

# Expert opinion on the management of hepatitis C infection in Kuwait

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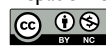
**Abstract:** Chronic hepatitis C virus (HCV) infection is a leading cause of death, especially in immunocompromised patients. The lack of clear prevalence data in the Middle East makes it difficult to estimate the true morbidity and mortality burden of HCV. In Kuwait, estimating the burden of disease is complicated by the constant flow of expatriates, many of whom are from HCV-endemic areas. The development of new and revolutionary treatments for HCV necessitates the standardization of clinical practice across all healthcare institutions. While international guidelines from the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) do address this evolving treatment landscape, the cost-driven treatment prioritization of patients by these guidelines and unique HCV genotype presentation in the Kuwaiti population prompted the development of a more tailored approach. The predominant HCV genotypes prevalent in Kuwait are genotypes 4 and 1. The Kuwait Hepatology Club (KHC), comprising hepatologists across all major institutions in Kuwait, conducted several consensus meetings to develop the scoring criteria, evaluate all current evidence, and propose screening, diagnosis, and treatment suggestions for the management of HCV in this population. While these treatment suggestions were largely consistent with the 2016 AASLD and 2015 EASL guidelines, they also addressed gaps in the unmet needs of the Kuwaiti population with HCV.

**Keywords:** hepatitis C, diagnosis, treatment, management, Kuwait

## Introduction

The prevalence of hepatitis C virus (HCV) infection was recently estimated as 2.8% worldwide, amounting to >185 million people,<sup>1</sup> and has rapidly become a leading cause of death, especially in HIV-positive patients.<sup>2</sup> In the Middle East, where countries have varying degrees of health service infrastructure, there is a distinct lack of clear epidemiology data. Most epidemiological studies have been conducted by independent scientists and are based on the seroprevalence of HCV in specific groups.<sup>3</sup> Many foreign workers in Kuwait are coming from regions that are considered HCV endemic. HCV prevalence in Kuwait is estimated to be around 0.8% in Kuwaiti nationals and 5.4% in expatriates.<sup>4</sup> The prevailing genotypes are genotypes 1 and 4, with genotype 4 as the most common.<sup>5</sup>

Historically, options for HCV treatment have been limited. Interferon (IFN)- $\alpha$  and ribavirin (RBV), the main options, had inadequate efficacy results and severe adverse effects. However, in recent years, dramatic improvements in the therapeutic landscape have vastly improved the outcomes for the patients with chronic HCV. This quickly multiplying



new generation of direct-acting antiviral agents (DAAs) poses a unique challenge to healthcare governing bodies who must keep up with the rapid pace of therapy development. International guidelines created by the American Association for the Study of Liver Diseases (AASLD)<sup>6</sup> and the European Association for the Study of the Liver (EASL)<sup>7</sup> are regularly updated with general recommendations for the management of patients with HCV. DAAs have introduced a promising new era of shortened HCV therapy, free of adverse events associated with previous standard therapies like IFNs. However, the genetic diversity of HCV in different regions and the lagging approval pace of new therapies mean that these recommendations must be tailored to the local population.

There are no recommendations yet for the management of HCV infection in Kuwait. The purpose of this article is to assist hepatologists and other healthcare professionals in the optimum management of patients with chronic HCV within the current national regulatory and therapeutic landscape in Kuwait.

## Methods

The Kuwait Hepatology Club (KHC) includes representatives from the following six major hospitals that treat HCV infections in Kuwait: Mubarak Alkaber Hospital, Al-Amiri Hospital, Al-Jahraa Hospital, Al-Adan Hospital, Al-Sabah Hospital, and Farwaniya Hospital. From September 14, 2015, the KHC conducted three consensus meetings to draft an expert opinion on hepatitis C treatment in Kuwait. During these meetings, evidence from published literature and international guidelines (ie, from AASLD and EASL) was combined with real-world experience from the KHC's expert panel to tailor the international recommendations to the local Kuwaiti clinical practice. Therefore, these statements should be viewed as the preferred approaches to care of the expert panel, rather than guidelines. The robustness of evidence was assessed for its quality and its relevance to Kuwaiti

clinical practice patterns. Scoring criteria were adapted from AASLD<sup>6</sup> and EASL<sup>7</sup> guidelines (Table 1).

## Diagnosis of acute and chronic HCV

The diagnosis of HCV infection is accomplished by immunoserologic assays and nucleic acid tests.<sup>8</sup> The most commonly used immunoserologic test is the third-generation ELISA. It is easy to perform and inexpensive, making it a suitable initial test for diagnosing HCV infection. However, this antibody test has several limitations.<sup>9</sup> For instance, in acute infection, it may take 8 weeks for seroconversion to take place.<sup>10</sup> Moreover, in immunocompromised settings (ie, in organ transplant recipients, hemodialysis, and HIV patients), seroconversion may be hampered, limiting the use of anti-HCV assays in the initial diagnosis.<sup>11</sup> Therefore, a nonreactive anti-HCV test will not definitively rule out infection in these patients. The detection of antibodies indicates one of the following: 1) current infection; 2) past infection that has resolved; and 3) false positivity.<sup>12</sup> Nucleic acid testing, using a highly sensitive polymerase chain reaction (PCR) assay for detecting HCV RNA, is more expensive and more technically demanding than the immunoserologic tests. Detecting HCV RNA indicates current infection.<sup>11</sup> Therefore, the KHC's expert panel suggested repeatedly testing after 3 months to rule out current infection.

The KHC's expert panel also suggested anti-HCV antibody assay as a first-line test in patients suspected of acute HCV (Table 2). If negative, the test should be repeated after 6–12 weeks to rule out seroconversion. Alternatively, if the initial antibody test is negative, testing for HCV RNA by PCR can be performed immediately and repeated after 12 weeks. In immunocompromised individuals, both anti-HCV and PCR should be performed as first-line tests and should be repeated 12 weeks later. In cases where chronic infection is suspected, the KHC's expert panel suggested starting with the antibody test. All reactive tests should be confirmed by

**Table 1** Scoring criteria developed by the KHC

	Notes	Grading
<b>Evidence quality</b>		
High	Data derived from multiple randomized clinical trials or equivalent (Phase III studies)	A
Moderate	Data derived from a single randomized trial, nonrandomized studies, meta-analyses, or equivalent	B
Low	Expert opinion, case studies, or standard of care	C
<b>Relevance</b>		
Strongly relevant to Kuwaiti practice	Favorable opinion of procedure/therapy based on relevance to Kuwaiti clinical practice and local HCV patient population (eg, evidence focuses on genotype 4, which is more prevalent in Kuwait)	1
Weakly relevant to Kuwaiti practice	Inconclusive or poor opinion of procedure/therapy based on relevance to routine Kuwaiti clinical practice or typical Kuwaiti population with HCV	2

**Abbreviations:** KHC, Kuwait Hepatology Club; HCV, hepatitis C virus.

PCR to diagnose current infection definitively. If HCV RNA is negative, PCR should be repeated after 12 weeks.

