# SASLT guidelines: Update in treatment of hepatitis C virus infection, 2024

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## Abstract

Hepatitis C virus (HCV) infection has been a major global health concern, with a significant impact on public health. In recent years, there have been remarkable advancements in our understanding of HCV and the development of novel therapeutic agents. The Saudi Society for the Study of Liver Disease and Transplantation formed a working group to develop HCV practice guidelines in Saudi Arabia. The methodology used to create these guidelines involved a comprehensive review of available evidence, local data, and major international practice guidelines regarding HCV management. This updated guideline encompasses critical aspects of HCV care, including screening and diagnosis, assessing the severity of liver disease, and treatment strategies. The aim of this updated guideline is to assist healthcare providers in the management of HCV in Saudi Arabia. It summarizes the latest local studies on HCV epidemiology, significant changes in virus prevalence, and the importance of universal screening, particularly among high-risk populations. Moreover, it discusses the promising potential for HCV elimination as a public health threat by 2030, driven by effective treatment and comprehensive prevention strategies. This guideline also highlights evolving recommendations for advancing disease management, including the treatment of HCV patients with decompensated cirrhosis, treatment of those who have previously failed treatment with the newer medications, management in the context of liver transplantation and hepatocellular carcinoma, and treatment for special populations.

**Keywords:** Hepatitis C, epidemiology, elimination, Saudi Arabia, cirrhosis, hepatocellular carcinoma, pregnancy, direct acting antiviral, treatment, management, guidelines

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**Submitted:** 20-Sep-2023 **Revised:** 27-Nov-2023 **Accepted:** 03-Dec-2023 **Published:** 03-Jan-2024

| Access this article online | |
|---|---|
| Quick Response Code: | **Website:** https://journals.lww.com/sjga |
| | **DOI:** 10.4103/sjg.sjg_333_23 |



**How to cite this article:** Alghamdi AS, Alghamdi H, Alserehi HA, Babatin MA, Alswat KA, Alghamdi M, *et al.* SASLT guidelines: Update in treatment of hepatitis C virus infection, 2024. Saudi J Gastroenterol 2024;30:S1-42.

## INTRODUCTION

In 2012, the Saudi Society for the Study of Liver Disease and Transplantation (SASLT) created an evidence-based guideline for diagnosing, managing, and treating hepatitis C virus (HCV) infection. In 2016, the guidelines were revised and updated in response to changes in the epidemiology of HCV as well as the development of new medications and management strategies. Nonetheless, given the continued evolution of HCV treatment and elimination strategies, it is critical to conduct a comprehensive and critical review of the literature, and align with the treatment options best suited for the region. Therefore, the SASLT Board of Directors has established a working group primarily composed of hepatology and infectious disease practitioners to evaluate the progress towards HCV elimination in Saudi Arabia, and the available optimal treatment options.

The members performed a thorough review of the literature on all facets of HCV treatment, critically evaluating all accessible literature, and categorizing the available evidence according to its relevance. The resulting document and recommendations were discussed comprehensively and agreed upon by the members of the HCV working group. The guidelines were approved subsequently by the SASLT Board of Directors based on best available evidence and customized for patients in Saudi Arabia, with recommendations on treating and eliminating the disease using the latest direct-acting antiviral therapies.

These guidelines aim to improve care for HCV patients in the country by encouraging multi-disciplinary care and providing clinicians with recommended approaches to treatment.

**Grading of recommendations based on quality of evidence:**

- Grade A: Recommendation based on at least one high-quality randomized controlled trial or at least one high-quality meta-analysis of methodologically sound randomized controlled trials.
- Grade B: Recommendation based on high-quality case-control or cohort studies or a high-quality systematic review.
- Grade C: Recommendation based on non-analytic studies (case reports or case series).
- Grade D: Recommendation based on expert opinion only.

**Strength of each recommendation:**

- Level 1: strong, based on quality of evidence, patient outcome, and cost.
- Level 2: weak, with variability in values, preferences, and less certainty.

### Goals of this guideline

These are as follows:

1. To complement and update the previous SASLT guidelines in the management of HCV in Saudi Arabia.
2. To provide an evidence-based approach for the management of HCV-infected patients.
3. To reach the goal of World Health Organization (WHO) targets in HCV elimination as a public health threat by 2030. Succeeding in this aim would result in a decrease in liver-related complications, deaths, the need for liver transplantations, and hepatocellular carcinoma rate.

## EPIDEMIOLOGY, SCREENING, AND THE CHALLENGE OF HCV ELIMINATION

### HCV prevalence in Saudi Arabia

Previous descriptions of HCV epidemiology in Saudi Arabia relied heavily upon HCV seroprevalence studies, which are typically cross-sectional in design and are done in select populations such as blood donors. Population-based studies are generally not feasible in most parts of the world, including in Saudi Arabia. As it remains, there is no large community-based study reporting on the actual prevalence of HCV in the country. However, data from blood donor screening indicated prevalence rates of 0.4–1.1%.[1] Subsequently, pre-marital screening data in a mostly young population showed an average prevalence of anti-HCV serology to be 0.33%, after testing more than 2 million people.[2]

The Saudi Ministry of Health (MOH) has collaborated with the Center for Disease Analysis Foundation (CDAF), a non-profit organization based in Denver, USA, to assess the baseline points and set progress targets using epidemiological data, modeling tools, and decision analytics. The first round of collaboration with CDAF was completed in 2016,[3] revealing that the estimated anti-HCV prevalence in Saudi Arabia was about 0.7%, with approximately 70% of these individuals having active infections,[3] resulting in an estimated overall presence of about 100,000 viremic HCV-infected individuals. Based on this 2016 modeling with an estimated anti-HCV prevalence of 0.7% in Saudi Arabia,[3] the elimination goal was set to diagnose 90% of HCV infections and treat 80% of viremic HCV cases by the year 2034, reducing the incidence by 90% in 2042 and achieving overall elimination by 2050.[4]

The Saudi national screening program was based on the Rapid Point of Care anti-HCV test conducted by the MOH and other governmental organizations in primary healthcare centers (PHCs). The Abbott Bioline™ (Chicago, IL, USA) HCV test is an immunochromatographic point-of-care rapid finger-prick test for the qualitative

detection of antibodies specific to HCV in human serum, plasma, or whole blood. This test requires only one drop of blood, and the result is available in 10–15 minutes, with a sensitivity of 100% and a specificity of 99.4%.

A second round of modeling with CDAF using more recent data [unpublished data on file, The Ministry of Health (MOH)] indicates that the anti-HCV prevalence in Saudi Arabia is 0.23%, with a slightly higher prevalence in males (0.25%) compared to females (0.20%). Furthermore, 61% of the affected individuals are above 40 years of age, and approximately 43% of them have an active infection, resulting in an age-adjusted viremic prevalence of 0.1%.

In 2021 alone, the Saudi MOH screened 154,771 individuals in PHC for HCV. Among them, 350 (0.23%) tested positive for anti-HCV and subsequently underwent polymerase chain reaction (PCR)-based testing as per guidelines. Out of these, 80 (0.052%) cases were found to be HCV RNA-positive. Almost all PCR-positive cases were linked to care and treated. Based on these data and after adjusting for age to avoid skewing the age distribution in the real data, it is estimated that 0.1% of the Saudi population, or approximately 31,700 individuals, are actively infected with HCV. Moreover, 25,400 PCR-positive individuals have been previously diagnosed, and 22,657 (89.2%) of them were treated since 2014, with a cure rate of more than 95% (unpublished data, Saudi MOH). After 8 years of implementing the HCV strategy, a second round of CDA modeling was completed in May 2023, concluding that Saudi Arabia is on track for HCV elimination by 2030.[5] This is mainly due to a lower prevalence of the disease (as shown by real-life MOH 2021 data) than previously estimated. Additionally, the aggressive approach of successfully treating almost all HCV RNA-positive cases, implementing of strict infection control measures in all healthcare sectors, the availability of safe blood supply throughout the Kingdom, and the relative absence of intravenous drug use (IVDU) as an important mode of HCV transmission, has allowed for disease control measures in the country.

## Screening and treatment strategy for elimination by 2030

Saudi Arabia is aiming to eliminate HCV as a public health threat by 2030. This elimination goal is in line with global targets set by the WHO and Saudi Vision 2030 plan. The elimination strategy of HCV in Saudi Arabia is based on case finding, linkage-to-care, and early therapy. Case finding is achieved through the national screening program, and aggressive therapy is facilitated by expanded access to care. Family physicians, hepatologists, gastroenterologists, and infectious disease specialists have full privileges to test and treat with direct-acting antiviral (DAA) agents, complemented by a country-wide long-standing strategy to prevent new infections. Since the launch of the test-and-treat program in 2016, it is believed that most cases with a history of HCV infection have been linked to care, assessed for treatment, or already treated, and followed up until cure. Based on a large Saudi genotype study published in 2013, more than 80% of HCV cases in Saudi Arabia were found to be in individuals over 40 years of age. As a result, mass community-wide national HCV screening was initiated in 2018, with the aim of testing everyone above the age of 40 years at least once in their lifetime, including high-risk groups.[6] After a year of screening, it was expanded to all individuals in Saudi Arabia, irrespective of their age. Over the course of 5 years since 2018, more than 13 million people (13,432,508) have been screened for HCV, identifying 15,509 (0.12%) seropositive cases, of which 6597 (0.05%) were HCV RNA-positive, constituting 42.5% of all seropositive cases (unpublished data, Saudi MOH). Almost all PCR-positive cases were linked to care, treated, and followed up until cure.

In addition to the screening activities, HCV cases were captured through a long-standing pre-marital screening program for HCV since 2004, enhanced screening for special populations such as dialysis patients, blood donors, patients with history of IVDU, prisons, and selected hospital-based screenings. In Saudi Arabia, HCV screening and treatment were made free of charge to all citizens and expatriate residents. Moreover, the MOH increased the number of hospitals and healthcare centers offering DAA treatment for HCV in the Kingdom. Various stakeholders are involved in this initiative, including all governmental and non-governmental organizations (NGOs) and private healthcare sectors. Relevant NGOs were engaged in screening and treatment of HCV, playing a crucial role in accessing difficult-to-reach communities.

The MOH launched multiple initiatives to improve testing and enhance screening and case detection. This included the "Check and Reassure" initiative, which aimed to accelerate HCV testing and reach chronic cases that were not yet diagnosed, and to enhance MOH efforts for elimination. This initiative aimed to test 30% of individuals visiting PHCs for any reason. An electronic registry for screening was introduced to register all tested cases, whether positive or negative, in a single database. A clear and strict treatment pathway was developed and continuously supervised by an expert committee for HCV RNA-detected cases, making treatment standardized, easy for the patients, and practical, using the latest available DAAs. All patients with active HCV were considered for treatment as soon as possible. Low-risk patients were treated in PHC settings,

while high-risk patients (e.g., cirrhosis, renal impairment, multiple co-morbidities, post-liver transplant) were treated by specialists (hepatologists/gastroenterologists) in referral centers and followed up until cured.

Assuming HCV prevalence remains constant in Saudi Arabia, approximately 31,700 viremic cases need to be treated to eradicate the disease by 2030, rather than merely eliminating it. Alternatively, the goal can be achieved by treating around 1700 HCV-infected patients annually for the next 7 years (2024–2030) to meet the WHO targets.

In summary, as of 2023, the anti-HCV prevalence in Saudi Arabia is 0.23%, and the overall HCV RNA-positive prevalence is 0.1%. Based on these recent, real-life 2021 Saudi MOH data, the country appears to be on track to achieve HCV elimination and meeting the 2030 WHO and Saudi Vision targets.

## DIAGNOSIS OF HCV

The detection of anti-HCV antibodies is the primary method utilized for screening HCV infection. The commonly used tests are enzyme immunoassays (EIAs), which have a sensitivity/specificity of greater than 99% in detecting anti-HCV.[7] EIA can detect HCV antibodies as early as 6–8 weeks after exposure.[8] Overall, HCV antibody tests exhibit a strong positive predictive value for HCV exposure. Rapid diagnostic tests (RDTs) represent an attractive alternative to EIA detecting anti-HCV antibodies in finger-stick capillary whole blood and/or oral (crevicular) fluid with very high sensitivity and specificity. HCV antibody RDTs offer the advantages of simplicity, limited need for instrumentation, minimal training required, and rapid performance at room temperature.[9] If anti-HCV antibodies are detected, a sensitive molecular method such as PCR, transcription-mediated amplification (TMA), or branched DNA (b-DNA) should be used to determine HCV RNA, with a lower limit of detection of ≤15 international units (IU)/mL. All HCV nucleic acid molecular tests can detect the presence of virus and measure the viral load in the blood. Viral RNA testing is also recommended when there is clinical suspicion of HCV, high transaminase levels, and negative antibody testing, such as may occur in immunocompromised states and early acute HCV infection.[10]

HCV core antigen (HCVAg) serves as a reliable marker for viremic infection, demonstrating a strong correlation with HCV RNA quantification, and can be used as an alternative to HCV RNA to diagnose HCV viremia. It is worth noting that the detection of HCVAg necessitates a centralized laboratory. However, unlike HCV RNA, HCVAg exhibits enhanced stability at room temperature, enabling safe transport without refrigeration. Furthermore, the advantage of utilizing the same testing platform for both HCVAg and HCV antibodies should be emphasized. It is important to acknowledge that the analytical sensitivity of HCVAg detection is lower compared to PCR-based assays for HCV RNA. Numerous studies have reported a lower limit of detection for HCVAg, ranging from 3000 to 10,000 IU/mL of HCV RNA, whereas PCR-based assays can detect HCV RNA at levels as low as 12–15 IU/mL. Consequently, the diagnostic sensitivity of HCVAg for chronic HCV infection is approximately 90%, but it maintains a high level of specificity exceeding 98%.[11]

One of the primary obstacles to the treatment of HCV following a positive HCV antibody test result is the limited availability of HCV RNA testing to confirm active viremic HCV infection and the subsequent need for treatment. To expedite access to HCV RNA testing, WHO recommends the implementation of reflex testing. Reflex testing refers to the performance of a linked HCV RNA (or HCVAg) test in all individuals who initially test positive for HCV antibodies during screening as an additional key strategy to promote linkage to care and treatment.

There are two methods by which reflex HCV RNA testing can be implemented: laboratory-based reflex testing and clinic-based reflex testing. Laboratory-based reflex testing involves a testing algorithm in which patients undergo a single clinical encounter and provide one blood sample (which may be divided into two tubes), which is then sent to the laboratory. If the initial HCV antibody test is positive, the same sample is automatically used for a prompt reflex HCV RNA nucleic acid test (NAT) or HCVAg test.

Clinic-based reflex testing refers to a testing strategy where individuals have only one clinical encounter/visit for an initial rapid diagnostic HCV antibody test, but with two blood draws. The first blood specimen, obtained through capillary (finger-stick) whole blood, is tested using a rapid diagnostic HCV antibody test. If the result is positive, a reflex second blood specimen collection is immediately conducted for HCV RNA detection of current infection. The second blood sample for HCV RNA testing can be either sent to a laboratory for HCV RNA NAT or HCVAg testing or tested onsite using a point-of-care (PoC) HCV RNA NAT assay.[12]

HCV genotype and subtype can be determined via various methods, including direct sequence analysis, reverse hybridization, and genotype-specific real-time PCR. It is worth noting that with the introduction of pangenotypic HCV treatment regimens, the necessity

of HCV genotyping prior to treatment initiation for all individuals has been diminished. However, in cases where cirrhosis and/or previous unsuccessful HCV treatment are evident, pre-treatment genotyping is advisable, as treatment regimens may vary based on genotype.[13]

## Non-invasive assessment of liver fibrosis

Liver biopsy continues to serve as the definitive diagnostic test for assessing the various degrees of fibrosis, although it is an invasive procedure that can be associated with serious complications and have limitations. Liver biopsy is not necessary as an initial step for commencing HCV therapy. However, in situations involving recognized or suspected mixed etiologies such as metabolic syndrome, auto-immunity, or alcoholism, liver biopsy may be deemed necessary.

Non-invasive assessment of liver fibrosis in patients with HCV has become a significant area of research and clinical practice. These non-invasive approaches have emerged as patient-friendly alternatives to evaluate liver fibrosis in a more effective manner. There are several non-invasive methods available for assessing liver fibrosis in patients with HCV. These methods can be broadly classified into two categories: biochemical markers and imaging techniques.

