):e14304. doi: 10.1111/ijcp.14304. Epub 2021 May 17. PMID: 33930223.

59. Cheema SUR, Rehman MS, Hussain G, Cheema SS, Gilani N. Efficacy and tolerability of sofosbuvir and daclatasvir for treatment of hepatitis C genotype 1 & 3 in patients undergoing hemodialysis- a prospective interventional clinical trial. BMC Nephrol. 2019 Nov 28;20(1):438. doi: 10.1186/s12882-019-1631-4. PMID: 31779583; PMCID: PMC6883698.

60. Wu SH, Chu CJ, Huang YH, Hou MC. Successful treatment with sofosbuvir and daclatasvir plus ribavirin in acute hepatitis C-infected patients with hepatic decompensation. J Chin Med Assoc. 2019 Jul;82(7):595-598. doi: 10.1097/JCMA.0000000000000107. PMID: 31274790.

61. Gao M, Nettles RE, Belema M, et al. Chemical genetics strategy identifies an HCV NS5A inhibitor with a potent clinical effect. Nature 2010; 465: 96– 100. DOI: 10.1038/nature08960

62. Berger C, Romero-Brey I, Radujkovic D, et al. Daclatasvir-like inhibitors of NS5A block

early biogenesis of hepatitis C virus-induced membranous replication factories independent of RNA replication. Gastroenterology 2014; 147: 1094–105. DOI: 10.1053/j.gastro.2014.07.019

63. Center for Drug Evaluation and Research. Clinical pharmacology and biopharmaceutics review(s). Daclatasvir. Application no. 20-6843. 2014.

64. Yash Gandhi, Timothy Eley, Aberra Fura, et al. Daclatasvir: A Review of Preclinical and Clinical Pharmacokinetics. Clin Pharmacokinet 2018 57:911–928 DOI: 10.1007/s40262-017-0624-3

65. Amin ML. P-glycoprotein inhibition for optimal drug delivery. Drug Target Insights. 2013;7:27-34. DOI: 10.4137/DTI.S12519

66. Wessler JD, Grip LT, Mendell J, Giugliano RP. The P-glycoprotein transport system and cardiovascular drugs. J Am Coll Cardiol. 2013;61:2495-502. DOI: 10.1016/j.jacc.2013.02.058

67. Li W, Zhao W, Liu X, et al. Biotransformation of daclatasvir in vitro and nonclinical species: formation of the main metabolite by pyrrolidine d-oxidation and rearrangement. Drug Metab Dispos. 2016;44:809–20. DOI: 10.1124/dmd.115.068866

68. Schrezenmeier E, Hoffmann F, Jaeger C, Schrezenmeier J, Lisec J, Glander P, Algharably E, Kreutz R, Budde K, Duerr M, Halleck F. Pharmacokinetics of Daclatasvir, Sofosbuvir, and GS-331007 in a Prospective Cohort of Hepatitis C Virus-Positive Kidney Transplant Recipients. Ther Drug Monit. 2019 Feb;41(1):53-58. doi: 10.1097/FTD.0000000000000567. PMID: 30422962.

69. Eley T, Garimella T, Li W, et al. Asunaprevir: a review of preclinical and clinical pharmacokinetics and drug-drug interactions. Clin Pharmacokinet. 2015;54:1205–22. DOI: 10.1007/s40262-015-0299-6

70. Bifano M, Adamczyk R, Hwang C, Kandoussi H, Marion A, Bertz RJ. An open-label investigation into drug-drug interactions between multiple doses of daclatasvir and single-dose cyclosporine or tacrolimus in healthy subjects. Clin Drug Investig. 2015;35:281–9. DOI: 10.1007/s40261-015-0279-5

71. Garimella T, You X, Wang R, et al. A review of daclatasvir drug-drug interactions. Adv Ther. 2016;33:1867–84. DOI: 10.1007/s12325-016-0407-5

72. Dore GJ, Lawitz E, Hezode C, et al. Daclatasvir plus peginterferon and ribavirin is non-inferior to peginterferon and ribavirin alone and reduces the duration of treatment for HCV genotype 2 or 3 infections. Gastroenterology 2015; 148: 355–66. DOI: 10.1053/j.gastro.2014.10.007

73. Chayama K, Suzuki F, Suzuki T, et al. All-oral dual combination of daclatasvir plus asunaprevir compared with telaprevir plus peginterferon alfa/ ribavirin in treatment-naive Japanese patients chronically infected with HCV genotype 1b: results from a Phase 3 study. Hepatology 2014; 60(Suppl. 1): 1135A.

74. Jensen D, Sherman KE, Hezode C, et al. Daclatasvir and asunaprevir plus peginterferon alfa and ribavirin in HCV genotype 1 or 4 non-responders. J Hepatol 2015 DOI: 10.1016/j.jhep.2015.02.018