## Screening for hepatitis C infection

The AASLD guidelines suggest screening select high, such as individuals who inject drugs, hemodialysis patients, healthcare workers, children born to HCV-infected women, HIV-infected individuals, individuals who received blood or blood products before 1992, and those born between 1945 and 1965.<sup>6</sup> The AASLD and Centers for Disease Control and Prevention (CDC) do not recommend testing average-risk individuals.<sup>6,10–12</sup>

While endorsing the AASLD and CDC screening guidelines, the KHC's expert panel took into consideration data suggesting that targeted screening may miss a significant proportion of infected individuals and expanding screening practices to the general population may be cost-effective.<sup>13</sup> Currently, the Ministry of Health in Kuwait includes testing for HCV infection in the mandatory premarital and preemployment medical screening protocols, the practice that the KHC members find meritorious. For screening purposes, the panel suggested using the antibody test initially. If positive, current infection should be confirmed by PCR using another blood sample. A negative antibody test does not warrant further testing (Table 2).

## Pretherapeutic assessments

It is important to determine comorbid conditions and disease severity for the implementation of corrective actions and to tailor therapy. Noninvasive tests and liver function tests are important to determine the fibrotic damage to the liver.<sup>6</sup> The KHC voted that routine liver stiffness measurements and liver function tests are necessary to assess disease severity. It is also important to determine at-risk behaviors, alcohol consumption, underlying comorbidities, and hepatitis B virus, or HIV co-infection to differentially assess patient disease

severity. However, liver biopsies or histology examinations are rarely performed and testing for IL-28 genotypes was deemed unnecessary.

## Goals and endpoints of HCV therapy

The ultimate goal of HCV therapy, as defined by AASLD, is to cure HCV infection and to prevent hepatic cirrhosis, decompensation of cirrhosis, hepatocellular carcinoma, severe extra-hepatic manifestations, and death.<sup>6</sup> Achieving a sustained virologic response (SVR), as a therapeutic endpoint, in HCV-infected patients will reduce all-cause mortality and the consequences of liver-related disease, including end-stage liver disease and hepatocellular carcinoma.

## Treatment of HCV

### Therapeutic landscape

The HCV uses the nonstructural (NS) 3 protease and NS5A and NS5B polymerase enzymes for posttranslational processing and replication. These enzymes have become prime targets for HCV therapy. Protease inhibition interrupts posttranslational processing by blocking the catalytic site. In contrast, RBV monophosphate mimics inosine 5'-monophosphate and is a competitive inhibitor of inosine 5'-monophosphate dehydrogenase, an enzyme involved in the de novo synthesis of guanine nucleotides. Table 3 lists the therapeutic regimens currently approved and applied in Kuwaiti clinical practice.

### Expert opinion on genotype-specific therapy

The most common genotypes are genotypes 4 and 1.<sup>5</sup> Treatment options for both are summarized in Table 4, with 12 weeks being the most popular duration for most regimens. Consistent with the AASLD 2016 updated guidelines, the KHC suggested moving away from 24-week regimens unless a case is difficult to treat.

**Table 2** Workshop: Kuwait standard of practice for diagnostics tests

First-line test	Frequency of retesting	Confirmatory test	Frequency of retesting
<b>Acute</b>			
Anti-HCV antibody (AI)	6–12 weeks (in general population)	Anti-HCV antibody	6 weeks after diagnosis
HCV RNA quantitative test	12 weeks	HCV RNA quantitative test	After 12 weeks, if negative
Anti-HCV + HCV RNA	12 weeks (in immunocompromised patients)	None, if both are positive	
<b>Chronic</b>			
Anti-HCV antibody	24 weeks	HCV RNA quantitative test	Before therapy
HCV RNA quantitative test			
Anti-HCV + HCV RNA		HCV RNA quantitative test	12 weeks, only if anti-HCV antibody was positive and RNA was negative

**Abbreviation:** HCV, hepatitis C virus.

**Table 3** Therapies currently available in Kuwait

Regimens <sup>a</sup>	Name
PrO	Paritaprevir (75 mg)/ritonavir (50 mg) + ombitasvir (12.5 mg)
PrOD	Paritaprevir (75 mg)/ritonavir (50 mg) + ombitasvir (12.5 mg)/dasabuvir (250 mg)
SOF/LDV	SOF (400 mg) and LDV (90 mg)
DAC/SOF	DAC (60 mg)/SOF (400 mg)

**Note:** <sup>a</sup>These regimens may be administered with or without ribavirin depending on prior therapy experience, genotype status, or underlying demographic characteristics and comorbidities.

**Abbreviations:** DAC, daclatasvir; LDV, ledipasvir; PrO, paritaprevir/ritonavir-ombitasvir; PrOD, PrO and dasabuvir; SOF, sofosbuvir.

High evidence grading (A1) was given to the AASLD-approved regimens for treatment-naïve and treatment-experienced patients, with some caveats. Grazoprevir/elbasvir, although approved by the European Medical Agency (EMA), is not yet available in Kuwait so is not mentioned in this expert opinion. The simeprevir (SIM)/sofosbuvir (SOF) regimen has been deprioritized because the Q80K screening test is not available in Kuwait, making it difficult to predict a positive outcome for these noncirrhotic patients.

**Table 4** Summary of KHC treatment suggestions for GT1, GT4, and special populations

	Preferred	Alternative	Not recommended
<b>GT1 (regimens are listed alphabetically, SVR12 rates are included as percentages)</b>			
Treatment naïve			
GT1a (noncirrhotic)	DAC/SOF × 12 weeks (A1): 98% <sup>22</sup> PrOD + RBV × 12 weeks (A1): >95% <sup>14</sup> SIM/SOF × 12 weeks <sup>a</sup> (B2): 95% <sup>23</sup> SOF/LDV × 12 weeks (A1): 97% <sup>19</sup>		SOF + RBV × 24 weeks (A1); PEG/RBV + PIs (SOF, TPV, and BOC) × 48 weeks (A1); monotherapy (PEG or RBV <sup>b</sup> ) (A1)
GT1a (comp cirrhotic) <sup>a</sup>	SOF/LDV × 12 weeks (A1): 96% <sup>21</sup>	PrOD + RBV × 12 weeks (A1): >80% <sup>18</sup> SIM/SOF ± RBV × 24 weeks <sup>a</sup> (B2): 96% <sup>23</sup> DAC/SOF ± RBV × 24 weeks (A1): 82% (decomp) <sup>16</sup>	
GT1b (noncirrhotic)	DAC/SOF × 12 weeks (A1): 100% <sup>22</sup> PrOD × 12 weeks (A1): 99% <sup>15</sup> SOF/LDV × 12 weeks (A1): 87% <sup>20</sup> SIM/SOF × 12 weeks <sup>a</sup> (B2): 95% <sup>24</sup>		
GT1b (comp cirrhotic)	PrOD × 12 weeks (A1): 100% <sup>16</sup> SOF/LDV × 12 weeks (A1): 96% <sup>21</sup>	SIM/SOF ± RBV × 24 weeks <sup>a</sup> (B2) SOF/DAC ± RBV × 24 weeks (A1)	
Treatment experience with PEG/RBV			
GT1a PEG/RBV experienced (noncirrhotic)	DAC/SOF × 12 weeks (A1): 81.6% <sup>16</sup> PrOD + RBV × 12 weeks (A1): 96% <sup>17</sup> SIM/SOF × 12 weeks <sup>a</sup> (B2): 96% <sup>25</sup> SOF/LDV × 12 weeks (A1): 94% <sup>20</sup>		
GT1a PEG/RBV experienced (comp cirrhotic)	SOF/LDV × 24 weeks (A1): 97% <sup>17</sup> SOF/LDV + RBV × 12 weeks (A1): 96% <sup>17</sup>	PrOD + RBV × 24 weeks (A1): >95% <sup>17</sup> SIM/SOF ± RBV × 24 weeks <sup>a</sup> (B2): 80% <sup>16</sup> SOF/DAC ± RBV × 24 weeks (A1)	
GT1b PEG/RBV experienced (noncirrhotic)	DAC/SOF × 12 weeks (A1): 82.6% PrOD × 12 weeks (A1): 100% <sup>40</sup> SIM/SOF × 12 weeks <sup>a</sup> (B2): 95% <sup>25</sup> SOF/LDV × 12 weeks (A1): 98% <sup>20</sup>		
GT1b PEG/RBV experienced (comp cirrhotic)	PrOD × 12 weeks (A1): 100% <sup>16</sup> SOF/LDV + RBV × 12 weeks (A1): 96% <sup>21</sup> SOF/LDV × 24 weeks (A1): 97% <sup>21</sup>	SIM/SOF ± RBV × 24 weeks <sup>a</sup> (B2): 76% <sup>16</sup> SOF/DAC ± RBV × 24 weeks (A1)	