1. Biochemical markers involve the measurement of specific serum biomarkers associated with liver fibrosis. These biomarkers can include various proteins, enzymes, and cytokines that are released or altered during the fibrogenic process. Commonly employed clinical tests for liver fibrosis include FibroTest, the aspartate aminotransferase-to-platelet ratio index (APRI), and the Fibrosis-4 (FIB-4) score. These tests analyze blood samples and utilize specialized algorithms to provide a quantitative evaluation of liver fibrosis. FibroTest (or FibroSure) requires patient information such as age and sex, along with values for a-2-macroglobulin, haptoglobin, apolipoprotein A1, gamma-glutamyl transferase (GGT), and total bilirubin. ActiTest is a variant of FibroTest that additionally incorporates alanine aminotransferase (ALT), thereby reflecting both liver fibrosis and necro-inflammatory activity. The sensitivity of FibroTest in detecting liver fibrosis ranges from 60% to 75%, while its specificity ranges from 80% to 90%. The APRI is primarily employed for the diagnosis or exclusion of cirrhosis. In an initial assessment, an APRI score of ≤0.5 accurately excluded cirrhosis in 81% of patients. However, the index does not differentiate between lower levels of fibrosis.[14,15]
2. Imaging techniques utilize various imaging modalities to assess liver fibrosis without the need for invasive procedures. Commonly utilized methods for liver fibrosis assessment include transient elastography (FibroScan), magnetic resonance elastography (MRE), and acoustic radiation force impulse (ARFI) imaging. These techniques provide a quantitative measurement of liver stiffness, which is correlated with the degree of liver fibrosis. Among these methods, transient elastography is the most frequently used modality to assess liver stiffness. In a meta-analysis, the mean AUROC for the diagnosis of significant fibrosis, severe fibrosis, and cirrhosis by FibroScan was 0.84 [95% confidence interval (CI), 0.82–0.86], 0.89 (95% CI, 0.88–0.91), and 0.94 (95% CI, 0.93–0.95), respectively. The amount of fibrosis can be quantified very easily and reliably and is feasible in more than 95% of the patients. However, the accuracy of the test is hampered by obesity, ascites, and narrow intercostal spaces. Falsely elevated scores can occur in cases of acute hepatitis or liver congestion, as observed in cardiac failure. In certain instances, obtaining measurements in such patients can be virtually infeasible. Combining transient elastography with serum markers increases the accuracy of predicting fibrosis and cirrhosis.[14,16,17]

Recommendations:

1. Diagnosis of HCV infection is based on the detection of anti-HCV antibodies by enzyme immunoassay or rapid diagnostic tests and confirmed by either HCV RNA test or HCVAg (Grade A1).
2. In immunosuppressed patients with undetectable anti-HCV antibodies and in cases of suspected acute hepatitis, HCV RNA test should be a part of initial evaluation (Grade A1).
3. Reflex testing for HCV RNA (or HCVAg) should be applied to all individuals who initially test positive for HCV antibodies, as an additional key strategy to promote and shorten the linkage to care and treatment (Grade A1).
4. HCV genotype testing may be considered for those in whom it may alter treatment recommendations (Grade A1).
5. Liver biopsy is `valuable for assessing the status and level of liver inflammation, the potential progression of fibrosis, and the presence or absence of cirrhosis. It should be reserved for conditions where there is uncertainty or additional diseases need to be ruled out (Grade A1).
6. The initial evaluation of the fibrosis stage should rely on non-invasive modalities, such as the measurement of liver stiffness by FibroScan or the assessment of serum biomarkers. Among these biomarkers, the APRI and FIB-4 panels are particularly advantageous due to their cost-effectiveness and established reliability (Grade A1).

## TREATMENT OF HEPATITIS C VIRUS INFECTION

### The primary goal of HCV therapy and endpoint

The main goal of HCV therapy is to eradicate the virus and cure the infection to prevent hepatic and non-hepatic complications, improve the quality of life, eliminate infection-related social stigma, and stop transmission.

Sustained virological response 12 (SVR12) is defined as undetectable serum or plasma HCV RNA levels using a sensitive molecular method with a lower limit of detection (≤15 IU/mL) 12 weeks after the end of therapy. As an alternative to testing HCV RNA, the absence of detectable HCVAg 12 weeks after therapy can be employed to define SVR12 for patients who initially had detectable HCVAg prior to treatment. Long-term follow-up studies have demonstrated that achieving SVR corresponds to a definitive cure for HCV infection in virtually all cases. All individuals infected with HCV should be educated on how to prevent transmission and how to avoid being re-infected after treatment.[18,19]

In patients with advanced fibrosis (F3) and cirrhosis (F4), achieving SVR may reduce the incidence of HCC and hepatic decompensation compared to patients without SVR. However, despite that the incidence of HCC is reduced in these patients, the risk is not eliminated. Therefore, it is crucial to continue surveillance for HCC in these patients.[20]

### Indications and contraindications for hepatitis C therapy with DAAs

#### *Indications for therapy*

The DAA treatments are recommended for all adult patients with active HCV infection, with urgency given to patients with significant fibrosis ≥2, including cirrhosis with or without decompensation; patients co-infected with HIV or hepatitis B virus (HBV); solid organ transplant recipients with HCV RNA positivity, including those with recurrence after liver transplantation; patients with extra-hepatic HCV-related complications such as cryoglobulinemia vasculitis, HCV-related renal disease, or HCV-related malignancy; females of childbearing age who desire pregnancy; and patients identified with active HCV infection through a pre-marital screening program, regardless of their disease stage.

#### *Contraindications for therapy*

Generally, DAAs are not recommended for HCV patients with a short life expectancy due to co-morbidities that cannot be improved by HCV therapy, liver transplantation, or other specific treatments. Contraindications for HCV DAA drugs are limited to a few specific situations. When choosing a DAA, it is crucial to consider the severity of liver failure and the specific DAA being administered, and to avoid medications that may diminish DAA efficacy or contribute to virological failure. Treatment regimens containing NS3/4A protease inhibitors, like glecaprevir or voxilaprevir, are not recommended for patients with decompensated [Child-Turcotte-Pugh (CTP) B or C] cirrhosis or those who have previously experienced episodes of decompensation, as the concentrations of NS3/4A protease inhibitors in these individuals are substantially higher, potentially leading to liver injury.[21] Additionally, it should be noted that certain medications are contraindicated when co-administered with specific DAA regimens, as detailed in the drug–drug interaction table [Table 1]. For instance, the concomitant use of CYP/P-glycoprotein inducers, such as carbamazepine, with any of the DAA regimens can significantly reduce DAA levels, thereby increasing the risk of virological failure.

Recommendations:

1. The primary objective of treating HCV-infected individuals is virological cure, as defined by SVR. Elimination of HCV is associated with reduced all-cause mortality and liver-related complications (Grade A1).
2. All patients with acute or chronic HCV infection must be offered treatment without delay (Grade A1).
3. Urgent treatment is recommended for HCV-infected individuals with significant fibrosis (≥F2), including cirrhosis with or without decompensation, clinically significant HCV extrahepatic conditions, solid organ/stem cell transplant recipients, concurrent co-morbidities (HBV and HIV co-infections, diabetes), and those at risk of transmitting HCV (Grade A1).
4. DAAs are not recommended for HCV patients with a short life expectancy (<12 months) due to non-HCV-related co-morbidities that cannot be improved by HCV therapy, liver transplantation, or other specific treatments (Grade B2).
5. NS3/4A protease inhibitors containing DAA regimens (e.g., voxilaprevir and glecaprevir) are not recommended in HCV patients with a current or past history of decompensated liver disease or a current CTP score of ≥7 because of the increased risk of liver failure with NS3/4A protease inhibitors (Grade A1).

### The available DAAs in Saudi Arabia

The direct-acting antivirals target multiple steps of the HCV replication cycle. These drugs block specific HCV non-structural proteins (NSs) that are essential for virus replication. They are highly effective in achieving a cure,

**Table 1: Drug–drug interactions: Medications not recommended to be taken concurrently with DAAs**

| Concurrent drugs | SOF/DCV | SOF/VEL | SOF/VEL/VOX | GLE/PIB |
|---|---|---|---|---|
| **Antiarrhythmics** | | | | |
| Amiodarone | Avoid | Avoid | Avoid | Use with caution and consider monitoring for amiodarone toxicity |
| Dronedarone | Avoid | Avoid | Avoid | |
| **Anticoagulant and antiplatelet agents** | | | | |
| Dabigatran | Close monitoring for bleeding signs (↑ dabigatran concentration) | Close monitoring for bleeding signs (↑ dabigatran concentration) | Avoid | Avoid |
| Edoxaban | Close monitoring for bleeding signs (↑ edoxaban concentration) | Close monitoring for bleeding signs (↑ edoxaban concentration) | Avoid | Close monitoring for bleeding signs (↑ edoxaban concentration) |
| **Anticonvulsants and barbiturates** | | | | |
| Phenytoin | Avoid | Avoid | Avoid | Avoid |
| Phenobarbital | Avoid | Avoid | Avoid | Avoid |
| Amobarbital | Avoid | Avoid | Avoid | Avoid |
| Carbamazepine | Avoid | Avoid | Avoid | Avoid |
| Oxcarbazepine | Avoid | Avoid | Avoid | Avoid |
| Eslicarbazine | Avoid | Avoid | Avoid | Avoid |
| Primidone | Avoid | Avoid | Avoid | Avoid |
| **Anti-hypertensives** | | | | |
| Aliskiren | Safe | Safe | Monitor for side effects of Aliskiren | Avoid |
| **Anti-mycobacterials** | | | | |
| Rifampicin | Avoid | Avoid | Avoid | Avoid |
| Rifabutin | Avoid | Avoid | Avoid | Avoid |
| Rifapentine | Avoid | Avoid | Avoid | Avoid |
| **HIV antiretrovirals** | | | | |
| Protease Inhibitors | | | | |
| Atazanavir/ritonavir | ↓DCV to 30 mg | Safe | Avoid | Avoid |
| Atazanavir/cobicistat | ↓DCV to 30 mg | | Avoid | Avoid |
| Darunavir/ritonavir | Safe | | Monitor if twice daily dose is administered | Avoid |
| Darunavir/cobicistat | Safe | | Safe | Avoid |
| Lopinavir/ritonavir | Safe | | Avoid | Avoid |
| **Non-nucleoside reverse transcriptase inhibitors** | | | | |
| Efavirenz | ↑DCV to 90 mg | Avoid | Avoid | Avoid |
| Etravirine | ↑DCV to 90 mg | Avoid | Avoid | Avoid |
| Nevirapine | ↑DCV to 90 mg | Avoid | Avoid | Avoid |
| **Calcineurin inhibitors** | | | | |
| Cyclosporine | Safe | Safe, monitoring cyclosporin levels is recommended | Avoid | Safe, but avoid in patients requiring cyclosporin doses >100 mg/day (↑GLE/PIB concentration) |
| **Cancer Therapies** | | | | |
| Vinblastine | Safe | Monitor for side effects of cancer therapy /doses may require alteration | Avoid | Avoid |
| Vincristine | | | Avoid | Avoid |
| Methotrexate | | | Avoid | |
| Imatinib | | | Avoid | |
| Lapatinib | | | Avoid | |
| Nilotinib | | | Avoid | |
| Mitoxantrone | | | Avoid | |
| Irinotecan | | | Avoid | |
| **Cholesterol-lowering agents** | | | | |
| Atorvastatin | Use with caution. Monitor for statins adverse events/ dose reduction may be required | Use with caution. Monitor for statins adverse events/dose reduction may be required | Avoid | Avoid |
| Simvastatin | | | Avoid | Avoid |
| Lovastatin | | | Avoid | Avoid |
| Rosuvastatin | | | Avoid | |
| Fluvastatin | | | Avoid | |
| Pitavastatin | | | Avoid | |
| **COVID-19 antivirals** | | | | |
| Nirmatrelvir/ritonavir | Safe | Safe | Check ALT levels during and post treatment | Avoid |

*Contd...*

**Table 1: Contd...**

| Concurrent drugs | SOF/DCV | SOF/VEL | SOF/VEL/VOX | GLE/PIB |
|---|---|---|---|---|
| | | **Contraception products** | | |
| Ethinyl estradiol containing contraception products | Safe | Safe | Avoid | Avoid |
| | | **Heart failure agents** | | |
| Bosentan | Avoid | Avoid | Avoid | Avoid |
| | | **Herbals** | | |
| St. John's wort | Avoid | Avoid | Avoid | Avoid |
| | | **Macrolide antimicrobials** | | |
| Troleandomycin | ↓DCV to 30 mg | Caution. May increase concentration of velpatasvir | Avoid | Avoid |

SOF: Sofosbuvir, DCV: Daclatasvir, VEL: Velpatasvir, VOX: Voxilaprevir, GLE: Glecaprevir, PIB: Pibrentasvir



are safe, and require short durations of therapy. The Saudi Food and Drug Authority (SFDA) has registered multiple DAAs [Table 2] for treating patients with HCV infection, including the NS3/4A protease inhibitors glecaprevir (GLE) and voxilaprevir (VOX), the NS5B nucleotide inhibitor generic (SOF), and the NS5A replication complex inhibitors velpatasvir (VEL), pibrentasvir (PIB), ledipasvir (LDV), and generic daclatasvir (DCV). Non-generic drugs are available as fixed-dose combination tablets (Harvoni®, Epclusa®, Vosevi®, Maviret®), while generic versions of DAAs include those of SOF (Sovira®, Sofocure®) and DCV (Levera®) tablets. Notably, LDV/SOF (Harvoni®) is no longer offered in Saudi Arabia. The available DAAs in the country are pangenotypic and can be used to treat patients with HCV infection with various clinical characteristics and co-morbidities.

Pan-genotypic regimens are recommended as the first treatment option for all individuals with chronic HCV infection. Previously, there were several genotype-specific regimens for the treatment of HCV infection, but they are no longer used in Saudi Arabia and have been excluded from this consensus statement. These old treatment options include elbasvir plus grazoprevir, simeprevir, SOF plus ledipasvir, SOF plus ribavirin (RBV), and paritaprevir (ritonavir-boosted) plus ombitasvir plus dasabuvir, with or without RBV.

## DAA treatment monitoring

The currently available pangenotypic DAAs are highly effective drugs, with reported cure rates exceeding 95% in most cases for treatment-naïve patients with or without compensated cirrhosis. Consequently, it is imperative that all patients being considered for treatment undergo a comprehensive pre-treatment assessment in order to achieve the desired SVR [Table 3]. This evaluation serves as the basis for successful viral outcomes by establishing therapeutic and cooperative relationships. Patients should be provided with access to educational materials, psychological, alcohol, and drug counseling, and information on how to prevent the transmission of HCV and avoid reinfection with the virus. Non-immune patients should be proposed to receive hepatitis B virus (HBV) and hepatitis A virus (HAV) vaccinations.

Recommendations:

1. Pangenotypic DAA regimens have become the established standard of care for the treatment of HCV infection (Grade A1).
2. A comprehensive pre-treatment assessment is recommended for all individuals with HCV infection who are being considered for DAA therapy (Grade A1).
3. Patients should be provided with resources such as educational materials as well as psychological, alcohol, and drug counseling. Additionally, they should be given information on HCV transmission prevention and strategies to avoid HCV reinfection (Grade B1).

## Pre-treatment virologic assessment

Patients with HCV infection are considered treatment-naïve if they have never received any form of anti-HCV therapy. In contrast, those who have been treated with any HCV therapy [conventional interferon (IFN) ± RBV, pegylated IFN (PegIFN) ± RBV, or DAAs] are considered treatment-experienced. It is essential to record any prior treatment history for HCV infection, including the treatment regimen, length, adherence, and response. These factors may affect the selection of the treatment regimen and/or duration of treatment. Patients who have not responded to a prior DAA regimen often have HCV variants that are resistant to treatment.

For patients who are HCV antibody-positive, a PCR assay for HCV RNA should be used to verify the current (active) HCV infection. Quantitative laboratory-based PCR is considered

**Table 2: Direct-acting Antiviral Agents (DAAs) registered by Saudi FDA for prescription in Saudi Arabia**

| DAA | Abbreviation | Class | Trade name | Dosage recommendation in adults | Warning[¶] |
|---|---|---|---|---|---|
| Generic Sofosbuvir | SOF | NS5B polymerase nucleotide inhibitor | SOVIRA 400 mg film-coated tablet SOFOCURE 400 mg film-coated tablet | Sovira/Sofocure 400 mg tablet with Levera 60 mg[¤] tablet once daily with or without food | -Risk of HBV reactivation in current or prior HBV infection -Risk of symptomatic bradycardia when coadministered with amiodarone |
| Generic Daclatasvir | DCV | NS5A replication complex inhibitor | LEVERA 60 mg film-coated tablet | | |
| Sofosbuvir with Velpatasvir | SOF/VEL | NS5B polymerase nucleotide inhibitor and NS5A replication complex inhibitor | EPCLUSA 400 mg/100 mg Film-coated tablet | Epclusa (400 mg/100 mg) fixed-dose tablet once daily, with or without food | -Risk of HBV reactivation in current or prior HBV infection -Risk of symptomatic bradycardia when coadministered with amiodarone |
| Sofosbuvir with Velpatasvir and Voxilaprevir | SOF/VEL/VOX | NS5B polymerase nucleotide inhibitor, NS5A replication complex inhibitor, and NS3/4A protease inhibitor | VOSEVI 400 mg/100 mg/100 mg film coated tablet | Vosevi (400 mg/100 mg/100 mg) fixed-dose tablet once daily, with food. | -Risk of HBV reactivation in current or prior HBV infection -Risk of symptomatic bradycardia when coadministered with amiodarone -Risk of liver decompensation in Child-Turcotte-Pugh B or C cirrhosis or history of prior liver decompensation |
| Glecaprevir with Pibrentasvir | GLE/PIB | NS3/4A protease inhibitor and NS5A polymerase inhibitor | MAVIRET 100 mg/40 mg film-coated tablet | Maviret (100 mg/40 mg) 3 tablets taken at the same time once daily with food | -Risk of HBV reactivation in current or prior HBV infection -Risk of liver decompensation in Child-Turcotte-Pugh B or C cirrhosis or history of prior liver decompensation |

[¶]Warning regarding drug–drug interactions, see section on drug–drug interactions. [¤]↓DCV dose to 30 mg is recommended in co-medications with strong CYP3A inhibitors, such as clarithromycin, HIV protease inhibitors, and cobicistat-containing antiretrovirals, ↑DCV dose to 90 mg is recommended with moderate CYP3A inducers such as bosentan and non-nucleoside reverse transcriptase inhibitors

part of the pre-treatment assessment in a hospital setting. PoC tests for HCV RNA can be used in non-hospital settings and can yield real-time results in less than 2 hours. These PoC assays have demonstrated excellent diagnostic performance when used in various settings and populations.[22]

In the previous SASLT HCV practice guidelines, it was necessary to identify HCV genotypes before beginning genotype-specific DAAs.[23] However, with the currently approved pangenotypic DAA regimens, it is no longer necessary to perform genotyping before commencing HCV therapy in treatment-naïve patients using first-line treatment regimens. However, there are a few situations in which genotyping is important or useful. For instance, when considering initiating therapy for treatment-naïve compensated cirrhotic patients with SOF-DCV or SOF/VEL, it is recommended to perform genotyping.[24-26] Those with genotype 3 should undergo baseline NS5A resistance-associated substitution (RAS) testing.[27] If RAS testing is unavailable or unaffordable, the addition of RBV is recommended. HCV genotyping is also important when treating HCV patients with decompensated cirrhosis, when genotype-specific DAAs are being prescribed, and when considering the re-treatment of patients who previously failed HCV treatment. Additionally, genotyping may be useful for individuals at high risk of re-infection, where a genotype switch can differentiate re-infection from relapse.