(Continued)

**Table 4** (Continued)

	Preferred	Alternative	Not recommended
Treatment experience with SOF + RBV			
GT1 SOF + RBV experienced (noncirrhotic)	SOF/LDV + RBV × 12 weeks (A1): 100% <sup>20</sup>		
GT1 SOF + RBV experienced (cirrhotic)	SOF/LDV + RBV × 24 weeks (A1): 97% <sup>21</sup>		
Treatment experience with PI-based regimen			
GT1 PI + PR experienced (noncirrhotic)	DAC/SOF × 12 weeks (A1): 82.6% <sup>16</sup> SOF/LDV × 12 weeks (A1): 98% <sup>20</sup>		IFN-free regimen including SIM or paritaprevir (A1); PEG/RBV alone (A1); SIM + PEG/RBV (A1); SOF + PEG/RBV (A1); TPV + PEG/RBV (A1); BOC + PEG/RBV (A1); monotherapy with PEG, RBV, DAA (A1)
GT1 PI + PR experienced (cirrhotic)	DAC/SOF ± RBV × 24 weeks (A1): 97.1% <sup>16</sup> SOF/LDV + RBV × 12 weeks (A1): >80% <sup>20</sup> SOF/LDV × 24 weeks (A1): 100% <sup>20</sup>		
Treatment experience with SIM/SOF			
GT1 SIM/SOF experienced (noncirrhotic)	RAV testing and treat according to results <sup>c</sup> SOF-based dual treatment + RBV × 24 weeks SOF-based triple/quadruple treatment × 12–24 weeks + RBV		
GT1 SIM/SOF experienced (cirrhotic or in immediate need of treatment)	RAV testing and treat according to results <sup>c</sup> SOF-based dual treatment + RBV × 24 weeks SOF-based triple/quadruple treatment × 12–24 weeks + RBV		
GT1	NS3/NS5A RAV testing and treat according to results SOF-based dual treatment + RBV × 24 weeks SOF-based triple/quadruple treatment × 12–24 weeks + RBV		
GT4			
GT4 (noncirrhotic, compensated)	PrO + RBV × 12 weeks (A1): 100% <sup>37</sup> SOF/LDV × 12 weeks (B1): 94% <sup>38</sup>		PEG/RBV ± SIM × 24–48 weeks (A1); SOF/RBV + PEG × 12 weeks (A1); monotherapy (PEG or RBV or DAA) (A1); TPV- or BOC-based regimens (A1)
GT4 PR experienced (noncirrhotic)	PrO + RBV × 12 weeks (A1): 100% <sup>37</sup> SOF/LDV × 12 weeks (A1): 94% <sup>38</sup>		PEG-IFN/RBV with or without TPV or BOC (A1); monotherapy with PEG-IFN, RBV, or DAA (A1)
GT4 PR experienced (compensated cirrhotic)	PrO + RBV × 12 weeks (A1): 96% <sup>35,36</sup> SOF/LDV + RBV × 12 weeks (A1): 95% <sup>39</sup> SOF/LDV × 24 weeks (A1)		
<b>Unique patient population in GT1 and GT4 patients: decompensated cirrhosis (CTP B or C)</b>			
GT1 or GT4 (CTP B or C)	DAC/SOF + RBV × 12 weeks <sup>d</sup> (A1): 83% <sup>41</sup> SOF/LDV + RBV × 12 weeks (A1): 87% (B) and 86% (C) <sup>42</sup>		IFN-based treatment (A1); monotherapy PEG-IFN, RBV, or DAA (A1); TPV, BOC, or SIM-based PrOD (A1)

(Continued)

Table 4 (Continued)

	Preferred	Alternative	Not recommended
GT1 or GT4 RBV ineligible	DAC/SOF × 24 weeks <sup>a</sup> (A1)		
GT1 or GT4 (SOF experienced)	SOF/LDV × 24 weeks (A1)		
	SOF/LDV + RBV × 24 weeks (A1)		
<b>Unique patient population in GT1 and GT4 patients: liver transplant<sup>e</sup></b>			
GT1 or GT4 in allograft, comp cirrhotic, naive, and experienced	DAC/SOF + RBV × 12 weeks (A1): 87% <sup>44</sup> and 94% <sup>41</sup>		
	SOF/LDV + RBV × 12 weeks (A1): 96% <sup>45</sup>		
GT1 or GT4 in allograft comp cirrhotic, naive, RBV ineligible	DAC/SOF × 24 weeks (A1)		
	SOF/LDV × 24 weeks (A1)		
GT1 or GT4 in allograft, decompensated (CTP class B and C) naive and experienced	SOF/LDV + RBV × 12 weeks (A1)		
GT1 in allograft, including comp cirrhotic		SOF/SIM ± RBV × 12 weeks (B2)	
GT1 in allograft, including F0–F2		PrOD + RBV × 24 weeks (A1)	
HCV in allograft with comp cirrhotic			PEG-IFN (A1); monotherapy PEG-IFN, RBV, or DAA (A1); TPV and BOC (A1)
HCV in allograft with decompensated cirrhosis			PEG-IFN (A1); SIM (B2); PrOD or PrO or RBV (A1); monotherapy PEG-IFN, RBV, and DAA (A1); TPV and BOC (A1)
<b>Unique patient population in GT1 and GT4 patients: renal impairment</b>			
Severe CKD (creatinine clearance <30 mL/min or end-stage renal disease)	GT1b: PrOD (no D for GT4) × 12 weeks (A1): 90% <sup>46</sup>	GT1a: PrOD + RBV × 12 weeks (A1)	
Mild or moderate CKD (creatinine clearance 30–80 mL/min)	No dosage adjustment needed for: PrOD/PrO (A1), SIM (A1), or SOF (A1)		

**Notes:** <sup>a</sup>For cirrhotic patients, some regimens are classified as alternative regimens because they have longer duration, potentially reduced efficacy, and/or limited supporting data compared with the preferred regimens. <sup>b</sup>Low-dose RBV (600–800 mg) can be used with patients who have an initial hemoglobin value of <11 g/dL (evidence rating: C1). <sup>c</sup>The KHC voted that there was no need to defer treatment in GT1 SIM/SOF-experienced noncirrhotic patients. SOF/LDV may be given. The KHC was divided on whether to wait for FibroScan results before SOF/LDV could be administered. <sup>d</sup>Dose-adjust cytochrome P450 3A/4 inducers. <sup>e</sup>The KHC stated that not enough postliver transplant patients are seen in Kuwait.

**Abbreviations:** BOC, boceprevir; DAA, direct-acting antiviral agent; DAC, daclatasvir; GT, genotype; HCV, hepatitis C virus; IFN, interferon; KHC, Kuwait Hepatology Club; LDV, ledipasvir; NS, nonstructural; CKD, chronic kidney disease; CTP, Child–Turcotte–Pugh; PEG, PEGylated; PIs, protease inhibitors; PR, PEG-IFN and RBV; PrO, paritaprevir/ritonavir-ombitasvir; PrOD, PrO and dasabuvir; RAV, resistance-associated variants; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response; TPV, telaprevir.

## Genotype 1

### Paritaprevir/ritonavir-ombitasvir and dasabuvir (PrOD) in treatment-naïve patients

Paritaprevir is a protease inhibitor (PI) that is administered with ritonavir, ombitasvir is an NS5a inhibitor, and dasabuvir is a nonnucleoside analog polymerase inhibitor. This regimen is approved in Kuwait for the treatment of genotype 1 patients and is frequently combined with RBV, except for genotype 1b cirrhotic and noncirrhotic patients. Based on the updated 2016 AASLD guidelines and the following pivotal clinical trials, the KHC suggested PrOD plus RBV for 12 weeks in treatment-naïve compensated cirrhotic genotype 1a patients with an evidence rating of A1 (Table 4).

The SAPPHERE-I trial demonstrated 96% of SVR rates in treatment-naïve noncirrhotic patients treated with PrOD plus RBV for 12 weeks.<sup>14</sup> These results were consistent with genotype 1a (95% of SVR) and genotype 1b (98% of SVR). Genotype 1b treatment-naïve noncirrhotic patients achieved 99% of SVR rate in PrOD regimens with and without RBV.<sup>15</sup> Genotype 1a treatment-naïve noncirrhotic patients achieved 90% of SVR with PrOD + RBV and 97% of SVR with PrOD–RBV. Another trial in cirrhotic patients, TURQUOISE-II, investigated the combination of PrOD and RBV for 12 and 24 weeks.<sup>16</sup> Consistent with the previous trial, 95% of treatment-naïve patients achieved SVR in both groups. A subanalysis of genotypes 1a and 1b revealed 100%

of SVR rates for genotype 1b in both arms, whereas genotype 1a achieved 92% at 12 weeks and 93% at 24 weeks.

#### *PrOD in treatment-experienced patients*

The KHC suggested the PrOD plus RBV regimen for 12 weeks in treatment-experienced noncirrhotic genotypes 1a and 1b patients, with an evidence rating of A1 based on the evidence from the SAPPHERE II and TURQUOISE II trials. However, in genotype 1a cirrhotic patients, PrOD plus RBV can be reserved as alternative therapy.

In the SAPPHERE II trial, noncirrhotic patients previously treated with PEGylated IFN (PEG-IFN) and RBV (PEG/RBV) achieved >95% of SVR in genotypes 1a and 1b on PrOD plus RBV treatment for 12 weeks.<sup>17</sup> The TURQUOISE-II trial revealed that genotype 1b cirrhotic patients who had failed prior treatments achieved 100% of SVR rates, irrespective of their previous treatment response, when treated with PrOD for 12 or 24 weeks.<sup>16</sup> Genotype 1a patients with an inadequate previous treatment response, however, did not achieve as significant an SVR rate (>80%).<sup>18</sup>

#### *SOF/ledipasvir (LDV) in treatment-naive patients*

SOF is a nucleotide analog polymerase inhibitor and LDV is an NS5A inhibitor. In the ION-1 trial, treatment-naive patients achieved 97% of SVR at 12 weeks and 100% at 24 weeks. The ION-3 trial explored an 8-week regimen with SOF/LDV in combination with RBV.<sup>19</sup> With the exception of those patients with a low HCV viral load, more relapse cases were seen in the 8-week regimen and, thus, the KHC voted against this shortened duration of treatment.

#### *SOF/LDV in treatment-experienced patients*

Consistent with AASLD, the KHC suggested the use of SOF/LDV in genotype 1 treatment-naive and treatment-experienced patients, with an evidence rating of A1. In the ION-2 trial, SOF/LDV demonstrated significant SVR rates at both 12 (94%) and 24 (99%) weeks in treatment-experienced genotype 1 patients.<sup>20</sup> An integrated efficacy and safety analysis of >500 pooled Phases II and III cirrhotic treatment-naive and treatment-experienced patients revealed significant response rates (96%) on a 12-week regimen of SOF/LDV with and without RBV despite previous therapy failure.<sup>21</sup>

#### *Daclatasvir (DAC) and SOF in treatment-naive and treatment-experienced patients*

DAC is another NS5A inhibitor. The KHC suggested this regimen based on the following evidence, with a rating of A1. Sulkowski et al<sup>22</sup> conducted a trial of DAC/SOF in previously

treated and untreated chronic HCV patients. Treatment-naive noncirrhotic patients achieved a high sustained viral response of undetectable HCV by 12 weeks (SVR12) of 98% with or without RBV. The ALLY-1 trial revealed that 82% of patients who had decompensated cirrhosis treated with DAC/SOF plus RBV for 12 weeks achieved SVR12.<sup>16</sup>

#### *SIM and SOF in treatment-naive patients*

SIM is a PI. Based on the following evidence, the KHC suggested deprioritizing this regimen in treatment-naive, noncirrhotic patients, given that evidence published in favor of SIM/SOF was not conclusive enough to out value the existing alternative therapies (evidence rating: B2). SIM/SOF in combination with RBV was investigated in the COSMOS trial for 12 and 24 weeks.<sup>23</sup> In treatment-naive patients, ~95% achieved SVR12 rates at 12 and 24 weeks. In a diverse, longitudinal, observational cohort, HCV-TARGET 2.0, 89% of patients achieved significant SVR4 rates after 12 weeks on SIM/SOF with or without RBV.<sup>24</sup> Genotype 1b patients had better SVR rates (95%) than genotype 1a patients (89%). Kwo et al<sup>25</sup> demonstrated in the OPTIMIST-1 trial that SIM/SOF-treated, treatment-naive, noncirrhotic patients achieved a high rate of SVR12 (97%), whereas cirrhotic patients achieved a lower SVR (85%). No difference was observed in Q80k resistance in these noncirrhotic types.<sup>25</sup> A TRIO cohort analysis also revealed that SIM/SOF-treated cirrhotic patients who were treatment naive achieved 88% of SVR when treated for 12 weeks with or without RBV.<sup>16</sup> Lawitz et al<sup>26</sup> discovered that genotype 1a patients with Q80K polymorphism achieved lower SVR (74%) than genotype 1a patients without the mutation (92%). The test for Q80K polymorphism is not currently available in Kuwait.