Recommendations

1. It is recommended to document the past HCV treatment experience, including the regimen used and the response achieved (Grade A1).
2. Performing HCV genotyping in pre-treatment assessments of all treatment-naïve patients without cirrhosis is not recommended (Grade B1).
3. It is not recommended to perform HCV genotyping in treatment-naïve patients with compensated cirrhosis if considering treatment with glecaprevir/pibrentasvir (Grade B1).
4. Performing HCV genotyping in treatment-naïve patients with compensated cirrhosis is recommended when considering treatment with either sofosbuvir and daclatasvir combination or sofosbuvir/velpatasvir fixed dose combination (Grade B1).

## Pre-treatment assessment of liver fibrosis

An evaluation of the stage of liver fibrosis should be performed before commencing treatment. However, if fibrosis assessment cannot be organized in a timely

**Table 3: Pre-treatment evaluation of treatment-naïve and compensated cirrhotic patients with chronic HCV infection**

| |
|---|
| Clinical Evaluation |
| • Prior HCV therapy and duration of infection |
| • Ongoing risk factors for viral transmission and reinfection |
| • Comorbidity factors for liver disease progression, e.g., HBV, HIV, DM, obesity, alcohol, etc. |
| • HBV and HAV vaccination history |
| • Psychosocial factors affecting medications and clinic follow-up adherence |
| • Symptoms of liver decompensations, e.g., jaundice, hematemesis, confusion, abdominal distension, lower limb swelling |
| • Clinical signs of cirrhosis or liver decompensations, e.g., jaundice, ascites, legs edema, etc. |
| Medications Evaluation |
| • Concurrent medications (prescription, over-the-counter, herbal and vitamin supplements, and recreational drugs) |
| Routine laboratory testing - within 3 months in cirrhotic and 6 months in non-cirrhotic patients |
| • Complete blood count (CBC) |
| • Liver biochemical tests [alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, total and direct bilirubin] |
| • International normalized ratio (INR) – additional test for patients with cirrhosis |
| • Calculated glomerular filtration rate (eGFR) |
| Virology Evaluation |
| • Quantitative HCV RNA |
| • HIV antigen/antibody test |
| • HBsAg, anti-HBc, anti-HBs, and anti-HAV IgG |
| • HCV genotyping (required in case of): a) Treatment-naïve patients with liver cirrhosis considering therapy with sofosbuvir/daclatasvir or sofosbuvir/velpatasvir[π] b) Genotype-specific direct-acting antiviral is going to be prescribed |
| Serum Pregnancy test: before starting antiviral therapy |
| Liver fibrosis evaluation |
| • Elastography (any of the following: FibroScan®, ARFI, SWE) |
| • Serum biomarker (any of the following: APRI, FIB-4, Hepascore, ELF test) |
| Evaluation of Patients with cirrhosis |
| • Liver ultrasound: screening for hepatocellular carcinoma (should be performed within 3 months before starting DAAs) |
| • Fibroscan + platelet count: Screening for clinically significant portal hypertension |

ARFI: Acoustic Radiation Force, SWE: shear wave elastography. [π]Cirrhotic patients with genotype 3 may need to be tested for baseline NS5A resistance-associated substitution (RAS), refer to treatment-naïve genotype 3 in the Treatment section

fashion, patients should immediately start HCV treatment, especially when there is a concern about loss to follow-up.

The presence of cirrhosis identifies patients who require lifelong surveillance for HCC and portal hypertension. Clinical signs of advanced liver disease and portal hypertension should be assessed. Biochemical markers of reduced liver function reserve on routine blood tests, such as low albumin levels, high bilirubin levels, and an increased international normalized ratio (INR), should also be evaluated.

When evaluating the stage of liver fibrosis, it is important to categorize HCV-infected patients as cirrhotic (F4) or non-cirrhotic (F0-3). Liver biopsy is an invasive procedure to evaluate the stage of liver fibrosis and is not recommended because of its risks and complications; therefore, non-invasive liver fibrosis tests are recommended in patients with HCV infection. Liver biopsy is usually reserved for patients in whom there are doubts about the etiology of liver disease. Transient elastography (FibroScan®; EchoSens, Paris, France) is the most commonly used method for assessing HCV-related liver fibrosis and diagnosing cirrhosis as it has been thoroughly evaluated and validated in patients with chronic HCV infection and is more accurate than serum biomarkers for detecting cirrhosis.[28] A liver stiffness measurement (LSM) of more than 12.5 kPa [AUROC (0.90–0.93), negative predictive value (NPV) 95–98%] using FibroScan® is a suitable cutoff point for determining individuals with cirrhosis.[29]

In cases where transient elastography is not available, serum biomarkers such as FIB-4 score >3.25 [AUROC (0.83–0.92), specificity 92%, positive likelihood ratio (LR+) 6.9] can be used to indicate the presence of cirrhosis.[30] It should be noted that the FIB-4 score can be calculated online or downloaded on smartphones. It is also worth noting that imaging findings such as liver nodularity with or without splenomegaly are important radiologic signs of cirrhosis that should also be considered when making decisions.

Recommendations

1. It is recommended that all patients with HCV undergo evaluation for advanced fibrosis using non-invasive testing with either elastography such as FibroScan or serum biomarkers such as the FIB-4 score (Grade A1).
2. Detecting cirrhosis is crucial for identifying patients who need long-term management of chronic liver disease (Grade A1).

## Pre-treatment HBV and HIV testing and concurrent liver diseases

Individuals with high-risk factors for HIV infection should be tested before DAA therapy. Patients co-infected with HIV are at risk of accelerated liver fibrosis progression.[31] All patients infected with HCV should be tested for HBV co-infection and evidence of prior HAV infection.

Individuals with HBV/HCV co-infection and detectable viremia are more likely to experience disease progression, decompensation, and HCC.[32,33] The viral kinetics of HBV/HCV co-infection tend to be inversely related, with high HCV viremia usually accompanied by low or even undetectable HBV DNA. Occasionally, HBV may be the predominant virus.[34,35] This viral interference effect may have a significant impact on HBV replication after HCV

eradication with DAAs. Studies have indicated that HBV can be re-activated during or after DAA treatment in HBV/HCV co-infected patients who were not receiving HBV suppression therapy.[36-38] Monitoring and management of HCV/HBV co-infection should follow the SASLT practice guidelines for the management of HBV infection.[39] In patients who are not immune to HBV or HAV infection, vaccinations should be offered after completing DAA therapy.

It is also important to ascertain if any other liver disease is present as this can increase the likelihood of cirrhosis and necessitates continued management, even after the virus is eradicated. At the initial clinical encounter, it is important to evaluate for any significant co-morbidities such as heavy alcohol consumption, diabetes, obesity, and steatotic liver disease. Patients with diabetes may be prone to hypoglycemia when HCV infection is eliminated.[40,41] Therefore, those taking diabetes medications should be warned that their anti-diabetes therapy may need to be adjusted to avoid the risk of symptomatic hypoglycemia.

Recommendations:

1. Before initiating DAA treatment, it is essential to test all patients for active HBV co-infection using HBV surface antigen (HBsAg) testing and for prior infection with HBV core antibody (anti-HBc) and HBV surface antibody (anti-HBs) testing (Grade B1).
2. Patients who test positive for HBsAg should undergo evaluation to determine whether their HBV DNA meets the SASLT criteria for HBV treatment and to consider initiation of antiviral therapy for HBV (Grade B1).
3. It is advisable to conduct testing for HIV infection in patients with high-risk factors for HIV infection (Grade B1).
4. Vaccination against HAV and HBV is recommended for all susceptible patients with HCV infection (Grade D1).
5. Regular monitoring for hypoglycemia is recommended during and after treatment in patients with diabetes who are taking anti-diabetes medications (Grade C1).

## Drug–drug interactions with DAA regimens

Before beginning treatment with a DAA, a comprehensive and thorough drug history must be obtained. This history should include all prescribed medications, over-the-counter drugs, herbal and vitamin supplements, and any recreational drug use. The information should be documented in the patient's medical file.

Drug–drug interactions (DDIs) are a potential problem for any DAA regimen. The metabolic pathways most commonly associated with DDI include CYP450, drug uptake transporters such as organic anion transporting polypeptide (OATP), and drug efflux transporters such as P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).[42] DAAs can serve as substrates, inhibitors, and/or inducers of metabolic enzymes and transporters, resulting in increased toxicity or decreased efficacy of drugs taken concurrently and vice versa. In general, NS5A inhibitors interact with transporters, such as P-gp, BCRP, and OATP, but not with CYP enzymes, which limits their potential for DDIs with certain medications. Interactions with NS3/4A protease inhibitors can be complex because they are often sensitive to both OATP and/or CYP3A4, which can result in DDIs through both CYP and transporter inhibition. SOF has the most desirable DDI profile as it does not inhibit or induce any of the CYP isoenzymes or transporters and is only transported by P-gp and BCRP.[43]

Whenever feasible, an interacting concomitant medication should be discontinued or changed to an alternative with a lower risk of potential interactions during HCV treatment. When considering potential interactions with DAAs, important classes of drugs to take into account include proton pump inhibitors, statins, ethinyloestradiol-containing contraceptive agents, St. John's wort, antimicrobials, anti-epileptic agents, amiodarone, immunosuppressive agents [such as cyclophilin inhibitors and mammalian target of rapamycin (mTOR) inhibitors], and antiretroviral agents [Table 1]. The solubility of DAAs decreases with increasing gastric pH. Therefore, it is essential to evaluate whether patients on gastric acid suppressive therapy actually need to be on it, and if so to adjust the dose accordingly [Table 4].[44] However, the license for the fixed dose combination of glecaprevir and pibrentasvir (GLE/PIB) states that no dose adjustment is required when taken with omeprazole 40 mg, and there is no need to alter the timing of antacid administration.[45] For women of reproductive age, co-medication with NS3/4A protease inhibitors (e.g., VOX and GLE) with any ethinylestradiol-containing contraception is not recommended due to the risk of hepatotoxicity. However, the use of progestogen-containing contraception is permissible.

It is also important to note that the combination of SOF with a second DAA for the treatment of HCV should not be used in combination with amiodarone as this could lead to serious symptomatic bradycardia.[46] Patients taking warfarin should be informed of the potential for changes in their anticoagulation levels. It is recommended to monitor INR levels both during and after treatment to detect any sub-therapeutic anticoagulation. Before starting treatment with any DAA regimen, it is strongly recommended to check for interactions with a patient's current medications

**Table 4: Recommended doses of gastric acid suppressive therapy co-administered with ledipasvir (LDV) and velpatasvir (VEL) based regimens[¶]**

| Gastric acid suppressive therapy | Drug | Dose |
|---|---|---|
| Proton pump inhibitors (PPI)[€] | Omeprazole | 20 mg once daily |
| (Dose equivalent to omeprazole 20 mg once daily) | Lansoprazole | 30 mg once daily |
| | Esomeprazole | 20 mg once daily |
| | Pantoprazole | 40 mg once daily |
| | Rabeprazole | 20 mg once daily |
| H2 blockers[¤] | Famotidine | 20 mg twice daily |
| (Dose equivalent to famotidine 20 mg twice daily) | Nizatidine | 150 mg twice daily |
| Antacids | Aluminum and magnesium hydroxide | Separate antacid administration by 4 h |

[¶]The license for glecaprevir/pibrentasvir does not require any dose adjustment when omeprazole 40 mg is administered, and there is no need to alter the timing of antacid administration. Daclatasvir is not affected by gastric acid-suppressive therapies. Sofosbuvir is not affected by PPI or H2 blockers but separating the sofosbuvir dose by 2 h from antacid could be considered (optional)- weak interaction. [€]VEL or LDV based DAA regimen should be given with food and taken 4 h before the proton pump inhibitor. [¤]Ranitidine and cimetidine are no longer registered by Saudi FDA



using the University of Liverpool's Hepatitis Drug Interactions website (https://www.hep-druginteractions.org/) or by downloading the app on a mobile device. The University of Liverpool's Hepatitis Drug Interactions website is an invaluable resource containing regularly updated information. Furthermore, patients should be instructed to seek medical advice before starting any new medication while undergoing DAA therapy.

Recommendations:
1. Before initiating DAA therapy, it is advisable to assess potential DDIs with any concurrent medication. If feasible, discontinue or switch to an alternative medication with a lower risk of interaction during HCV treatment (Grade D1).
2. It is recommended that all patients consult a healthcare professional before initiating any new medication while undergoing DAA therapy (Grade D1).

## Safety of DAAs with or without ribavirin

### *DAA adverse events, pregnancy, and nursing mothers*

Educating patients and their caregivers about the potential side effects of DAA therapy and ways to manage them is an essential part of treatment, and necessary for a successful outcome in all patients. DAAs are generally well tolerated and have a favorable safety profile, with <1% treatment discontinuation in clinical trials due to adverse events.[47,48] The most frequently reported side effects (in ≥5%) of DAAs were headache, nausea, diarrhea, and fatigue. The safety of DAA regimens in pregnant women and nursing mothers has not been established; therefore, women of childbearing age should be counseled before beginning HCV treatment. It is advisable to wait until the HCV DAA therapy is completed before attempting pregnancy.

When RBV is included in the DAA regimen, patients should be informed of the precautions associated with its use. RBV is significantly teratogenic and embryocidal.[49] These effects were observed even at doses as low as one-twentieth of the recommended human dose of RBV. Extreme caution must be exercised to prevent pregnancy in patients and in female partners of male patients. Women of childbearing age should be advised to use at least two reliable forms of contraception during treatment, and for a period of 6 months after treatment is completed. Men whose partners are of childbearing age should be warned to avoid pregnancy while they are on RBV-containing regimens, and for up to 6 months after completing the regimen. Women of childbearing potential should undergo a serum pregnancy test before starting an RBV-containing treatment regimen. The concerns regarding pregnancy and the use of DAAs are further explored and the options highlighted in the section on the Treatment of Chronic HCV in Special Groups.

Recommendations:
1. Women of childbearing age undergoing DAA treatment are advised against pregnancy and breastfeeding (Grade D1).
2. Both men and women of childbearing age should be cautioned to refrain from pregnancy while undergoing RBV-containing antiviral regimens, and this precautionary measure should be extended for a duration of up to 6 months after discontinuing RBV (Grade D1).
3. Women of childbearing age intending to initiate treatment with DAA and/or RBV are recommended to undergo a serum pregnancy test prior to the commencement of the antiviral therapy (Grade D1).

### *HCV NS3/4A Protease inhibitors induced liver injury*

Several HCV protease inhibitors have been associated with liver injury. In rare instances, mild-to-moderate elevations in ALT or alanine aspartate (AST) to >5 times the upper limit of normal (ULN) are observed in <1% of those treated with the fixed-dose combination of GLE/PIB or SOF/VEL/VOX.[50] Additionally, a few cases of hepatic decompensation (<1%) during treatment of patients with pre-existing cirrhosis have been reported.[21,51] Episodes

of hepatic decompensation typically occur 2 to 6 weeks after treatment initiation and are marked by symptoms of fatigue, itching, and jaundice, along with notable rise in serum bilirubin but only slight increases in serum ALT and AST and alkaline phosphatase (ALP) levels.[51] It is recommended that the DAA be immediately stopped if there is a ≥10-fold increase in ALT values from baseline at any point during treatment, or an increase in ALT <10-fold that is accompanied by symptoms such as weakness, nausea, vomiting, jaundice, or a significant rise in bilirubin, ALP, or INR. If ALT levels increase by less than 10-fold from baseline without any symptoms, they should be monitored closely with repeat testing every 2 weeks. If levels remain consistently high, discontinuation of DAA therapy should be considered.[27]

Recommendations:

1. In the event of an increase in ALT values of ≥10-fold from baseline during DAA treatment, irrespective of the presence of hepatitis symptoms, discontinuation of DAA therapy is advised (Grade B1).
2. DAA therapy should be halted if ALT increases by less than 10-fold from baseline and is accompanied by symptoms or signs of hepatitis, such as weakness, nausea, vomiting, jaundice, and elevated levels of bilirubin, ALP, or INR (Grade B1).
3. Asymptomatic elevation of ALT levels, less than 10-fold from the baseline value, should be carefully monitored, with follow-up testing every 2 weeks. If consistently high levels persist, discontinuation of DAA therapy may become necessary (Grade B1).