#### *SIM and SOF in treatment-experienced patients*

Similar to the treatment suggestions for treatment-naive patient for SIM/SOF, the KHC suggested deprioritizing this regimen in treatment-experienced patients based on the following evidence (evidence rating: B2). In the COSMOS trial, treatment-experienced patients achieved 91% of SVR rates when treated for 12 and 24 weeks.<sup>15</sup> The OPTIMIST-1 trial also demonstrated high SVR rates (95%) in treatment-experienced, noncirrhotic patients.<sup>25</sup> However, cirrhotic patients who had failed previous treatments only managed 77% of SVR. The TRIO cohort analysis revealed that SIM/SOF-treated patients who were treatment experienced achieved 87% of SVR rates in noncirrhotic patients and 76% of SVR rates in cirrhotic patients.<sup>16</sup> The rate of SVR12 in PI

failures was 82 and 80% in patients with the previous failure of PEG-IFN and RBV (PR) therapy.<sup>16</sup>

#### *Not recommended for genotype 1*

Based on current evidence, other regimens such as SIM + PEG/RBV,<sup>27–29</sup> SOF + PEG/RBV,<sup>30,31</sup> telaprevir (TPV) + PEG/RBV,<sup>32</sup> and boceprevir (BOC) + PEG/RBV<sup>33,34</sup> are not more effective than the above regimens in duration or efficacy. Pending more robust data supporting the efficacy of these regimens, the KHC prioritized them as not recommended therapies (evidence rating: A1) (Table 4).

Regimens with PEG-IFN with RBV or with TPV or BOC are not recommended in patients with genotype 1.<sup>6</sup> In patients with decompensated cirrhosis with moderate-to-severe hepatic impairment (Child–Turcotte–Pugh [CTP] class B or C), IFN-based therapy and monotherapy with PEG/RBV-, DAA-, TPV-, BOC-, SIM-, or PrOD-based regimens are not recommended (Table 4).<sup>6</sup>

#### **Genotype 4**

##### *Paritaprevir/ritonavir-ombitasvir (PrO) and RBV*

Consistent with AASLD and EASL, the KHC suggested the use of the PrO + RBV regimen for the treatment of genotype 4 patients, based on its strong evidence rating of A1. The AGATE I trial revealed that the PrO + RBV regimen achieved 97% of SVR rates in genotype 4 patients with cirrhosis.<sup>35</sup> The AGATE II trial focused on Egyptian patients with HCV who had cirrhosis.<sup>36</sup> Sensitivity analysis showed that PrO + RBV demonstrated the SVR12 rates of 97% (30/31) at 12 weeks and 96% (27/28) at 24 weeks in these patients excluding those who discontinued study drug prematurely with no on-treatment failure or those with missing follow-up data in the SVR12 window.<sup>36</sup> The PEARL-1 trial demonstrated that PrO + RBV was highly successful in achieving an SVR12 rate of 100% in treatment-naïve and treatment-experienced, genotype 4 noncirrhotic patients.<sup>37</sup>

##### *SOF/LDV*

In a proof-of-concept study, the SOF/LDV combination demonstrated 95% of SVR in 21 genotype 4 patients.<sup>38</sup> Another study in 44 patients with genotype 4 confirmed the SVR12 rate of 93%.<sup>39</sup> This regimen is preferred by the KHC for the treatment of genotype 4 patients (evidence rating: B1).

#### *Not recommended for genotype 4*

Regimens with PEG-IFN with RBV or with TPV or BOC are not recommended in patients with genotype 4 with or

without cirrhosis based on the results from the PEARL-II and TURQUOISE-III trials, respectively (evidence rating: A1).<sup>40,41</sup>

#### **Special populations in genotype 1 and genotype 4**

##### *Patients with decompensated cirrhosis*

##### *DAC and SOF*

Based on the following evidence, the KHC suggested DAC/SOF for the treatment of decompensated cirrhosis in patients with genotype 1 HCV infection (evidence rating: A1). The ALLY-1 study demonstrated that a 12-week regimen of DAC/SOF successfully treated genotype 1 patients with advanced cirrhosis (CTP class B and C; n=60) achieved the SVR rates of 83%.<sup>42</sup>

##### *SOF and LDV*

Based on the following evidence, the KHC suggested SOF/LDV for the treatment of patients with genotypes 1 or 4 HCV infection and decompensated cirrhosis (evidence rating: A1). In a large, multicenter, randomized controlled trial, SOLAR-1, 108 patients with HCV genotype 1 or 4 infection and who had decompensated cirrhosis (CTP class B or C) achieved the SVR rates of 87% (CTP B) and 86% (CTP C) when treated for 12 weeks. These rates were slightly improved when CTP B (89%) patients and CTP C patients (87%) received 24 weeks of SOF/LDV therapy.<sup>43</sup> Similar results were seen in a multicenter randomized controlled trial, SOLAR-2, of 108 patients with HCV genotypes 1 and 4 who had decompensated cirrhosis and achieved 87% of SVR after 12 weeks of treatment with SOF/LDV and 89% of SVR after 24 weeks.<sup>44</sup>

##### *Patients who have received liver transplants*

##### *SAC and SOF*

Based on the following evidence, the KHC suggested DAC/SOF for the treatment of postliver transplant patients with genotype 1 or 4 HCV infection (evidence rating: A1). The ALLY-1 study demonstrated that a 12-week regimen of DAC/SOF-helped genotype 1 patients with recurrent HCV infection posttransplant achieved 94% of SVR12.<sup>42</sup> In another trial of 64 liver transplant recipients with HCV genotype 1 infection, patients treated with DAC/SOF achieved an SVR12 rate of 87%.<sup>45</sup>

##### *SOF and LDV*

Based on the following evidence, the KHC suggested DAC/SOF for the treatment of postliver transplant patients with genotype 1 or 4 HCV infection (evidence rating: A1). In the SOLAR-1 study, 223 liver transplant recipients with genotype



1 or 4 HCV infection achieved an SVR rate of 96% when treated with SOF/LDV for 12 or 24 weeks.<sup>46</sup>

### Patients with renal impairment

#### PrOD

Based on the following evidence, the KHC suggested the PrOD regimen for the treatment of patients with renal impairment, with the caveat that PrOD should be avoided in patients with CTP B or C (evidence rating: A1).