## Monitoring patients during and after DAA treatment

Owing to the high efficacy of DAA regimens, the lack of need for response-guided therapy, and the much-improved side effects profile, close monitoring of individuals undergoing DAA therapy is generally not required [Table 5]. During treatment, follow-up intervals should be tailored to each individual to ensure adherence, assess any adverse reactions and potential DDIs, and monitor blood test results for patient safety. It is important to note that the addition of RBV to DAA regimens will necessitate more frequent monitoring visits to measure hemoglobin levels. Lower doses of RBV should be initiated in patients with decompensated cirrhosis. For many individuals, no evaluation will be necessary during treatment, and a review at 12 weeks post-treatment can be arranged to confirm SVR and assess liver function.

On-treatment and end-of-treatment virological assessments are generally not recommended; however, they may be considered if there are concerns about treatment adherence. The management of dose interruptions should be tailored to the length of the interruption and the amount of DAA therapy completed. Those who have interrupted their doses should be monitored and supported more closely for the remainder of their treatment. A useful approach[27] is presented in Table 6.

**Table 5: Monitoring patients during and after DAA treatment for HCV infection**

| On-treatment and post-treatment monitoring for virological response | |
|---|---|
| First clinic visit (assessment visit) | HCV RNA [Table 3] |
| Week 12 post treatment (SVR12) | LFT + HCV RNA |
| **Monitoring after SVR** | |
| Obtained SVR12 + [not F3 or cirrhosis + normal LFT results]<br>• Do not require clinical follow-up for HCV<br>• Remind the patients that the presence of anti-HCV antibodies is to be expected and does not indicate active infection, nor does it provide immunity against reinfection (educate the patient on how to avoid reinfection) | |
| Obtained SVR12 + [abnormal LFT results]<br>• Evaluate for other liver diseases (refer to gastro-hepatologist if HCV management was at primary health care setting).<br>• Investigations to be considered (iron studies, ANA, ASMA, anti-LKM antibodies, total IgG and IgM, AMA, celiac serology, copper level, ceruloplasmin level and a-1-antitrypsin level, fasting glucose level, fasting lipid levels) | |
| Obtained SVR12 + [F3 or cirrhosis]<br>• Requires long-term monitoring enrolment in surveillance programs for:<br>a) HCC (F3 and cirrhosis)–liver ultrasound±serum alpha-fetoprotein level<br>b) esophageal varices (only cirrhosis)–gastroscopy | |
| Obtained SVR12 + risk of reinfection<br>• Annual HCV RNA testing | |

SVR, sustained virologic response; LFT: Liver function test; ALT, alanine aminotransferase; HCV: Hepatitis C virus; PCR, polymerase chain reaction; AMA, anti-mitochondrial antibody; ANA, anti-nuclear antibodies; ASMA, anti-smooth muscle antibodies; LKM, liver-kidney microsome; HCC, hepatocellular carcinoma

Recommendations:

1. For individuals eligible for simplified treatment, minimal clinical follow-up is advised. A clinic visit 12 weeks post-treatment is sufficient to evaluate liver function and SVR (Grade D1).
2. Routine HCV RNA testing during treatment is not necessary unless there are specific concerns regarding compliance with DAA medication or the development of viral resistance (Grade B1).
3. Patients should receive comprehensive education regarding the correct usage of DAAs, including information about appropriate dosage, frequency, effects related to food intake, handling of missed doses, and potential side effects. Emphasizing the importance of adherence to the treatment regimen is essential (Grade D1).

**Table 6: Management of DAA treatment interruption[π]**

A. DAA interruption is in the first 4 weeks of DAA therapy:
1. Interruption ≤7 days … Resume same DAA regimen and complete planned duration.
2. Interruption ≥8 days … Resume same DAA regimen immediately and obtain HCV RNA the same day of restarting DAA:
   a) If HCV RNA is negative … Resume same DAA regimen and complete planned duration, may extend to additional 4 weeks if cirrhotic or genotype 3.
   b) If HCV RNA is detected (>25 IU/ml) or cannot be obtained … Resume same DAA regimen and extend treatment duration for additional 4 weeks.

B. DAA interruption is after 4 weeks of DAA therapy:
1. Interruption ≤7 days …Resume same DAA regimen and complete planned duration.
2. Interruption 8–20 consecutive days … Resume same DAA regimen immediately and obtain HCV RNA the same day of restarting DAA:
   a) If HCV RNA is negative … Resume same DAA regimen and complete planned duration, may extend to additional 4 weeks if cirrhotic or genotype 3.
   b) If HCV RNA is detected (>25 IU/ml) or cannot be obtained… STOP and retreat according to retreatment recommendations.
3. Interruption ≥21 days … STOP DAA and obtain HCV RNA … If SVR 12 is not achieved, retreatment should be done in accordance with the retreatment recommendations.

[π]Based on AASLD 2023 guidance recommendations

## Post-treatment follow-up in patients achieving sustained virologic response

All patients undergoing treatment for HCV should mandatorily obtain confirmation of SVR at 12 weeks post treatment (SVR12). In situations where there exists a potential risk of patients failing to adhere to follow-up visits, it may be deemed acceptable to assess HCV RNA levels beyond 4 weeks post-treatment completion (SVR4), as more recent data indicate a high concordance between SVR4 and SVR12 results.[52,53]

Individuals who do not have advanced fibrosis (F3) or cirrhosis and whose liver enzymes and function tests are normal after achieving SVR no longer require clinic follow-ups and can be managed as if they never had HCV infection. It is important to remind patients who have achieved SVR that the presence of anti-HCV antibodies is to be expected and does not indicate active infection, nor does it provide immunity against re-infection. The medical records of patients who have achieved SVR should be updated to indicate that they are no longer infected with HCV. Individuals with persistent risk factors for HCV reinfection, such as in IVDU, should undergo annual HCV RNA tests. Individuals with continued abnormal liver function test results after SVR should be evaluated for other causes of liver diseases.

Patients with cirrhosis should be enrolled in surveillance programs for HCC and clinically significant portal hypertension (CSPH). The SASLT guidelines recommend that HCC surveillance be undertaken in HCV patients with advanced fibrosis or cirrhosis irrespective of SVR12 outcome.[54] HCC surveillance should involve having an ultrasound of the liver done every 6 months, with or without alpha fetoprotein (AFP).[54] The risk of HCC in patients with HCV-induced cirrhosis who achieved SVR is decreased significantly but not completely eliminated, compared to those who did not receive treatment or those who did not achieve an SVR.[55]

Non-invasive screening for CSPH should be performed in accordance with Baveno VII consensus recommendations. This screening includes the use of transient elastography (TE) with LSM (e.g., most commonly by FibroScan®) and platelet counts.[56] Patients with HCV-induced cirrhosis can be assumed to have CSPH if they meet any of the following criteria:

(1) The LSM value is ≥25 kPa.
(2) The LSM value is 20–25 kPa and the platelet count is $<150 \times 10^9$/L.
(3) The LSM value is between 15 and 20 kPa and the platelet count is $<110 \times 10^9$/L.

Patients diagnosed with CSPH should be started on non-selective beta-blocker (NSBB) therapy as primary prophylaxis, to reduce the risk of liver decompensation and variceal bleeding. Once NSBB treatment is initiated, screening endoscopy is not required. For patients with compensated cirrhosis who are unable to take NSBBs due to contraindications or prior intolerance, gastroscopy for variceal screening is recommended if their LSM is ≥20 kPa or their platelet count is $\leq 150 \times 10^9$/L. Patients with cirrhosis who do not require NSBB therapy or screening gastroscopy should have their CSPH monitored annually using LSM (FibroScan®) and platelet counts. If LSM rises (≥20 kPa) or the platelet count drops ($<150 \times 10^9$/L), screening gastroscopy should be performed to check for varices.

In the absence of co-factors for liver diseases, those with compensated cirrhosis who achieved SVR and demonstrated consistent post-treatment improvements with LSM values <12 kPa and a platelet count $>150 \times 10^9$/L can be discontinued from portal hypertension surveillance (LSM and endoscopy), but they should continue HCC surveillance (liver ultrasonography with or without AFP). The assessment of regression of advanced liver fibrosis after DAA treatment by non-invasive tests can be confounded by the inflammatory response, leading to the false impression that fibrosis reversal is more pronounced due to a decrease in inflammation. Therefore, it is important to note that non-invasive tests, including FibroScan®, may over-estimate fibrosis regression and should not be used to evaluate advanced fibrosis regression after DAA treatment as they are not reliable.[56-59]

Recommendations:

1. Performing quantitative HCV RNA testing 12 or more weeks after the completion of DAA therapy to confirm SVR12 is recommended (Grade A1).
2. Annual HCV RNA testing is recommended for individuals with persistent risk factors for HCV reinfection (Grade D1).
3. Quantitative HCV RNA testing can be performed at any point after 4 weeks of completing DAA therapy in cases where there is a risk of loss to follow-up to confirm SVR4, which has high concordance with SVR12 (Grade C1).
4. Individuals with no cirrhosis or advanced fibrosis (F3) who achieved SVR and exhibit normal liver function test results should be managed as if they had never experienced HCV infection (Grade B1).
5. Surveillance for HCC with liver ultrasound examination, with or without (AFP), every 6 months is recommended for patients with F3 fibrosis or cirrhosis, irrespective of SVR outcomes (Grade B1).
6. The adoption of the Baveno VII recommendations for the diagnosis of clinically significant portal hypertension (CSPH) and endoscopic surveillance for varices is recommended (Grade D1).
7. Non-invasive testing is not recommended for evaluating the regression of liver fibrosis after achieving SVR12 as it is not reliable (Grade C1).

### Follow-up of untreated patients and patients with definitive treatment failure

Patients who have not been treated and those who have not responded to treatment should be monitored regularly (6–12 months). Patients with treatment failure should be evaluated to determine the cause (adherence, drug resistance, DDI, and reinfection). Re-treatment should be considered as necessary (refer to the retreatment recommendations section). Patients with cirrhosis should be monitored for HCC and portal hypertension, as previously recommended.

Recommendations:

1. It is recommended that patients for whom treatment is delayed should have their liver disease monitored regularly (6–12 months) (Grade C1).
2. The assessment of liver disease progression every 6–12 months is recommended for patients who are not retreated or have failed previous DAA regimens, utilizing liver function tests, complete blood count (CBC), and INR (Grade C1).
3. Surveillance for HCC with liver ultrasound examination, with or without (AFP), every 6 months is recommended for patients with advanced fibrosis and cirrhosis (Grade A1).

## TREATMENT OF HCV WITHOUT CIRRHOSIS AND WITH COMPENSATED CIRRHOSIS

Current treatment for HCV has become easier with the availability of pan-genotypic therapy. This simpler and highly effective treatment, which has few side effects, has led to an increase in healthcare professionals prescribing antiviral therapy and the number of people undergoing treatment. This streamlined approach is recommended for patients without cirrhosis who have not previously received treatment [Table 7]. The choice of treatment should be based on individual patient data, including potential DDIs. Patients receiving antiviral therapy should undergo a thorough assessment for any underlying conditions that may affect treatment response or regimen selection. All patients should have access to HCV care providers during treatment, but the frequency of clinic visits and blood tests may vary depending on the treatment regimen and individual patient needs [Tables 8 and 9].

### Genotype 1

Highly potent DAA combination regimens are recommended for patients with genotype 1 infection due to their high efficacy and excellent minimal side effect profile.

### Recommended regimens

*Glecaprevir/Pibrentasvir*

In a series of clinical investigations, the efficacy of a daily fixed-dose combination comprising glecaprevir (GLE) at a dosage of 300 mg and pibrentasvir (PIB) at a dosage of 120 mg was examined. This combination is typically administered in the form of three pills, each containing 100 mg of GLE and 40 mg of PIB. In the context of the VOYAGE-1 phase III study, a cohort of 362 non-cirrhotic Asian patients infected with various HCV genotypes (genotype 1a: 5%; genotype 1b: 45%; genotype 2: 38%; genotype 3a: 4%; genotype 3b: 3%; genotype 6: 5%) underwent treatment with the fixed-dose

**Table 7: Eligibility criteria for simplified treatment[π]**

| |
|---|
| Individuals diagnosed with chronic hepatitis C (regardless of genotype) who do not have cirrhosis or have compensated cirrhosis (Child-Turcotte-Pugh A) and have not undergone previous hepatitis C treatment are eligible for simplified treatment.<br>Liver biopsy is not mandatory. Cirrhosis can be presumed if a patient's FIB-4 score >3.25 or any of the following criteria are met based on previous test results:<br>• Transient elastography indicates cirrhosis (FibroScan stiffness >12.5 kPa)<br>• Non-invasive serologic tests show values above specified cutoffs indicating cirrhosis (e.g., FibroSure, Enhanced Liver Fibrosis Test)<br>• Clinical signs of cirrhosis (such as liver nodularity and/or splenomegaly on imaging, platelet count <150,000/mm$^3$)<br>• Previous liver biopsy confirming cirrhosis |

[π]Based on AASLD 2023 guidance recommendations

**Table 8: Treatment of naïve hepatitis C without cirrhosis**

| | Glecaprevir 300 mg/ Pibentasvir 120 mg | Sofosbuvir 400 mg/ Velpatasvir 100 mg | Sofosbuvir 400 mg and Daclatasvir 60 mg |
|---|---|---|---|
| Genotype 1 | 8 w | 12 w | 12 w |
| Genotype 2 | 8 w | 12 w | 12 w |
| Genotype 3 | 8 w | 12 w | 12 w |
| Genotype 4 | 8 w | 12 w | 12 w |
| Genotype 5-6 | 8 w | 12 w | 12 w |



combination of GLE/PIB for a duration of 8 weeks. The study demonstrated a global SVR12 rate of 97%. Among patients infected with genotype 1, the SVR12 rate was 99.4% (178/179 patients) with no virological failures observed.[60] In the ENDURANCE-1 phase III study, 703 non-cirrhotic patients with genotype 1, who were either new to DAA treatment or had failed previous IFN-based therapy, were enrolled. These participants were randomly assigned to receive either 8 or 12 weeks of GLE/PIB treatment.[61] Among the participants, 43% had genotype 1a, 85% had minimal liver fibrosis (F0 or F1), and 62% were treatment-naive. The study demonstrated high response rates, with 99% achieving SVR12 (348/351) in the 8-week group and 99.7% (351/352) in the 12-week group. The 8-week treatment was proven to be as effective as the 12-week treatment, meeting the study's predefined criteria for non-inferiority.

In the CERTAIN-1 phase III study, Japanese patients infected with HCV genotype 1, the majority of whom had genotype 1b infection (97%), were subjected to a treatment regimen for 8 weeks. The study yielded an SVR12 rate of 99% (128/129 patients) with no instances of virological failure observed.[62] The SURVEYOR-1 study showed positive results for 8 weeks of treatment in non-cirrhotic patients, with 33/34 patients achieving SVR12, and no treatment failures.[48] A combined analysis of 602 DAA-naive, non-cirrhotic genotype 1 patients treated with 8 weeks of GLE/PIB across six clinical trials demonstrated an SVR12 rate of 99.2%.[63]

Real-world data from Germany and Italy further confirmed high efficacy in treatment-naive, non-cirrhotic genotype 1 patients treated with 8 weeks of GLE/PIB. Both German and Italian cohorts achieved 100% SVR rates when accounting for those who completed treatment, excluding dropouts or individuals lost to follow-up.[64,65]

Subsequently, the EXPEDITION-1 and EXPEDITION-2 studies examined the effectiveness of GLE/PIB treatment in patients who were cirrhotic and were either DAA-naive or had prior DAA experience. In EXPEDITION-1, 99% of patients with various genotypes (1, 2, 4, 5, or 6) achieved SVR12 after 12 weeks of GLE/PIB, with only one relapse observed in a genotype 1a patient. For genotype 1a patients, the SVR12 rate was 98%.[66] EXPEDITION-2, involving HIV/HCV-co-infected adults with genotypes 1–6, showed a 98% SVR12 rate overall and no treatment failures in genotype 1 patients.[67] Both studies revealed that the specific genotype sub-type (1a vs. 1b) and the presence of certain genetic substitutions did not affect SVR12 outcomes in DAA-naive genotype 1 patients.

In the phase III EXPEDITION-8 study, a cohort of 343 treatment-naïve patients with various HCV genotypes (95 genotype 1a, 136 genotype 1b, 26 genotype 2, 63 genotype 3, 13 genotype 4, 1 genotype 5, and 9 genotype 6) and compensated cirrhosis underwent an 8-week treatment regimen with GLE/PIB. The study yielded a global SVR12 rate of 98%. The SVR12 rates by genotype were 98% for genotype 1, 100% for genotype 2, 95% for genotype 3 (with 1 relapse), and 100% for genotypes 4, 5, and 6.[68] In a retrospective real-world study, 494 treatment-naïve patients with compensated cirrhosis were included. Among them, 74%, 12%, 12%, and 1% were infected with genotypes 1, 2, 3, and 4–6, respectively. These patients were treated with 8 weeks of GLE/PIB, and the overall SVR12 rate was 96%, with a specific rate of 96% (264/276) for genotype 1.[69] The CREST study was another real-world, multi-center study that included 325 treatment-naïve, compensated cirrhosis patients with genotypes 1–6, which were treated with GLE/PIB for 8 weeks. Overall, SVR12 was achieved in 99% in those completing 8 weeks treatment and available follow-up data, including 99.5% (182/183) in genotype 1 patients.[70]

### *Sofosbuvir/velpatasvir*

Sofosbuvir/velpatasvir is usually given in a 12-week fixed-dose combination of SOF (400 mg) and VEL (100 mg) for treating genotype 1 infection. In the ASTRAL-1 study, a diverse cohort of patients infected with HCV genotypes 1–6 and exhibiting various stages of liver disease up to compensated cirrhosis were included, except those infected with genotype 3. The trial utilized a double-blinded and placebo-controlled design and enrolled participants from 81 sites spanning North America, Europe, and Hong Kong. Among the 624 patients who received at least one dose of the drug (with 116 patients receiving a placebo), 121

**Table 9: Treatment of naïve hepatitis C with compensated cirrhosis**

| | Glecaprevir 300 mg/ Pibentasvir 120 mg | Sofosbuvir 400 mg/ Velpatasvir 100 mg | Sofosbuvir 400 mg and Daclatasvir 60 mg |
|---|---|---|---|
| Genotype 1 | 8 w | 12 w | 12 w with RBV or 24 w without RBV |
| Genotype 2 | 8 w | 12 w | 12 w with RBV or 24 w without RBV |
| Genotype 3 | 8 w | 12 w with RBV | 12-24 w with RBV |
| Genotype 4 | 8 w | 12 w | 12 w with RBV or 24 w without RBV |
| Genotype 5-6 | 8 w | 12 w | — |



had compensated cirrhosis, and 201 had prior treatment experience.[71] Patients with HCV genotype 1 infection underwent a 12-week treatment regimen with the fixed-dose combination of SOF/VEL. The study demonstrated an SVR12 rate of 98% (206/210 patients) in individuals infected with genotype 1a, with one reported relapse. Similarly, patients infected with genotype 1b exhibited an SVR12 rate of 99% (117/118) with one relapse observed. The presence of specific genetic variations (NS5A RASs) did not affect SVR12 rates for genotype 1.[72] In the POLARIS-2 study, 99% of patients with genotype 1a and 97% of patients with genotype 1b achieved SVR12 after 12 weeks of treatment with SOF/VEL, with only one relapse observed for each sub-type.[47]

The high SVR12 rates achieved with 12 weeks of the SOF/VEL regimen without RBV have been confirmed in a large number of real-world analyses. One study included 5,552 patients from 12 cohorts. These cohorts comprised 13.3% treatment-experienced patients, 20.7% compensated cirrhotic patients, 30.2% genotype 1 patients, 29.5% genotype 2 patients, 32.9% genotype 3 patients, 4.7% genotype 4 patients, and 3.7% patients with HIV co-infection. Among genotype 1 patients, SVR12/24 was 99.1% (1,599/1,613) in the overall cohort and 98.3% (349/355) in compensated cirrhosis. The rates according to the sub-type of patients with HCV genotype 1 were as follows: 98.7% (466/472) for genotype 1a, 98.8% (325/329) for genotype 1b, 100% (2/2) for genotype 1 with a mixed sub-type, and 99.5% (806/810) for genotype 1 with an unknown sub-type.[73] In a retrospective-prospective, observational, multi-center real-world analysis that focused on treating adults using SOF/VEL with or without RBV for a 12-week duration, the results demonstrated high effectiveness and good tolerance of SOF/VEL among patients, irrespective of viral genotype, liver disease severity, and co-morbidities. A total of 3,480 patients were included, with 87% harboring genotypes 1 and 2. The overall SVR12 rate was 99.4%, including 99.5% for genotype 1 and 99.4% for genotype 2. Furthermore, patients with compensated cirrhosis, decompensated cirrhosis, and chronic kidney disease stages 4–5 achieved SVR12 rates of 99.5%, 100%, and 100%, respectively.[74] In a comprehensive analysis of data from 1,209 HCV-infected patients across 20 cohorts in seven countries, the real-world effectiveness of 12 weeks therapy with SOF/VEL in individuals with mental health disorders was assessed. Among the 1,067 patients assessed, 45% had genotype 1, 17% had genotype 3, 30% had genotype 3, 6% had genotypes 4–6, and 2% had mixed or unknown genotypes, with 19% having cirrhosis. Overall, SVR12 was achieved in 97.4%, and the rates were greater than or equal to 95% when stratified by the type of mental health disorder and other complicating baseline characteristics, such as active injection drug use and antipsychotic drug use. The study provides evidence supporting the effectiveness of the SOF/VEL regimen in treating HCV in individuals with mental health disorders, highlighting high effectiveness and good adherence levels. The simplicity of the treatment algorithm and reduced drug interactions with central nervous system drugs make it a reliable option for this specific population.[75]

### *Daclatasvir and sofosbuvir*

The combination of DCV, an NS5A inhibitor, with SOF, an NS5B inhibitor, is effective against genotype 1 infection. In the randomized, open-label ALLY-2 study, a 12-week treatment with a combination of DCV and SOF achieved 96% SVR12 in DAA-naive HIV co-infected individuals with genotype 1a (n = 104) and 100% SVR12 in those with genotype 1b (n = 23).[76]

In an open-label study, 44 naive patients with HCV genotype 1 infection were assigned to receive DCV plus SOF, with or without RBV, for a duration of 24 weeks. The study was subsequently expanded to include an additional 123 patients with genotype 1 infection who were randomly assigned to receive DCV plus SOF, with or without RBV, for either 12 weeks (82 treatment-naive patients) or 24 weeks (41 patients who failed prior therapy with a protease inhibitor, PegIFN, and RBV). Among patients with genotype 1 infection, 98% of the 126 naive patients and 98% of the 41 experienced patients had an SVR12. High rates of SVR12 were observed among patients with HCV sub-types 1a and 1b (98% and 100%, respectively).[77] Similarly, in an open-label study with HIV and HCV co-infected patients, 12 weeks of DCV plus SOF resulted in SVR rates of 96.4% and 97.7%

for treatment-naïve (n = 83) and treatment-experienced patients (n = 44), respectively. Additionally, DCV plus SOF for 24 weeks, with or without RBV, has shown effectiveness for patients who failed prior therapy with a protease inhibitor, PegIFN, and RBV, achieving a success rate of 98% in 42 individuals.[78]

In a real-life study evaluating the effectiveness of DCV plus SOF in treating HCV genotype 1, 768 participants were treated for a duration of 12 weeks or 24 weeks. Using data from a French cohort of HCV-infected patients, the combination showed a high SVR12 rate of 95%. The SVR12 rates did not significantly differ between the 24-week [550/574 (96%)] and 12-week [179/194 (92%); $P = 0.068$] durations or between regimens with [165/169 (98%)] or without RBV [564/599 (94%); $P = 0.085$]. The SVR12 rate was greater than 97% in non-cirrhotic patients irrespective of the treatment duration or the addition of RBV. Among cirrhotic patients, the SVR12 rate was higher with the 24-week regimen compared to the 12-week regimen [423/444 (95%) vs. 105/119 (88%); $P = 0.005$]. The optimal treatment duration was 12 weeks for non-cirrhotic patients and 24 weeks for cirrhotic patients. The impact of RBV in this study was inconclusive due to a low number of patients receiving it.[79] In a randomized, open-label study to assess the effectiveness and safety of SOF combined with either DCV or simeprevir (SMV) in patients infected with genotype 1, who were previously unresponsive to PegIFN and RBV or were treatment-naive, 97% (121/127) of the enrolled patients achieved SVR12, with a higher rate in the DCV plus SOF group (100%) compared to SOF plus SMV (93%).[80]

## Genotype 2

Highly potent DAA combination regimens are recommended for patients with genotype 2 infection due to their high efficacy and excellent minimal side effect profile.

## Recommended regimens

### *Glecaprevir/pibrentasvir*

In the context of the VOYAGE-1 phase III study, a cohort of 362 non-cirrhotic Asian patients infected with various HCV genotypes (genotype 1a: 5%; genotype 1b: 45%; genotype 2: 38%; genotype 3a: 4%; genotype 3b: 3%; genotype 6: 5%) underwent treatment with the fixed-dose combination of GLE/PIB for a duration of 8 weeks. The study demonstrated a global SVR12 rate of 97%. Among patients infected with genotype 2, the SVR12 was 98% (136/139).[60] In the phase II SURVEYOR-2 study, conducted in patients without cirrhosis, the SVR12 rate after 8 weeks of GLE/PIB treatment was 98% in both treatment-naïve and treatment-experienced patients with genotype 2 infection. The presence of specific genetic variations at baseline had minimal impact on the success rates.[48] The CERTAIN-2 study confirmed the high effectiveness with an SVR12 of 98% after an 8-week simplified regimen using GLE/PIB in patients without cirrhosis.[81] In EXPEDITION-1, 99% of patients with various genotypes (1, 2, 4, 5, or 6) and compensated cirrhosis achieved SVR12 after 12 weeks of GLE/PIB. Only one relapse was observed in a genotype 1a patient. The SVR12 rate for genotype 2 patients was 100%.[66] In the phase III EXPEDITION-8 study, patients with various HCV genotypes and compensated cirrhosis underwent an 8-week treatment regimen with GLE/PIB. The study resulted in a global SVR rate of 98%. For genotype 2, the SVR12 rate was 100%.[68]

In a retrospective real-world study, 494 treatment-naïve patients with compensated cirrhosis were included. Among them, 74%, 12%, 12%, and 1% were infected with genotypes 1, 2, 3, and 4–6, respectively. These patients were treated with 8 weeks of GLE/PIB, and the overall SVR12 rate was 96%, with a specific rate of 98% (43/44) for genotype 2.[69] In the CREST study that included treatment-naïve, compensated cirrhosis patients, GLE/PIB for 8 weeks achieved SVR12 in 100% (19/19) in genotype 2 patients, analyzed on a per-protocol basis.[70]

### *Sofosbuvir/velpatasvir*

Sofosbuvir/velpatasvir is usually given in a 12-week fixed-dose combination of SOF (400 mg) and VEL (100 mg) for treating HCV genotype 2 infection. In the ASTRAL-1 study, a diverse cohort of patients infected with genotypes 1–6 and exhibiting various stages of liver disease up to compensated cirrhosis were included, except those infected with genotype 3. Among the 624 patients who received at least one dose of the drug (with 116 patients receiving a placebo), 121 had compensated cirrhosis, and 201 had prior treatment experience. Patients with HCV genotype 2 infection underwent a 12-week treatment regimen with the fixed-dose combination of SOF/VEL. The study demonstrated an SVR12 rate of 100% (104/104 patients) in cirrhotic (30%) and non-cirrhotic individuals infected with genotype 2.[71] In the phase III ASTRAL-2 study, 134 patients with genotype 2 HCV were treated with SOF/VEL. Among these patients, 14% had compensated cirrhosis, and they included both treatment-experienced and treatment-naive individuals. The results showed that those who received SOF/VEL for 12 weeks achieved a 99% SVR12 rate.[82] In the POLARIS-2 study, 100% of patients with genotype 2 achieved SVR12 after 12 weeks of treatment with SOF/VEL.[47]

Based on the largest real-world analysis of patients treated with SOF/VEL, in a study that included 5,552 patients from 12 cohorts, comprising 13% treatment-experienced patients, 21% compensated cirrhotic patients, 29% genotype 2 patients, and 4% patients with HIV coinfection, the SVR12 rate for patients with HCV genotype 2 was 99.3%.[73] In another retrospective-prospective, observational, multi-center real-world analysis, SOF/VEL with or without RBV administered for a 12-week duration demonstrated high effectiveness and good tolerance of SOF/VEL among patients, irrespective of viral genotype, liver disease severity, and co-morbidities. A total of 3,480 patients were included, with 86.8% having genotypes 1 and 2. The overall SVR12 rate was 99.4%, including 99.4% for genotype 2.[74]

### *Daclatasvir and sofosbuvir*

For individuals infected with genotype 2, a combination of DCV and SOF is a viable treatment option wherein prior studies, such as ALLY-2, have shown promising results.[76] In a group of 12 genotype 2 patients treated with DCV plus SOF for 12 weeks, a 100% SVR12 rate was achieved. Another study involving 26 patients treated with DCV plus SOF, with or without RBV, showed a 92% SVR12 rate after 24 weeks of treatment.[77] In a prospective, open-label observational study focusing on a subset of treatment-naïve or -experienced HCV genotype 2 patients with contraindications to RBV, including advanced fibrosis, compensated cirrhosis, and early decompensated cirrhosis (CTP B), with co-morbidities were enrolled. Nineteen patients were randomly assigned to receive either 12 or 24 weeks of the DCV plus SOF combination. Regardless of the treatment duration, all participants achieved SVR12. The findings of this study support the use of DCV plus SOF in genotype 2 patients without cirrhosis for 12 weeks or for 24 weeks in cirrhotic individuals unable to tolerate RBV, including those with decompensated disease.[83]

Real-life data from the French ANRS CO22 HEPATHER genotype 2 cohort including 45 patients demonstrated SVR12 rates of 88% and 91% after 12 and 24 weeks of treatment with DCV plus SOF, with or without RBV, respectively.[84] In a US Veteran Affairs facility, the combination of DCV plus SOF was studied in a large real-life cohort of HCV genotype 2-infected (n = 2,939) individuals. In a population that has historically been linked to sub-optimal treatment outcomes, the SVR12 rates in genotype 2 patients did not differ between DCV plus SOF (95%) and SOF/VEL (94%) or between DCV plus SOF and RBV (88%) and SOF/VEL plus RBV (90%). Importantly, patients between different cohorts were not well matched as patients in the RBV containing arms had higher rates of cirrhosis, decompensated disease, prior HCV treatment, lower platelets, and higher FIB-4 scores.[85] In a real-world study on 32 patients with HCV genotype 2 from Taiwan, DCV plus SOF combination was administered for 12 weeks. Among them, 50% had cirrhosis, including six with decompensation. Fourteen patients were treated with DCV plus SOF, while 18 received DCV plus SOF and RBV. All 31 patients (100%) who completed follow-up achieved SVR12.[86]

## Genotype 3

Highly potent DAA combination regimens are recommended for patients with genotype 3 infection due to their high efficacy and excellent minimal side effect profile.

## Recommended regimens

### *Sofosbuvir/velpatasvir*

The treatment of HCV-infected genotype 3 patients was assessed with the fixed-dose combination of SOF/VEL in the ASTRAL-3 study, and the results showed that 12 weeks of SOF/VEL treatment was superior to 24 weeks of SOF plus RBV treatment.[26] In this study, 552 patients (74% treatment-naïve, 26% treatment-experienced, 29% with compensated cirrhosis) were enrolled and the SVR12 rate was 98% (160/163) in treatment-naïve non-cirrhotic patients compared to 90% (141/156) with SOF plus RBV. Overall, 90% (104/116) patients who were treatment-experienced or had cirrhosis achieved SVR12 with the SOF/VEL regimen, including 93% (40/43) in treatment-naïve patients with compensated cirrhosis, 91% (31/34) in treatment-experienced patients without cirrhosis, and 89% (33/37) in treatment-experienced patients with compensated cirrhosis. Additionally, in the POLARIS-2 study which focused on genotype 3-infected, non-cirrhotic patients who were either treatment-naive or had prior treatment with IFN, 12 weeks of SOF/VEL demonstrated a high SVR12 rate of 97% (86/89). Importantly, there were no virologic failures.[47] In the phase III POLARIS-3 study, treatment-naïve and IFN-experienced patients with cirrhosis were treated with SOF/VEL/VOX for 8 weeks or with SOF/VEL for 12 weeks as the control arm. The study enrolled patients who had not previously received treatment with DAAs. Overall, both groups achieved an SVR12 of 96%, including in SOF/VEL for 12 weeks (105/109). There were no virologic failures; only four patients in the SOF/VEL arm had the NS5A RASs (Y93H), and all achieved SVR.[47]

The high SVR rates achieved with 12 weeks of the SOF/VEL regimen without RBV have been confirmed

in a large number of real-world studies, including an integrated analysis spanning seven countries across Europe, USA, and Canada. Among genotype 3 patients, SVR12/24 was 98.3% (1,649/1,677) in the overall cohort and 96.9% (314/324) in compensated cirrhosis.[73,87] However, one study from Asia (China, Thailand, Vietnam, Singapore, and Malaysia) focusing on genotype 3b patients revealed an SVR12 rate of 86% among 84 patients, regardless of the presence of underlying cirrhosis.[88] For genotype 3a patients, 95% achieved SVR12. Among non-cirrhotic patients with genotype 3b, 89% achieved SVR12, despite the presence of certain genetic variations (NS5A RASs at A30K or L31M, or both). In another study involving 90 treatment-naive, non-cirrhotic patients, 8 weeks of SOF/VEL treatment showed an SVR12 rate of 96%.[89]

Nonetheless, for cirrhotic patients with genotype 3 infection, RBV remains an essential component of treatment. In a randomized controlled trial conducted across 29 sites in Spain, 204 genotype 3-infected patients with compensated cirrhosis were assigned to receive SOF/VEL for 12 weeks or SOF/VEL plus RBV for 12 weeks. Patients who did not receive RBV achieved SVR12 in 91% versus 96% in those who received RBV, with virologic failure rates of 6% and 2%, respectively. The presence of specific genetic variations (NS5A RASs) at baseline influenced the treatment response. In the SOF/VEL without RBV arm, SVR12 was higher in patients without NS5A RASs compared to those with baseline NS5A RASs (96% vs. 84%, respectively). In the SOF/VEL plus RBV arm, baseline NS5A RASs had less effect on the proportion of patients achieving SVR12 (99% vs. 96%, respectively). Similarly, data from a real-world cohort study based on the English HCV Treatment Registry showed higher SVR12 rates with SOF/VEL plus RBV, compared to those without RBV in genotype 3 patients with compensated cirrhosis [98.0% (192/196) vs. 92% (200/218)]. Crucially, the addition of RBV did not make a significant difference in patients with no, mild, or moderate fibrosis (F0–F3).[90] A meta-analysis of seven studies including 1,088 genotype 3-infected patients with compensated cirrhosis revealed a marginally higher SVR12 rate of 97.2% with SOF/VEL plus RBV compared to 93.8% with SOF/VEL without RBV. However, the inclusion of two unpublished abstracts limited the scope of inference from this analysis.[91] In summary, these findings highlight the importance of RBV and genetic factors in the successful management of genotype 3-infected patients with cirrhosis.[92]

In a study conducted across multiple centers in Germany, 293 patients with genotype 3 infection were examined, with 25% having cirrhosis and 4% having prior experience with DAAs. These patients were treated with a 12-week regimen of SOF/VEL, either with or without RBV. There was only one case of virologic failure observed in a patient with DAA treatment experience.[93] Among the five cirrhotic patients with genotype 3 and specific genetic variations (RASs), all were given RBV alongside SOF/VEL and successfully achieved SVR12. It is crucial to consider the specific sub-type and genetic variations (RASs) when determining SVR12 rates in cirrhotic genotype 3-infected patients who are being treated with SOF/VEL. If NS5A resistance testing or RBV is not available, alternative therapies could be considered for genotype 3 patients.