In a Phase II study of 20 patients with genotype 1 and stage 4 or 5 (estimated glomerular filtration rate <30 mL/min/1.73 m<sup>2</sup>) CKD without cirrhosis, a PrOD combination regimen was administered with or without RBV.<sup>47</sup> All patients achieved SVR4. Regimens containing ofosbuvir<sup>48</sup> and SIM<sup>49</sup> have been found to be effective in mild CKD.

### Genotypes 2, 3, 5, and 6

Genotypes 2, 3, 5, and 6 are very rare in Kuwait. KHC refers to the AASLD guidelines should patients present with any of these genotypes, with caveats for local availability of recommended therapy or testing options, as shown in Table 5.

## General suggestions for the management of HCV

Although the KHC's expert panel suggestions were mostly consistent with AASLD, there were a few caveats.

### Assessments prior to starting antiviral therapy

The AASLD recommends noninvasive testing and, in some cases, liver biopsies prior to starting antiviral therapy,<sup>6</sup> whereas in clinical practice, the KHC does not routinely include these tests. Instead, a "treat all" strategy is used to manage HCV infections (evidence rating: C1).<sup>50</sup>

### Assessments during antiviral therapy

The AASLD recommends discontinuing RBV therapy in patients with a history of cardiovascular disease whose hemoglobin levels drop <8.5 g/dL.<sup>6</sup> The KHC suggests that severe anemia needs not to be an indication to discontinue therapy (evidence rating: C1).<sup>51</sup>

### Suggested testing for diagnosing acute HCV infection

The KHC identified the preferred criteria for the diagnosis of acute HCV infection as

- Positive anti-HCV IgG and a documented negative anti-HCV IgG in the previous 12 months, or
- Positive serum HCV RNA test and a documented negative serum HCV RNA and negative anti-HCV IgG in previous 12 months, or
- Positive serum HCV RNA test with an acute rise of alanine transaminase >5 times the upper limit of normal, or 3.5 times the high baseline alanine transaminase level with an absence of other causes of acute hepatitis.

**Table 5** Summary of KHC treatment suggestions for genotypes 2, 3, 5, and 6

	Preferred	Alternative	Not recommended
<b>GT2: treatment naïve</b>			
GT2 (noncirrhotic)	DAC/SOF (400 mg) × 12 weeks (no RBV for RBV-intolerant patients) (A1): 92% <sup>22</sup> SOF/RBV × 12 weeks (A1): 97% <sup>16</sup>		PEG-IFN and RBV for 24 weeks (A1); monotherapy with PEG-IFN, RBV, or a direct-acting antiviral (A1); TPV-, BOC-, or LDV-containing regimens (A1)
GT2 (comp cirrhotic)	DAC/SOF (400 mg) × 16–24 weeks (RBV-intolerant patients) (A1): 100% <sup>22</sup> SOF/RBV × 16–24 weeks (A1): 100% <sup>16</sup>		
<b>GT2: treatment experienced</b>			
GT2 PEG-IFN/RBV experienced	DAC/SOF (400 mg) × 12 weeks (A1): 92% <sup>22</sup> SOF/RBV × 12 weeks (A1): 91% <sup>45</sup>		PEG-IFN and ± TPV or BOC, LDV/SOF (A1); monotherapy with PEG-IFN, RBV, or a direct-acting antiviral (A1)
GT2 PEG-IFN/RBV experienced (comp cirrhosis)	DAC/SOF (400 mg) × 16–24 weeks (RBV-intolerant patients) (A1) SOF/RBV × 16–24 weeks (A1): 79% <sup>45</sup>	SOF (400 mg) + RBV + PEG-IFN × 12 weeks (A1)	
GT2 SOF/RBV experienced	DAC/SOF (400 mg) × 24 weeks (RBV-intolerant patients) (A1): 100% <sup>30</sup> SOF/RBV + PEG-IFN × 12 weeks (A1)		
<b>GT2: treatment-naïve and treatment-experienced patients with HCV infection in the allograft, including those with compensated cirrhosis</b>			
GT2	DAC/SOF + RBV (600 mg) × 12 weeks (A1) SOF + RBV × 24 weeks (A1)		Regimens containing PEG-IFN (A1); monotherapy with PEG-IFN, RBV, or a DAA (A1)
GT2 RBV intolerant or ineligible	DAC/SOF × 24 weeks (A1)		

(Continued)

Table 5 (Continued)

	Preferred	Alternative	Not recommended
<b>GT3 patients: treatment-naïve and treatment-experienced patients including those with compensated cirrhosis</b>			
GT3	DAC/SOF (400 mg) ± RBV × 12 weeks (A1): 97% SOF (400 mg) + RBV + PEG-IFN × 12 weeks (A1): 56% <sup>16</sup>	SOF (400 mg) + RBV + PEG-IFN × 24 weeks (DAC and IFN ineligible) (A1)	PEG-IFN and RBV for 24–48 weeks (A1); monotherapy with PEG-IFN, RBV, or a direct-acting antiviral (A1); TPV-, BOC-, or SIM-based regimens (A1)
GT3 (cirrhosis)	DAC/SOF (400 mg) ± RBV × 24 weeks: 58% SOF (400 mg) + RBV + PEG-IFN × 12 weeks (A1)		
GT3 (PEG-IFN/RBV experienced)	DAC/SOF × 12 weeks (A1) SOF + RBV + PEG-IFN × 12 weeks (A1): 83% <sup>16</sup>		PEG-IFN + RBV × 24–48 weeks (A1); monotherapy with PEG-IFN, RBV, or a direct-acting antiviral (A1); TPV-, BOC-, or SIM-based regimens (A1)
GT3 (PEG-IFN/RBV experienced, comp cirrhosis)	DAC/SOF + RBV × 24 weeks (A1) SOF + RBV + PEG-IFN × 12 weeks (A1): 83% <sup>16</sup>		
GT3 SOF/RBV experienced	DAC/SOF (400 mg) + RBV × 24 weeks (IFN-intolerant patients) (A1) SOF/RBV + PEG-IFN × 12 weeks (A1): 93% <sup>16</sup>		
<b>Genotype 2 or 3 treatment-naïve and -experienced patients with HCV genotype 2 infection in the allograft who have compensated cirrhosis</b>			
GT2, GT3 (comp cirrhosis)	DAC/SOF (400 mg) ± RBV × 12 weeks (A1) SOF (400 mg) + RBV + PEG-IFN × 24 weeks (A1)		Regimens containing PEG-IFN (A1); monotherapy with PEG-IFN, RBV, or a direct-acting antiviral (A1); TPV-, BOC-, GZP-, or EBV-based regimen (A1)
GT2, GT3 (PEG-IFN/RBV experienced, comp cirrhosis)	DAC/SOF (400 mg) × 24 weeks (A1)		
<b>Genotype 2 or 3 patients who have decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C) and who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma</b>			
GT2, GT3	DAC/SOF + RBV (600 mg) × 12 weeks (A1)		Any IFN-based therapy (A1); monotherapy with PEG-IFN, RBV, or a direct-acting antiviral (A1); paritaprevir-, ombitasvir-, or dasabuvir-based regimens (A1); TPV-, BOC-, SIM-, GZP- or EBV-based regimens (A1)
<b>Genotype 2 or 3 patients: treatment-naïve and treatment-experienced liver transplant recipients with decompensated cirrhosis (CTP class B or C) who have HCV genotype 2 or 3 infection in the allograft</b>			
GT2	SOF + RBV (initial 600 mg increase monthly by 200 mg/day as tolerated; 1000 mg [ $<75$ kg] to 1200 mg [ $>75$ kg]) × 24 weeks <sup>a</sup> (A1)		Regimens containing PEG-IFN; regimens containing SIM; fixed-dose combination of paritaprevir, ritonavir, and ombitasvir plus twice-daily dasabuvir and RBV; monotherapy with PEG-IFN, RBV, or a DAA; TPV-, BOC-, GZP-, and EBV-based regimens
GT3	SOF + RBV (initial 600 mg, increase as tolerated; 1000 mg [ $<75$ kg] to 1200 mg [ $>75$ kg]) × 24 weeks <sup>b</sup> (A1)		
<b>Genotype 2 or 3 patients: treatment-naïve and treatment-experienced liver transplant recipients with decompensated cirrhosis (CTP class B or C) who have HCV genotype 3 infection in the allograft</b>			
GT2	SOF + RBV (initial 600 mg increase monthly by 200 mg/day as tolerated; 1000 mg [ $<75$ kg] to 1200 mg [ $>75$ kg]) × 24 weeks <sup>a</sup> (A1)		No available data
GT3	SOF + RBV (initial 600 mg, increase as tolerated) × 24 weeks <sup>b</sup> (A1)		
<b>Genotype 5 and 6 patients: very few patients of these genotypes are seen in Kuwait</b>			
GT5, GT6	SOF/LDV × 12 weeks: 93% (GT5) <sup>39,c</sup>		No available data

**Notes:** <sup>a</sup>With consideration of the patient's creatinine clearance rate and hemoglobin level for up to 48 weeks. <sup>b</sup>No dose adjustment is required for tacrolimus or cyclosporine with SOF–RBV, SOF–LDV, or SOF–DAC. Because of high plasma concentrations of SIM, the concomitant use of SIM and cyclosporine A is not recommended in liver transplant recipients. No SIM dose changes are required with tacrolimus and sirolimus, but the patient's blood concentrations should be monitored regularly. When using the combination of ritonavir-boosted paritaprevir, ombitasvir, and dasabuvir, the tacrolimus dose must be adjusted to 0.5 mg once weekly or to 0.2 mg every 3 days, whereas the cyclosporine A dose must be adjusted to one-fifth of the daily dose given prior to HCV treatment once daily; prednisone use at doses  $\leq 5$  mg/day is permitted, but mTOR inhibitors are not recommended. <sup>c</sup>The KHC generally agreed with AASLD recommendation for the treatment of these patients. Currently, SOF/LDV is the only option available in Kuwait. Other AASLD-approved treatments are not approved yet.

**Abbreviations:** AASLD, American Association for the Study of Liver Diseases; BOC, boceprevir; CTP, Child–Turcotte–Pugh; DAC, daclatasvir; EBV, elbasvir; GT, genotype; GZP, grazoprevir; HCV, hepatitis C virus; IFN, interferon; KHC, Kuwait Hepatology Club; LDV, ledipasvir; PEG, PEGylated; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir; TPV, telaprevir.

Suggestions for medical management and monitoring in acute HCV infection

The KHC agreed with most of the AASLD recommendations for the medical management and monitoring of acute HCV infections, with one exception. Treatment of acute HCV infection after 24 weeks of presentation is not preferred except in special situations such as patients with CKD in whom spontaneous viral clearance is very uncommon.

Acute HCV infection in patients with CKD can progress very rapidly to cirrhosis. Treatment of acute HCV infection can be considered earlier in occupationally infected healthcare workers to prevent ongoing transmission events.

### Follow-up for patients who achieve an SVR

The KHC suggested that patients with advanced liver fibrosis (stages F3–F4) should be monitored by FibroScan and other noninvasive methods (evidence rating: B1).<sup>52</sup> Patients with known or suspected bridging fibrosis and cirrhosis are at increased risk of developing complications of advanced liver disease and may require more frequent follow-up and surveillance by ultrasound.

### Monitoring during chemotherapy and immunosuppression

The KHC determined that the major cause of death for patients with hepatocellular carcinoma is liver failure. Life expectancy may be compromised by underlying comorbidities. Functional improvement is important. Monitoring of HCV RNA is routinely practiced during chemotherapy (evidence rating: C1).

### Suggestions for managing patients with risk factors (eg, obesity and alcoholism)

The KHC's expert panel stated that multidisciplinary support involving diabetologists and dieticians is needed to manage these patients (evidence rating: A2).<sup>53</sup>

### Suggestions for monitoring quality of life (eg, patient-reported outcomes and work productivity)

The KHC's expert panel observed that although an integrated care infrastructure is important to optimally manage patients with HCV, parameters for assessing the quality of life are not routinely measured due to the lack of adequate ancillary support (evidence rating: A2).<sup>54</sup>

### Suggestions for elderly patients

The KHC stated that the exclusion of elderly persons from HCV screening policy should be avoided. All people living

with HCV infection should be considered for therapy, except those with a short-life expectancy (<6 months) due to nonliver-related or non-HCV-related comorbidities (evidence rating: B1).<sup>55</sup>

Elderly patients should be a major topic in HCV epidemiology research, awareness campaigns, and targeted screening (evidence rating: C1).<sup>56</sup>

In contrast to the AASLD guidelines, the KHC stated that HCV screening in elderly persons may be added to the screening colonoscopy program and may decrease viral transmission by colonoscopy. Use of shorter regimen courses, and avoidance of use of RBV because it has more adverse effects in elderly patients, is suggested (evidence rating: B2).<sup>57</sup> For people aged >50 years who are prescribed RBV-containing regimens, it is important to consider the complications of anemia and screen those who have a history of cardiovascular disease and who have had an electrocardiogram (ECG). For people with cardiovascular disease, a regimen that does not involve RBV may be most suitable (evidence rating: B2).<sup>57</sup>

### Suggestions for monitoring for pregnancy-related issues prior to and during antiviral therapy that includes RBV

In contrast to the AASLD, the KHC stated that antepartum HCV screening to decrease vertical transmission is preferred and may be cost-effective (evidence rating: C1).<sup>58–60</sup> Delaying pregnancy until HCV antiviral therapy is completed should be considered, as treatment courses with DAAs are short in duration (evidence rating: A1).<sup>61,62</sup> The KHC suggested two contraceptive measures. Patients treated with RBV should be counseled about the risk of teratogenicity, and patients of child-bearing age should be advised not to become pregnant during, and for 6 months after, therapy (evidence rating: A1).<sup>63,64</sup>

As the safety of DAAs during lactation has not yet been established, treating women who are breastfeeding is not recommended (evidence rating: A1).<sup>61,62</sup>