### *Glecaprevir/pibrentasvir*

The ENDURANCE-3 study compared the effectiveness of the fixed-dose combination of GLE/PIB versus DCV plus SOF for 12 weeks in 348 treatment-naïve, non-cirrhotic patients with genotype 3 infection. Later, the study was modified to include an open-label group receiving GLE/PIB for 8 weeks among 157 new patients. Those on GLE/PIB for either 8 or 12 weeks had an SVR12 rate of 95% as per the intention-to-treat analysis (222/233 participants on the 12-week regimen; 149/157 on the 8-week regimen).[94] In the SURVEYOR-2 study, a partially randomized, open-label, multi-center, 4-part, phase III study, the SVR12 rates were 91% (20/22) and 95% (21/22) in treatment-experienced patients with genotype 3 without cirrhosis treated for 12 or 16 weeks, respectively. A pooled analysis of phase II and III clinical trials in 693 genotype 3-infected patients showed SVR12 rates of 95% in both non-cirrhotic treatment-naïve patients receiving 8 weeks (198/208) and 12 weeks (280/294) of GLE/PIB. Treatment-naïve patients with cirrhosis had a 97% (67/69) SVR12 rate with 12 weeks of GLE/PIB. Treatment-experienced, non-cirrhotic patients had SVR12 rates of 90% (44/49) and 95% (21/22) with 12 and 16 weeks of GLE/PIB, respectively. Additionally, 94% (48/51) of treatment-experienced patients with cirrhosis treated for 16 weeks achieved SVR12.[95] In part 2 of the SURVEYOR-2 study, 12 weeks of GLE/PIB was compared to GLE/PIB plus RBV among 55 treatment-naive, genotype 3-infected participants with compensated cirrhosis. SVR12 was achieved in 96% (27/28) of patients in the RBV-free arm and in 100% (27/27) in the RBV-containing arm.[96] In part 3 of the SURVEYOR-2 study, treatment-naive or treatment-experienced (PegIFN and/or SOF with RBV) patients with compensated cirrhosis were treated

with GLE/PIB for 12 or 16 weeks, respectively, and SVR12 was achieved by 98% (39/40) of treatment-naïve and 96% (45/47) of treatment-experienced patients, respectively.[97] The EXPEDITION-8 study was a phase IIIb study that evaluated 8 weeks treatment duration of GLE/PIB in genotypes 1–6, treatment-naïve patients with compensated cirrhosis, including 63 with genotype 3. On per protocol analysis among the participants with genotype 3, 98% (60/61) achieved SVR12, with a single participant experiencing virologic failure (relapse).[68]

In two studies conducted in Asia, the VOYAGE-1 was a phase III study that included non-cirrhotic treatment-naive and -experienced patients with genotypes 1–6 (n = 363), who were treated with GLE/PIB for 8 weeks, and the second was VOYAGE-2 that included patients with compensated cirrhosis (n = 160) who were treated with GLE/PIB for 12 weeks (and for 16 weeks in treatment-experienced patients with genotype 3, irrespective of the presence of cirrhosis). Overall, SVR12 was 97% (352/363) after 8 weeks treatment with GLE/PIB in patients without cirrhosis, including 77% (20/26) in genotype 3. In patients with cirrhosis treated for 12 weeks, overall SVR12 was 99% (159/160), including 93% (13/14) with genotype 3.[60] This reduced SVR12 rate was mostly related to six patients with genotype 3b. Consequently, while both studies demonstrated high SVR12 rates for HCV genotypes 1–6, a numerically lower SVR12 rate of 58% (7/12) was observed in the limited number of patients with HCV genotype 3b infection without cirrhosis, compared to 93% (13/14) in patients with genotype 3a infection without cirrhosis.

Real-world data also support the efficacy of the 8-week GLE/PIB regimen for treatment-naive, non-cirrhotic patients with genotype 3 infection.[87,98] In a German study, 99% (162/164) of patients, and in an Italian study, 96% (46/48) of patients achieved SVR12 with this 8-week treatment regimen.[64,65] Similar results were reported from a registry-based study in Asia including treatment-naïve cirrhotic patients, with an SVR12 rate of 98% (169/172) in the mITT population.[99] Real-world studies have reported consistent results of high efficacy of GLE/PIB in treatment of chronic HCV. In a large meta-analysis that included 18 real-world cohorts including 12,531 individuals treated with GLE/PIB for 8 or 12 weeks, the overall SVR12 rates were 96.7% in the ITT population (n = 8,583) and 98.1% in the mITT population (n = 7,001), and for genotype 3 (n = 1,162 from 6 cohorts) they were 95% in ITT population and 97% in mITT population. In treatment-naïve genotype 3 patients without cirrhosis (n = 320) who received GLE/PIB for 8 weeks, the SVR12 rate was 99%.[100] In another real-world study that included genotype 3 treatment-naïve, compensated cirrhosis patients, the SVR12 rate was 96% (43/45).[69] In the CREST study that included treatment-naïve, compensated cirrhosis patients, GLE/PIB for 8 weeks achieved SVR12 in 97.5% (78/80) in genotype 3 patients, analyzed on a per-protocol basis.[70]

### *Daclatasvir and sofosbuvir*

A combination of DCV and SOF for 12 weeks in the ALLY-2 study in DAA-naive HIV-co-infected genotype 3-infected patients (n = 9) achieved 100% SVR.[76] In another randomized open-label study in 26 patients with genotype 3 treated for 24 weeks with or without additional RBV, the SVR12 was 92%.[77] In patients with genotype 3, a combination of DCV and SOF for 12 weeks had previously demonstrated high efficacy (96%) in patients without advanced liver disease.[25] An advanced degree of fibrosis significantly decreases the effectiveness of this regimen, which advocates for the addition of RBV in cirrhotics.[101] In the phase III ALLY-3+ open-label study, involving a cohort of 50 genotype 3 treatment-naïve (n = 13) or -experienced (n = 37) patients, the combination of DCV and SOF for 12 or 16 weeks alongside RBV was assessed. Patients had either advanced fibrosis (n = 14) or compensated cirrhosis (n = 36). Among those with cirrhosis, the overall SVR12 rate was 86% (31/36). In the 12-week treatment group, this rate was 83% (15/18). In the 16-week group, the SVR12 rate was 89% (16/18).[102] In the ALLY-3C phase III study, genotype 3 patients (n = 78) with compensated cirrhosis received DCV, SOF, and RBV for 24 weeks with an overall SVR12 rate of 87%. The SVR12 rates were 93% for treatment-naive patients and 79% for treatment-experienced patients.[103]

In a real-world experience from Pakistan, SOF plus DCV with or without RBV was administered for 12–24 weeks in treatment-naïve or -experienced (PegIFN plus RBV, with or without SOF) in genotype 3 patients, with or without cirrhosis. Overall, SVR12 was achieved in 98% (229/246) of patients.[104] In another large real-life cohort from a US Veteran Affairs facility, the combination of DCV plus SOF was studied in a large real-life cohort of HCV genotype 2- (n = 2,939) and genotype 3- (n = 2,824) infected individuals.[85] The SVR12 rates in genotype 3 patients did not differ between DCV plus SOF (91%) and SOF/VEL (92%) or between DCV plus SOF and RBV (88%) and SOF/VEL plus RBV (86%). Importantly, patients between different cohorts were not well matched, as patients in the RBV containing arms had higher rates of cirrhosis,

decompensated disease, prior HCV treatment, lower platelets, and higher FIB-4 scores. Another study evaluated the efficacy DCV plus SOF with a flat dose of 800 mg RBV compared to DCV plus SOF without RBV or DCV plus SOF with weight-based RBV in HCV genotype 3-infected individuals with compensated or decompensated cirrhosis. Treatment was administered for 24 weeks, with overall SVR12 of 94% (220/233). The SVR12 rate was lower in the DCV plus SOF group compared to the combination with flat-dose RBV and the weight-based RBV group (87% vs 98% and 97%, respectively).[105] Similar results were obtained in another real-life study of genotype 3-infected cirrhotic patients (8.5% with decompensated disease) where the addition of RBV to this regimen increased SVR12 rates to 100% (vs. 94% without RBV) after 24 weeks of therapy.[106]

## Genotype 4

Highly potent DAA combination regimens are recommended for patients with genotype 4 infection due to their high efficacy and excellent minimal side effect profile.

### Recommended regimens

#### *Glecaprevir/pibrentasvir*

In part 4 of the SURVEYOR-II study, the effectiveness of a shorter 8-week course of GLE/PIB treatment was investigated and included 46 patients with genotype 4, who were either treatment-naïve or -experienced, without cirrhosis. The SVR12 rate was 93% (43/46) with no virologic failures.[48] In the ENDURANCE-4 study as well, treatment-naïve and -experienced, non-cirrhotic genotype 4 patients received 12 weeks of GLE/PIB.[107] The majority had mild fibrosis (F0-1) and were treatment-naive. Out of these, 99% (75/76; no virological failures) achieved SVR12. There was no direct comparison between the 8-week and 12-week GLE/PIB treatment regimens in this study.[107]

In the EXPEDITION-1 study, patients with compensated cirrhosis, both treatment-naive and -experienced, were given GLE/PIB for 12 weeks. Among the 146 patients with various genotypes (1, 2, 4, 5, or 6), 99% (145/146) achieved SVR12, including 100% success rate (16/16) for those with genotype 4.[66] In the phase III EXPEDITION-8 study, 343 treatment-naïve patients (13 with genotype 4) with compensated cirrhosis were treated with 8 weeks of GLE/PIB. The global SVR rate was 98% (335/343) and 100% (13/13) for genotype 4.[68] A meta-analysis of real-world studies also demonstrated a high SVR12 rate of 98.3% (n = 55) for non-cirrhotic individuals with genotype 4 infection after 8 weeks of GLE/PIB treatment.[100] These findings led to the approval of an 8-week GLE/PIB regimen for DAA-naive, non-cirrhotic patients with genotype 4. However, data are more limited for cirrhotic individuals with genotype 4 treated with GLE/PIB for 8 weeks. One real-world study with a small number of treatment-naïve, cirrhotic genotype 4 patients revealed 100% (5/5) SVR12.[108] In the CREST study that included treatment-naïve patients with compensated cirrhosis, treatment with GLE/PIB for 8 weeks achieved SVR12 in 100% (14/14) of genotype 4 patients, analyzed on a per-protocol basis.[70]

#### *Sofosbuvir/velpatasvir*

In the ASTRAL-1 study, a 12-week treatment regimen of SOF/VEL was examined in genotype 4-infected patients, irrespective of the presence or absence of cirrhosis (23% with cirrhosis, 55% treatment-naïve, 45% treatment-experienced). Among 116 of the genotype 4 treatment-naive or -experienced patients, with or without compensated cirrhosis, all achieved SVR12 (100%).[71] In the SHARED-3 study, the effectiveness of a 12-week SOF/VEL regimen was examined in Rwanda in 61 genotype 4 patients, including sub-types 4k, 4r, 4v, 4q, 4l, 4b, and 4c, which frequently have resistance-associated substitutions that can increase rates of treatment failure. After 12 weeks of therapy with SOF/VEL, SVR12 was 97% (59/61).[109]

In the POLARIS-2 phase III study, DAA-naive patients were randomly assigned to either 8 weeks of SOF/VEL/VOX or 12 weeks of SOF/VEL. Among the 57 patients with genotype 4 in the SOF/VEL group, 98% achieved SVR12, with only one patient experiencing relapse.[47] Additionally, a real-world analysis pooled from 12 cohorts studied adults treated with 12 weeks of SOF/VEL. The results showed an SVR12 rate of 99.6% (238/239) in participants with genotype 4, regardless of whether they had compensated cirrhosis.[73]

#### *Daclatasvir and sofosbuvir*

In the ALLY-2 study, a small group of HCV genotype 4 patients co-infected with HIV (3 out of 203), who had not been treated before, achieved an SVR12 rate of 100% after 12 weeks of treatment with DCV plus SOF. In the ALLY-1 study, all four patients with genotype 4 and advanced cirrhosis achieved SVR12 (100%) after 12 weeks of treatment with SOF, DCV, and RBV.[110] In the European Multicenter Compassionate Use Program, 482 adults with chronic HCV infection at high risk for hepatic complications

received open-label DCV plus SOF for 24 weeks with the option of adding RBV. Genotype 4 patients achieved a SVR12 rate of 100% (19/19).[111]

In a real-world cohort from Saudi Arabia, 40 individuals with HCV genotype 4, including IFN-experienced (n = 21) and those with cirrhosis (n = 14), were treated with DCV plus SOF for 12 weeks. All patients achieved SVR12 (100%).[112] In the French temporary authorization for use (ATU) program, DCV-based regimens were given to patients with advanced liver disease, extra-hepatic manifestations, or post-transplant recurrence or those awaiting liver or kidney transplantation. Among genotype 4 patients (n = 215), 91% achieved SVR12. Prolonged treatment improved outcomes, with a 97% SVR12 rate in patients treated with DCV plus SOF and RBV for 24 weeks and an 88% rate for those treated for 12 weeks. Overall, 93% of patients treated with DCV plus SOF for 24 weeks and 84% of those treated for 12 weeks achieved SVR12.[113] In a large real-world cohort of genotype 4-infected individuals (n = 1,933) from a single center in Egypt, the overall SVR12 rate was 96%, with rates of 92% (346/375) in DCV plus SOF and 98% (466/477) in DCV plus SOF in combination with RBV. The presence of cirrhosis negatively impacted treatment outcomes.[114]

## Genotypes 5–6

Highly potent DAA combination regimens are recommended for patients with genotype 5–6 infection due to their high efficacy and excellent minimal side effect profile.

## Recommended regimens

### *Glecaprevir/pibrentasvir*

The phase II SURVEYOR-2 study demonstrated 100% SVR12 in 34 non-cirrhotic patients with genotype 4, 5, or 6 treated with GLE/PIB for 12 weeks.[48] Building on this success, the ENDURANCE-4 trial enrolled 121 DAA-naive or -experienced genotype 4, 5, or 6 patients without cirrhosis, for the same 12-week treatment.[107] Most enrolled patients had mild fibrosis (F0-1), and a majority were new to treatment. The overall SVR12 rate was 99%, reaching 100% for genotype 5 (26/26) and genotype 6 (19/19) patients.