### Suggestions for incarcerated individuals

Universal screening of incarcerated individuals is suggested (evidence rating: B1).<sup>65</sup> In fact, jails may be an ideal setting for identifying individuals with HCV infection (evidence rating: C2).<sup>66,67</sup>

In contrast to the AASLD, the KHC suggested a smooth transition process from HCV treatment within the prison to treatment in the community by official referral to regional hospitals without a lapse in treatment. Education on the

importance of HCV screening and treatment in HCV high-prevalence community settings (ie, the jail population) is crucial to containing the spread of HCV. Incarceration presents a unique opportunity for HCV therapy, due to controlled access to healthcare and stable accommodation (evidence rating: C1).<sup>68</sup>

### Suggestions for persons who inject drugs (PWIDs)

Initial HCV RNA testing in PWIDs is suggested because an anti-HCV test is expected to be positive because of reinfection after spontaneous or treatment-related viral clearance (evidence rating: A1).<sup>69–71</sup> In contrast to the AASLD, the KHC suggested that PWIDs can be successfully treated for HCV infection even with ongoing injection drug use (evidence rating: C2).<sup>72</sup> Suitable settings, specific models of care, and a multidisciplinary team approach have an important role in HCV treatment acceptance in PWIDs.<sup>73–78</sup>

Persons identified as abusing alcohol and as having alcohol dependence require treatment and consideration for referral to an addiction specialist (evidence rating: C2).<sup>79</sup> Integration of HCV therapy with addiction therapy in opioid substitution therapy centers is suggested to enhance HCV treatment uptake (evidence rating: C2).<sup>74</sup> Education and training of clinical staff at opioid substitution therapy centers to integrate HCV treatment with addiction treatment are suggested (evidence rating: B2).<sup>6,7</sup>

Body piercing procedures such as tattooing and Hijama should be monitored. Authorities should consider a needle-exchange program (evidence rating: B2).

### Suggestions for emerging therapies

A difference in patient treatment patterns noted by the KHC is that the non-Kuwaiti population is mostly treated with generics rather than new direct-acting agents.

### Common barriers to HCV

Despite advancements in the therapeutic landscape, barriers to achieving treatment goals, which are unique to HCV, exist locally. The KHC proposed the strategies listed in Table 6 to overcome these barriers.

HCV carries a strong negative connotation as a sexually transmitted disease. The KHC's expert panel highlighted the need for the education of healthcare providers and patients to counter the stigma associated with the disease. The need to create an expert group to influence government policy on HCV treatment was also suggested.

Patients may fear diagnosis because of misleading information about HCV being incurable. Another barrier is the cost and access to therapy. The club highlighted the immediate need to build a national registry to capture current and long-term detailed information on Kuwaiti patients with HCV. Collection of these data will help shape HCV management strategies. Additional measures discussed by the KHC to prevent the transmission of HCV are listed in Figure 1.

**Table 6** Common barriers to HCV treatment and potential strategies to address these barriers

Barrier	Strategy
Contraindications to treatment (eg, comorbidities, substance abuse, and psychiatric disorders)	Counseling and education
	Referral to services (eg, psychiatry and opioid substitution therapy)
	Optimize treatment with simpler and less-toxic regimens
Competing priority and loss to follow-up	Conduct counseling and education
	Engage case managers and patient navigators (HIV model)
	Colocalize services (eg, primary care, medical homes, and drug treatment)
Long treatment duration and adverse effects	Optimize treatment with simpler and better tolerated regimens
	Education and monitoring
	Directly observed therapy (tuberculosis model)
Lack of access to treatment (high cost, lack of insurance, geographic distance, and lack of availability of specialists)	Participate in models of care involving close collaboration between primary care practitioners and specialists
	Pharmaceutical patient assistance programs
	Colocalize services (primary care, medical homes, and drug treatment)
Lack of practitioner expertise	Collaboration with specialists (eg, via Project ECHO-like models and telemedicine)
	Develop accessible and clear HCV treatment guidelines
	Develop electronic health record performance measures and clinical decision support tools (eg, pop-up reminders and standing orders)

**Abbreviations:** ECHO, Extension for Community Health Outcomes; HCV, hepatitis C virus.

<p><b>Educate patients with current (active) HCV infection</b></p> <ul style="list-style-type: none"> <li>• Educate patients on interventions aimed at reducing progression of liver disease and preventing the transmission of HCV</li> </ul>
<p><b>Abstinence from alcohol</b></p> <ul style="list-style-type: none"> <li>• When appropriate, interventions to facilitate cessation of alcohol consumption should be advised for all persons HCV infection</li> </ul>
<p><b>Complete evaluation</b></p> <ul style="list-style-type: none"> <li>• Evaluation for other conditions that may accelerate liver fibrosis</li> </ul>
<p><b>Vaccination</b></p> <ul style="list-style-type: none"> <li>• Vaccination against hepatitis A and hepatitis B is recommended for all susceptible patients with HCV infection</li> </ul>
<p><b>Patients with HCV infection should be counseled:</b></p> <ul style="list-style-type: none"> <li>• To avoid sharing toothbrushes and dental or shaving equipment</li> <li>• To cover any bleeding wound to prevent the possibility of others coming into contact with their blood</li> </ul>
<p><b>PWIDs should be counseled:</b></p> <ul style="list-style-type: none"> <li>• To stop using illicit drugs and to enter a substance abuse treatment program</li> <li>• To avoid reusing or sharing syringes, needles, water, cotton, and other drug preparation equipment</li> <li>• To use new sterile syringes and filters, and disinfected cookers</li> <li>• To clean the injection site with a new alcohol swap and to dispose of syringes and needles after one use in a safe, puncture-proof container</li> </ul>
<p><b>Patients with HCV infection should be advised</b></p> <ul style="list-style-type: none"> <li>• To not donate blood and to discuss HCV serostatus prior to donation of body organs, other tissue, or semen</li> </ul>
<p><b>Patients with HIV infection and those with multiple sexual partners or STDs</b></p> <ul style="list-style-type: none"> <li>• Should be encouraged to use barrier precautions to prevent sexual transmission</li> <li>• Other patients with HCV infection should be counseled that the risk of sexual transmission is low and may not warrant barrier protection</li> </ul>
<p><b>Household surfaces and implements contaminated with visible blood from an HCV-infected patient</b></p> <ul style="list-style-type: none"> <li>• Should be cleaned using a dilution of one part household bleach to nine parts water</li> <li>• Gloves should be worn when cleaning up blood spills</li> </ul>

**Figure 1** Proposed initiatives to contain the transmission of HCV.

**Abbreviations:** HCV, hepatitis C virus; STD, sexually transmitted diseases; PWIDs, people who inject drugs.

## Conclusion

HCV remains a pressing public health issue in Kuwait, but this expert opinion marks the first step in standardizing HCV treatment practices and maximizing patient benefit. The approval of new oral HCV therapies has expanded the possibilities of achieving unprecedented control of HCV infections. With this changing landscape, new challenges arise that require all healthcare and regulatory sectors to collaborate and design strategies to seamlessly and safely integrate these new therapies into existing treatment algorithms and improve patient access to these medications.

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