A separate analysis in part 4 of the SURVEYOR-2 study investigated an 8-week course of GLE/PIB in DAA-naive, non-cirrhotic patients. In this study segment, 100% SVR12 was achieved for genotype 5 (2/2) and 90% for genotype 6 (9/10) with no virologic failures.[107] The ENDURANCE-5,6 study assessed the efficacy of GLE/PIB in DAA-naive patients with genotype 5 (n = 23) or 6 (n = 61) infection. Non-cirrhotic participants received an 8-week regimen, while those with cirrhosis (11% of patients) were treated for 12 weeks. The overall SVR12 rate was 98%, with only two virologic failures observed.[115]

EXPEDITION-1 studied GLE/PIB in DAA-naive (75%) or -experienced patients with compensated cirrhosis. Out of 146 patients with various genotypes, 99% achieved SVR12, including 100% for genotype 5 (2/2) and genotype 6 (7/7).[66] In two studies conducted in Asia, the VOYAGE-1 included non-cirrhotic treatment-naive and -experienced patients with genotypes 1–6 (n = 363), who were treated with GLE/PIB for 8 weeks, and the VOYAGE-2 included patients with compensated cirrhosis (n = 160) who were treated with GLE/PIB for 12 weeks. Overall, SVR12 was 97% (352/363) after 8 weeks treatment with GLE/PIB in patients without cirrhosis, including 100% (16/16) in genotype 6. In patients with cirrhosis treated for 12 weeks, overall SVR12 was 99% (159/160), including 100% (7/7) with genotype 6.[60]

EXPEDITION-8 evaluated 8 weeks of GLE/PIB in 280 treatment-naive patients with compensated cirrhosis and various genotypes, resulting in an SVR12 rate of 99% with no virologic failures.[116] An integrated analysis of patients with genotype 5 or 6 from various studies, including those mentioned above, showed similar response rates between 8 and 12 weeks of treatment, with no significant differences observed among cirrhotic patients treated for 8 weeks.[117]

In a real-world cohort from Asia, 125 patients with HCV genotype 6 were evaluated with an 8-week treatment regimen of GLE/PIB. Patients were mostly treatment-naïve (98%), and 79 (63%) had cirrhosis. After 8 weeks of treatment with GLE/PIB, SVR12 was achieved in 100% (125/125) of the patients.[118]

### *Sofosbuvir/velpatasvir*

The ASTRAL-1 study investigated the 12-week SOF/VEL treatment for patients with genotype 5 and 6 infections, both with and without cirrhosis. In the study, 24 genotype 5 treatment-naive participants with or without cirrhosis achieved SVR12 in 96% of cases (23/24). Additionally, all 38 genotype 6 treatment-naive individuals with or without cirrhosis in the study achieved SVR12.[71] In the POLARIS-2 phase III study, nine genotype 6 patients received SOF/VEL and all achieved SVR.[47]

Real-world studies further supported the effectiveness of 12-week SOF/VEL treatment for predominantly treatment-naive patients with genotype 6 infection. In one study from Southwest China involving 23 patients without clinical cirrhosis, the SVR12 rate was 100%.[119] Similarly, in a cohort of mostly Vietnamese patients in the United States (n = 43), where 12% had cirrhosis, the SVR12 rate was also 100%.[120] In a real-world cohort from Asia, 161 patients with HCV genotype 6 were evaluated for a 12-week regimen of SOF/VEL. Patients were mostly treatment-naïve (98%) and 86 (53%) had cirrhosis, of whom 4 (2.5%) had decompensated cirrhosis. After 12 weeks of treatment, SVR12 was 99% (160/161).[118] Another real-life cohort of 3,480 HCV-infected individuals from a nationwide registry in Taiwan (treatment-naïve 94%, cirrhosis 17%) treated with 12 weeks of SOF/VEL revealed an SVR12 rate of 99.7% (334/335).[74] A pooled analysis of 12 real-world cohorts, including patients with genotype 5 or 6 infection, showed an overall SVR12 rate of 98.5% (67/68). Notably, all 13 patients with compensated cirrhosis achieved SVR in this analysis.[73]

### *Daclatasvir and sofosbuvir*

The Vietnam SEARCH study is a pilot study from Asia, where 41 patients with genotype 6 were treated with 12 weeks of DCV plus SOF (without RBV). Included patients were all cirrhotics and DAA-naïve. SVR12 was achieved in 100% (41/41).[121]

In a large real-life cohort from Cambodia of genotype 6-infected individuals (n = 1,292) treated with DCV plus SOF, including patients with and without cirrhosis, 96% achieved SVR12 after 12 weeks of therapy with DCV plus SOF (without RBV).[122] A separate analysis from the same study, restricted to patients with compensated cirrhosis (60%), showed an SVR12 rate of 98%. In a real-life study from Vietnam, 151 individuals with genotype 6 were treated with 12 weeks of DCV plus SOF (with or without RBV), revealing an SVR12 of 97%. Liver fibrosis did not influence outcome.[123] In another study from China, 37 treatment-naïve, non-cirrhotic genotype 6 patients were treated with 12 weeks of DCV plus SOF and all achieved SVR12 (37/37).[119] In a systematic review of genotype 6 studies, three studies including 172 individuals were treated with DCV plus SOF for 12 weeks. The overall SVR12 rates ranged between 88% and 94%, and failure was mostly in those with cirrhosis and prior treatment experience.[124] No studies utilizing the combination of DCV plus SOF for the treatment of HCV genotype 5 were identified.

Recommendations:

1. It is advised to utilize simplified pan-genotypic anti-HCV treatment regardless of the genotype to improve access to HCV treatment and increase global infection cure rates (Grade A1).
2. For HCV-infected patients without cirrhosis who are treatment-naïve, the following pan-genotypic DAA-based regimens are recommended:
   a. The fixed-dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) in a single tablet administered once daily for 12 weeks (Grade A1).
   b. The fixed-dose combination of glecaprevir (300 mg) and pibrentasvir (120 mg) in three tablets containing 100 mg of glecaprevir and 40 mg of pibrentasvir, administered once daily with food for 8 weeks (Grade A1).
   c. The fixed-dose combination of sofosbuvir (400 mg) and daclatasvir (60 mg) administered once daily for 12 weeks (Grade B1).
3. For HCV-infected patients with compensated cirrhosis [Child-Turcotte-Pugh (CTP) A] who are treatment-naïve, the following pan-genotypic DAA-based regimens are recommended:
   d. The fixed-dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) in a single tablet administered once daily for 12 weeks in genotypes 1, 2, 4, 5, and 6 (Grade A1).
   e. The fixed-dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) in a single tablet administered once daily for 12 weeks in genotype 3 without baseline NS5A RAS Y93H, and if this test is not available, then the treatment can be given with weight-based ribavirin for 12 weeks (Grade B1).
   f. The fixed-dose combination of glecaprevir (300 mg) and pibrentasvir (120 mg) in 3 tablets containing 100 mg of glecaprevir and 40 mg of pibrentasvir, administered once daily with food for 8 weeks (Grade A1).
   g. The fixed-dose combination of sofosbuvir (400 mg) and daclatasvir (60 mg) with weight-based ribavirin administered once daily for 12-24 weeks (Grade B1).
4. Generic drugs can be utilized in HCV treatment if strict quality controls are met and guaranteed by the provider. Healthcare providers can consider generic options to reduce the cost burden of treatment and improve access to therapy, ensuring that the quality of the generic drugs is adequately verified (Grade A1).

## TREATMENT OF HEPATITIS C-RELATED DECOMPENSATED CIRRHOSIS

In patients with chronic HCV, the development of jaundice, variceal bleeding, ascites, or encephalopathy indicates the presence of decompensated cirrhosis. Patients with decompensated cirrhosis should be referred to a medical practitioner with expertise in that condition, ideally in a liver transplantation center. Treatment goals for such patients vary depending on their eligibility for liver transplantation. Patients with detectable HCV RNA at the time of liver transplantation will likely transmit the virus to their new liver, which could significantly reduce the graft's lifespan. The primary short-term goal of anti-HCV therapy for patients with decompensated cirrhosis who are not candidates for liver transplantation is to achieve SVR, which may result in some degree of liver fibrosis reversal, leading to improved clinical outcomes and increased chances of survival. For HCV-positive patients who are candidates for liver transplantation, the goal of HCV therapy is to completely suppress HCV RNA before transplantation, to prevent reinfection of the new liver with HCV and to improve post-transplantation outcomes.

All oral DAAs have been shown to improve the liver function of patients with decompensated cirrhosis, and patients with lower Model for End-stage Liver Disease (MELD) scores had a higher chance to be delisted.[125] In a real-world study, the clinical outcomes of 868 patients with compensated and decompensated cirrhosis who underwent DAAs treatment were analyzed. The patients had a median age of 59 years and were divided into two groups: 719 (83%) with CTP A cirrhosis and 149 (17%) with CTP B/C cirrhosis. SVR was achieved in 90% of CTP A patients and 81% of CTP B/C patients. During the 28-month median follow-up, disease progression was observed in 14% of CTP A patients and 64% of CTP B/C patients. In CTP B/C cirrhosis, a ≥2-point MELD decline did not translate into improved clinical outcome. The study showed that SVR was significantly associated with improved event-free survival in CTP A patients but not in CTP B/C patients.[126] Currently, various DAA treatment strategies are available for patients pre- and post-liver transplantation. However, the clinical and economic implications of these strategies require extensive exploration. Pre-liver transplantation treatment is cost-effective for patients with MELD ≤20 without HCC, while treatments after liver transplantation are cost-effective in cirrhotic patients with MELD >20 and in those with HCC. Patients with decompensated (CTP B or C) cirrhosis awaiting liver transplantation with a MELD score >20 and the waiting list time exceeding 6 months should be treated before transplantation.[127]

With the increased efficacy of DAAs in those with decompensated liver disease, a retrospective study conducted in 559 HCV-infected patients with decompensated cirrhosis achieved an SVR of 88%, where the all-cause mortality was also reduced. It was suggested that DAA treatment should be considered for any patient with HCV-related decompensated cirrhosis.[128] De-listing of HCV patients for clinical improvement has increased but remains infrequent, and many continue to experience considerable morbidity with ascites and hepatic encephalopathy in 46.5% and 30.5%, respectively.[129]

Use of DAA regimens containing protease inhibitors in advanced HCV-related cirrhosis is still discouraged. A recent real-world study from the REAL-C registry in advanced liver cirrhosis has shown that protease inhibitor-based DAA regimens were not associated with significant worsening of outcomes.[130] Similar worsening of CTP and MELD scores in protease inhibitor and non-protease inhibitory-based regimens was seen at 12 and 24 weeks post therapy (23.9% vs. 13.1%, $P = 0.07$ and 16.5% vs. 14.6%, $P = 0.77$). Nonetheless, more data are needed for protease inhibitors in this category of patients. Thus, it remains that fixed dose combinations of SOF and VEL or DCV plus SOF, excluding protease inhibitors, are the treatment of choice in patients with decompensated cirrhosis [Table 10].

The phase III, multi-center, randomized, open-label ASTRAL-4 study included 267 patients with treatment-naive (45%) or -experienced (55%) decompensated cirrhosis (CTP B at screening) with genotype 1, 2, 3, 4, or 6. The study randomly assigned patients to receive 12 weeks of an SOF/VEL with or without weight-based RBV (1000 mg/day for weight <75 kg; 1200 mg/day for weight ≥75 kg) or 24 weeks of SOF/VEL. Stratification was based on HCV genotype. Ninety-five percent of patients had a baseline MELD score ≤15. The SVR12 rates were 83% in the 12-week SOF/VEL arm, 94% in the 12-week SOF/VEL plus RBV arm, and 86% in the 24-week SOF/VEL arm. Among patients, 22 experienced virologic failure, including 20 patients with relapse and two patients (genotype 3) with on-treatment virologic breakthrough. The study found that

**Table 10: Treatment of hepatitis C-related decompensated cirrhosis**

| | Sofosbuvir 400 mg/ Velpatasvir 100 mg | Sofosbuvir 400 mg and Daclatasvir 60 mg |
|---|---|---|
| Genotype 1 | 12 W with RBV, or 24 W without RBV* | 12 W with RBV, or 24 W without RBV* |
| Genotype 2 | 12 W with RBV, or 24 W without RBV* | 12 W with RBV, or 24 W without RBV* |
| Genotype 3 | 12 W with RBV, or 24 W without RBV* | 12 W with RBV, or 24 W without RBV* |
| Genotype 4 | 12 W with RBV, or 24 W without RBV* | 12 W with RBV, or 24 W without RBV* |
| Genotype 5 and 6 | 12 W with RBV, or 24 W without RBV* | 12 W with RBV, or 24 W without RBV* |

*Contraindications to the use of ribavirin or with poor tolerance to ribavirin on treatment

the presence of baseline NS5A-resistant substitutions was not associated with virologic relapse. Among 39 patients with CTP B cirrhosis and genotype 3, the SVR rates were 50% (7/14) for 12 weeks of SOF/VEL, 85% (11/13) for 12 weeks of SOF/VEL plus RBV, and 50% (6/12) for 24 weeks of SOF/VEL.[131] In a phase II clinical study characterized by a single-arm, open-label design, conducted in adult patients with HCV-associated decompensated cirrhosis in France and the USA, the primary objective was to augment existing knowledge regarding the safety and efficacy of the SOF/VEL plus RBV regimen over 12 weeks in this patient cohort. The treatment involved a fixed-dose combination of SOF 400 mg/VEL 100 mg alongside weight-based RBV administered once daily for 12 weeks. In the per-protocol population comprising 25 patients, all individuals attained SVR12. The combination of SOF/VEL plus RBV demonstrated substantial efficacy, as evidenced by high SVR12 rates, and exhibited a generally well-tolerated profile in patients with HCV-associated decompensated cirrhosis.[132]

Daclatasvir has been utilized in various oral regimens for patients suffering from decompensated cirrhosis. The phase III ALLY-1 study administered DCV plus SOF and a low initial dose of RBV (600 mg) for 12 weeks to treatment-naive and experienced patients, with a predominant HCV genotype 1 infection, and those with advanced cirrhosis (CTP B and C; n = 60) and recurrent HCV infection post-transplant (n = 53) in two specific populations. The study found that the SVR12 rate was 83% among those with advanced cirrhosis and 94% among those with recurrent HCV infection post-transplant. The SVR12 rate was 76% among patients with HCV genotype 1a and 100% among patients with HCV genotype 1b in the population with advanced cirrhosis. The SVR12 rate was 94% among patients with CTP B cirrhosis and 56% among patients with CTP C cirrhosis in the population with advanced cirrhosis. In patients with HCV genotype 3, the SVR12 rates were 83% and 91%, respectively, in those with advanced cirrhosis and recurrent post-transplant HCV infection.[110]

In the European DCV compassionate-use program, patients with cirrhosis were treated with a combination of daily DCV and SOF for 24 weeks, with or without RBV. The program reported interim SVR12 rates for two cohorts. The first cohort was HCV/HIV co-infected patients with decompensated cirrhosis (CTP B and C) and all genotypes (n = 28). The SVR12 rates were 88% in patients treated with RBV and 80% in those without RBV. The second cohort comprised HCV genotype 3 patients (n = 45) with CTP B and C. The SVR12 rates were 86% and 80% in patients who received and did not receive RBV, respectively, and 100% and 75% in CTP C patients treated with and without RBV, respectively.[111,133]

Recommendations:

1. Patients with HCV-induced decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C, up to 12 points) should be referred to a medical practitioner with expertise in that condition (ideally in a liver transplant center) (Grade C1).
2. In patients awaiting liver transplantation, antiviral therapy can prevent graft reinfection (Grade A1).
3. Patients with decompensated (CTP B or C) cirrhosis without HCC awaiting liver transplantation with a MELD score ≤20 should be treated with antiviral therapy, and the effect of viral clearance on liver function assessed, since significant improvement in liver function may lead to de-listing selected cases (Grade B1).
4. Patients with decompensated (CTP B or C) cirrhosis without HCC awaiting liver transplantation with a MELD score >20 should be transplanted first, without antiviral treatment, and HCV infection should be treated after liver transplantation (Grade B1).
5. Patients with decompensated (CTP B or C) cirrhosis awaiting liver transplantation, with a MELD score >20 and the waiting list time exceeding 6 months, should be treated before transplantation (Grade B1).
6. Patients with decompensated cirrhosis (CTP B and C, up to 12 points) can be treated with daily fixed dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) and a low initial dose of RBV (600 mg, increased as tolerated to 1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) for 12 weeks in HCV genotypes 1–6 (Grade A1).
7. Patients with decompensated cirrhosis with contraindications to the use of RBV or with poor tolerance to RBV on treatment can be treated with daily fixed dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) for 24 weeks without RBV (Grade A1).
8. Patients with decompensated cirrhosis (CTP B and C, up to 12 points) can be treated with daily daclatasvir (60 mg), sofosbuvir (400 mg), and a low initial dose of RBV (600 mg, increased as tolerated to 1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) for 12 weeks in HCV genotypes 1–6 (Grade B2).
9. Patients with decompensated cirrhosis with contraindications to the use of RBV or with poor tolerance to RBV on treatment can be treated with the combination of daclatasvir (60 mg) and sofosbuvir (400 mg) for 24 weeks without RBV (Grade B2).

## RETREATMENT OF PATIENTS WITH DIRECT-ACTING ANTIVIRAL FAILURES

HCV treatment failure with DAAs is now uncommon due to the high efficacy of DAAs, particularly the new pangenotypic DAAs. However, certain patient and virus characteristics may

result in lower response rates (SVR of 90–95%). Examples of these characteristics include cirrhosis, genotype 3 infection, and viral resistance-associated substitutions (RASs).[134]

### Non-response to protease or NS5A inhibitors

Two Phase III clinical studies demonstrated the safety and efficacy of a 12-week course of the triple pangenotypic single-pill combination of SOF/VEL/VOX in HCV-infected patients who failed to achieve SVR with a DAA-based regimen.[135] The POLARIS-1 and POLARIS-4 studies demonstrated that 12 weeks of treatment with SOF/VEL/VOX resulted in high rates of SVR12 among patients with and without compensated cirrhosis, who had HCV of any genotype and had not achieved SVR after previous treatment with DAAs, including NS5A inhibitors. The cirrhotic patients represented 46% of the patients in the trials.[50] In the POLARIS-1 study, the overall SVR12 rate in the SOF/VEL/VOX group was 96%; the SVR12 rate was 99% among patients without cirrhosis and 93% among those with cirrhosis. In the 56 patients with genotype 3 infection and cirrhosis, SVR12 was achieved in 52 (93%). POLARIS-4 included patients who had previously not received any DAA except an NS5A inhibitor; the overall rate of SVR12 was 98% in those who received SOF/VEL/VOX and 90% in those who received SOF/VEL. In patients without cirrhosis, the SVR12 was 98% in patients treated with SOF/VEL/VOX and 94% in those receiving SOF/VEL, compared to 98% and 86%, respectively, in patients with cirrhosis. In both studies, the HCV genotype and RAS profile at the re-treatment baseline had no impact on the response rates and with good medication safety profiles. In a deferred treatment open-label sub-study for patients who were assigned in the blinded portion to the placebo arm of POLARIS-1 study, a salvage regimen with SOF/VEL/VOX for 12 weeks was highly effective (SVR12 of 97%), safe, and well tolerated.[136]

Several real-world studies from various countries found that rescue treatment with SOF/VEL/VOX, with or without RBV, resulted in high SVR12 rates of 90–97% in the retreatment of DAA-containing regimen failures.[24,137,138] The addition of RBV to SOF/VEL/VOX was studied in predominantly genotype 4 patients who had failed a prior DCV-containing regimen. The study randomized 315 patients to receive SOF/VEL/VOX (n = 158) versus SOF/VEL/VOX plus RBV (n = 157) for 12 weeks. The SVR12 rates by per-protocol analysis were 97.8% (138/141) and 98.5% (138/140), respectively.[105] In a recent systematic review and meta-analysis, which included 15 studies with a total of 1,796 HCV-infected patients with previous treatment failure, the SVR12 rates were 93% in the ITT populations (n = 1,517, from 11 cohorts) and 96% in the per-protocol populations (n = 1,187, from 10 cohorts). This analysis showed that SVR12 rates were lower in genotype 3-infected patients, cirrhotic patients, and those who had previous treatment with the SOF/VEL regimen. In general, a 12-week SOF/VEL/VOX rescue regimen is recommended for patients who have failed DAA treatment, except for patients with genotype 3 infection and compensated cirrhosis, who should add weight-based RBV to the regimen.

In the MAGELLAN-1 clinical study, the pangenotypic combination of GLE/PIB for 16 weeks was found to be safe and more efficacious than the 12-week regimen for retreating patients with prior treatment failure with DAAs, including regimens containing NS5A inhibitors. SVR12 was 89% (39/44) and 91% (43/47) in patients who received 12 and 16 weeks of GLE/PIB, respectively. The type of previous regimen received had an impact on the retreatment response rate seen in this study. Patients who had previously received only NS3/4A protease inhibitors (NS5A inhibitor-naive) achieved 100% SVR12 regardless of treatment duration. Those who had only used NS5A inhibitors had SVR12 rates of 88% and 94% after 12 and 16 weeks of treatment, respectively. However, patients with prior experience with both classes of inhibitors (NS3/4A and NS5A) had lower rates of SVR12, at 79% and 81%, respectively, when treated for 12 and 16 weeks.[139]

The recommended duration of GLE/PIB in MAGELLAN-1 part 2 study (16 weeks) was also supported by the findings of a larger open-label, randomized, phase IIIb study for chronic HCV genotype 1 infection, in patients who had previously received SOF plus an NS5A inhibitor. In this study, 16 weeks of GLE/PIB treatment resulted in SVR12 in more than 90% of patients, 94% in patients without cirrhosis and 97% in patients with cirrhosis.[140]

Part 3 of SURVEYOR-II is a phase III, partially randomized, open-label study that assessed the efficacy and safety of GLE/PIB in adults with chronic HCV genotype 3 infection, including those with compensated cirrhosis and/or prior HCV treatment experience. In this study, among treatment-experienced patients without cirrhosis, SVR12 was achieved by 91% and 95% of patients treated with GLE/PIB for 12 or 16 weeks, respectively. Among patients with cirrhosis, SVR12 was 98% in treatment-naive patients treated for 12 weeks and 96% in treatment-experienced patients treated for 16 weeks.[97]

### Non-response to glecaprevir and pibrentasvir

Retreatment with GLE/PIB plus RBV and SOF is recommended for people who have previously failed GLE/PIB treatment. This is supported by the findings of the MAGELLAN-3 study. Patients who failed GLE/PIB were retreated for 12 or 16 weeks. The retreatment regimen was once-daily GLE/PIB plus SOF and weight-based RBV for 12 weeks in patients without cirrhosis, non-genotype 3, and naive to protease inhibitor and/or NS5A inhibitor prior to

virologic failure, and 16 weeks in patients with compensated cirrhosis and/or prior NS5A inhibitor and/or protease inhibitor treatment, prior to the first GLE/PIB treatment. The overall SVR12 rate was 96% (22/23); one patient with genotype 1a infection treated with the 16-week combination of GLE/PIB, SOF, and RBV relapsed at post-treatment week 4.[141]

The POLARIS studies were conducted before GLE/PIB was available, and hence, it was unclear whether the recommended SOF/VEL/VOX rescue regimen is effective for patients who fail GLE/PIB. This was tested in a small prospective, non-randomized, observational study that found a high SVR12 rate of 94% (29/31) with 12 weeks of SOF/VEL/VOX for patients with prior GLE/PIB failure.[142]

Recommendations:

1. Patients with or without compensated cirrhosis who have previously failed DAAs (protease inhibitor and/or NS5A inhibitor containing regimen) should be treated with
   a. Daily fixed-dose combination of sofosbuvir, velpatasvir, and voxilaprevir for 12 weeks (Grade A1).
   **Addition of weight-based RBV to the regimen is recommended in patients infected with genotype 3 and compensated cirrhosis if no contraindication*
   b. Daily fixed-dose combination of glecaprevir/pibrentasvir for 16 weeks (Grade A1)
   *-Not recommended for patients with prior exposure to an NS5A inhibitor plus NS3/4 protease inhibitor regimens (e.g., elbasvir/grazoprevir).*
   *-Not recommended for patients with genotype 3 infection with prior exposure to sofosbuvir/NS5A inhibitor regimen*
2. Patients with or without compensated cirrhosis who have previously failed glecaprevir/pibrentasvir should be treated with
   a. Retreatment with combination with glecaprevir/pibrentasvir plus RBV and sofosbuvir for 16 weeks (Grade B2)
   b. Daily fixed-dose combination of sofosbuvir, velpatasvir, and voxilaprevir for 12 weeks (Grade B2)
3. Patients with or without compensated cirrhosis and multiple DAA failures, including sofosbuvir/velpatasvir/voxilaprevir or sofosbuvir plus glecaprevir/pibrentasvir, should be treated with
   a. Daily combination with glecaprevir/pibrentasvir plus RBV and sofosbuvir for 16 weeks (Grade B2)
   **Extension of treatment to 24 weeks should be considered in extremely difficult cases (e.g., genotype 3 with cirrhosis) or failure following sofosbuvir plus glecaprevir/pibrentasvir*
   b. Daily fixed-dose combination of sofosbuvir, velpatasvir, and voxilaprevir for 24 weeks (Grade B2).

## TREATMENT OF HEPATITIS C IN LIVER TRANSPLANT RECIPIENTS

HCV re-infection of the graft after a liver transplant is common. Therefore, HCV RNA testing and confirming the genotype when the patient is stable enough post-transplant to consider initiating antiviral therapy are essential. Determining the stage of liver disease post-transplantation is important for selecting appropriate antiviral therapy. Routine liver biopsy is uncommonly used in the management of HCV treatment after the development of DAAs.

All liver transplant recipients with HCV viremia should be treated. Patients who achieve SVR with treatment post-transplant have lower rates of liver fibrosis progression and lower mortality rates compared to those who fail therapy.[143] The optimal timing for commencing treatment post-transplant is uncertain. However, it is recommended to begin treatment within the first month after transplantation, provided that the patient is stable, in order to prevent the development of HCV-related fibrosing cholestatic hepatitis (FCH). HCV-related FCH is mostly observed in cases of HCV genotype 1, high immunosuppression, older donors or recipients, and HIV/HCV coinfection.[144]

Regimen selection is limited in Saudi Arabia, and treatment should be administered in transplant centers with care consideration to DDIs. PegIFN-based regimens are not recommended because of the toxicity, poor response rates, and the risk of rejection. The treatment options for HCV post-transplant in patients without cirrhosis or compensated cirrhosis for any genotype are GLE/PIB for 12 weeks or SOF/VEL for 12 weeks. For patients without cirrhosis, a combination of DCV plus SOF can be used for 12 weeks in HCV treatment post-transplantation.[145] This regimen (DCV-SOF) is the first-line treatment available in Saudi Arabia for HCV. Additionally, the generic SOF is utilized, which has demonstrated comparable SVR12 rates and the same favorable safety profile.[146]

For patients with decompensated cirrhosis, antiviral treatment should only be administered in a transplant center by expert transplant hepatologists. The main options for treatment-naïve patients include SOF/VEL plus low-dose RBV (600 mg daily with an increase to 1000 mg as tolerated) for 12 weeks. Data from multi-center series showed that patients who received DAAs with RBV had higher SVR at 12 weeks (97% vs. 94%). The treatment can be extended for 24 weeks without RBV in patients with RBV contraindication or intolerance.[147]

Drug selection for the treatment of HCV post-transplant may be influenced by the patient's immunosuppressive regimen. DAA regimens that contain a protease inhibitor have the potential to increase drug levels of calcineurin inhibitors (cyclosporine and, to a lesser extent, tacrolimus) and inhibitors of the mammalian target of rapamycin (mTOR; sirolimus and everolimus). Some combinations are not recommended, while others require close monitoring of immunosuppressive drug levels. The use of grazoprevir-elbasvir is not endorsed in post-liver transplant patients. This DAA regimen can increase tacrolimus levels by approximately 40%. Furthermore, if used with cyclosporine, grazoprevir levels increase by 15%.[148,149]

Recommendations:

1. All patients with post-transplant recurrence of HCV infection must be treated as soon as possible after stabilization (Grade A1).
2. For HCV post-transplant in patients without cirrhosis or compensated cirrhosis, the following pan-genotypic DAA-based regimens are recommended:
   a. The fixed-dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) in a single tablet administered once daily for 12 weeks (Grade B1).
   b. The fixed-dose combination of glecaprevir (100 mg) and pibrentasvir (40 mg) in 3 tablets, administered once daily with food for 12 weeks, with monitoring for drug–drug interaction (Grade B1).
   c. The fixed-dose combination of sofosbuvir (400 mg) and daclatasvir (60 mg) administered once daily for 12 weeks (Grade C2).
3. For HCV post-transplant in naïve patients with decompensated cirrhosis, the fixed-dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) in a single tablet administered once daily with low-dose RBV for 12 weeks (Grade B1). The treatment can be extended for 24 weeks without RBV in patients with RBV contraindication or intolerance (Grade B1).

## TREATMENT OF HEPATITIS C IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

HCV is considered one of the predominant causes of cirrhosis-related complications, such as HCC.[150] The 5-year survival rate for HCC patients is around 14%, and the annual rate of HCC occurrence is approximately 1–7% in patients with cirrhosis. Globally, the incidence of HCC is increasing, with a predicted rise from 841,000 cases in 2018 to 1.4 million cases in 2040.[150] Several heterogeneous factors can increase the risk of HCC, including gender, age, diabetes, and the degree of liver fibrosis. In Saudi Arabia, the recent increase in the number of more advanced HCV-related liver disease and cirrhosis has also resulted in a proportional rise in the number of HCC being diagnosed.[3] DAAs have demonstrated vastly improved rates of SVR in all stages of HCV-related liver disease and consequently a preventive effect on the development of HCC in patients with chronic HCV. However, DAA therapy initially sparked a debate about an increased incidence of de novo or recurrent HCC in patients who received DAA treatment and achieved SVR. The pathogenesis of this phenomenon is still unclear but is potentially related to a transient immunosuppressive phase after DAA treatment, in addition to the presence of tumor cells with more aggressive behavior, which may be the mechanism responsible for the rapid tumor growth in these patients. This equilibrium may be achieved through changes in angiogenesis and/or the immune system.[151]

However, several prospective studies have refuted the concept of DAA treatment increasing the risk of HCC. A French study that included 7,344 chronic HCV patients treated with DAAs and 2,552 untreated patients confirmed that DAA treatment was associated with a significant decrease in HCC.[152] Similarly, a prospective multi-center cohort study of 1,400 Latin American patients with chronic HCV (median follow-up: 16 months) showed that an SVR with DAA regimens was associated with a 73% relative risk reduction for de novo HCC, with a cumulative HCC incidence in cirrhotic patients of 0.02 and 0.04 at 12 and 24 months, respectively.[153] In a systematic review and meta-analysis that included 44 relevant studies covering a total of 107,548 person-years of follow-up, conducted to assess the incidence of HCC after HCV cure among patients with advanced fibrosis (F3) or cirrhosis, HCC development after HCV cure was found to be 2.1 per 100 person-years among patients with cirrhosis and 0.5 per 100 person-years among patients with F3 fibrosis. This indicates that the degree of fibrosis plays a major role. In a meta-regression analysis among patients with cirrhosis, older age and prior decompensation were associated with an increased incidence of HCC.[154]

Starting treatment for HCV before commencing therapy for HCC could reduce the response to HCV clearance. In a systematic review with meta-analysis, including 5,522 patients with HCV and HCC from 56 studies, the overall SVR rate was 88%. SVR12 was 90.4% in patients who received curative HCC management, 78.9% in patients who received mixed HCC management, and 82.5% in patients who received non-curative HCC management. In 27 studies enrolling both patients with prior or present HCC (n = 3,126) and patients without HCC (n = 49,138), the pooled SVR12 was 88.2% ($P < 0.001$) in the HCC population and 92.4% ($P < 0.001$) in the non-HCC population. A higher

SVR12 rate was observed in patients who received curative HCC therapy than in those who received non-curative therapy or were not treated for HCC.[155]

For those patients with HCC who have an indication for liver transplantation, the pre- or post-liver transplant antiviral treatment indications are similar to those in patients who do not have HCC. In an observational, multi-center, retrospective analysis of 179 HCV-positive patients treated with DAAs while awaiting liver transplantation in 18 French hospitals, the overall SVR12 results were higher in the decompensated cirrhosis group (92%) than in the HCC group (78.9%) who had been treated pre-transplant.[156] Pre-transplantation treatment of HCV is considered cost-effective for patients without HCC and MELD ≤20. Similarly, post-transplant treatments are also regarded as cost-effective for both cirrhotic patients with MELD >20 and those with HCC. However, it is crucial to bear in mind that the final choice of a specific regimen at the individual patient level should be personalized, considering clinical, social, and transplant-related factors.[127,157] These factors are of special consideration in Saudi Arabia where transplant waiting times generally exceed 6 months, and the institution of antiviral therapy may help bridge the impact of HCV infection-related disease progression.

The other concerns raised are about a higher HCC recurrence risk in HCV patients who had been treated for HCC. There are multiple factors related to HCC recurrence. In a study from Japan, it was demonstrated that tumor size, prior history of recurrence, and the number of HCC nodules were predictors of HCC recurrence.[158,159] A meta-analysis, including six studies with a follow-up of 1.35 and 4 years, indicated a 64% lower risk for HCC recurrence in patients treated with DAAs compared to controls (OR 0.36, 95% CI: 0.27–0.47; $P < 0.001$).[160] Another meta-analysis, including a total of 2,957 patients from 31 studies, found that DAA therapy reduces the risk of HCC recurrence compared to an IFN-containing regimen (RR 0.64, 95% CI: 0.51–0.81) and no intervention (RR 0.68, 95% CI: 0.49–0.94).[161] DAA exposure is not associated with an increased risk of HCC recurrence (HR 0.90, 95% CI: 0.70–1.16). At present, patients with HCV infection should be encouraged to initiate DAA therapy to prevent cirrhosis complications and HCC. Therefore, intensive screening is necessary to exclude HCC before initiating DAA, particularly in patients with cirrhosis.

The routine laboratory investigation and abdominal US are currently used to define cirrhosis and screen for HCC. There are different models available to predict individuals at a high risk of developing HCC. Applying these models in elimination strategies can help identify patients in low- and high-risk groups, thereby improving the detection rate and reducing the cost of the annual and semiannual screening program for HCC.

One such simple and accurate prognostic tool is the aMAP score, which comprises routinely available laboratory parameters (albumin, bilirubin, and platelets) along with age and sex, and it can effectively predict the risk of HCC development. In a study involving over 17,000 patients with viral hepatitis, the findings demonstrated that the aMAP score model exhibited excellent discrimination in assessing the 5-year HCC risk. Using a cut-off of less than 50 indicates a low-risk group, while those with a cut-off of 60 belong to a high-risk group, that should undergo intensive surveillance for HCC. The parameters included in the score are very common as shown below, and a mobile app or web-based calculator could easily calculate the score.[162]

aMAP risk score = $(\{0.06 \times \text{age} + 0.89 \times \text{sex (male: 1;female: 0)} + 0.48 \times [(\log^{10} \text{bilirubin} \times 0.66) + (\text{albumin} \times -0{:}085)] - 0.01 \times \text{platelets}\} + 7.4)/14{:}77 \times 100$. where age is in years, bilirubin in μmol/L, albumin in g/L and platelets in $10^3/mm^3$.

Recommendations:

The recommendations of treating HCV patients with HCC, must be stratified according to patient status, and can be selected in different groups:

1. Patients who have HCC without cirrhosis or with compensated (CTP A) cirrhosis and are eligible for potentially curative therapy such as liver resection or ablation, should delay DAA therapy until completion of HCC treatment (Grade A1).
2. Patients with HCC but without cirrhosis or with compensated (CTP A) cirrhosis, who are awaiting liver transplantation, should receive treatment for their HCV infection either before or after transplantation, following the general recommendations (Grade A1).
3. In centers with extended waiting times for liver transplantation in patients with HCC and HCV infection, it is recommended to initiate HCV treatment before transplantation. This approach can facilitate locoregional therapies and help reduce the risk of waiting list dropouts due to tumor progression (Grade B2).
4. Patients with a complete response to HCC therapy and who achieve SVR still face a continued risk of HCC recurrence. As a result, they should undergo indefinite post-SVR HCC surveillance through ultrasound every 6 months (Grade A1).
5. Patients who are palliated for HCC may be considered for HCV treatment depending on their overall prognosis and potential benefit (Grade B2).

## TREATMENT OF CHRONIC HEPATITIS C IN SPECIAL GROUPS

### Patients with renal impairment and on hemodialysis and renal transplant recipients

Patients with renal impairment, such as those with severe renal impairment (eGFR <30 ml/min/1.73 m²) and those with end-stage renal illness who need hemodialysis (HD) or peritoneal dialysis, are frequently infected with HCV. Worldwide, the frequency of HCV in patients receiving HD ranges from 2.6% to 22.9%.[163] According to reports, the prevalence rates for HCV in HD patients in Middle Eastern nations range from 14.5% to 94.7%; 68% in Saudi Arabia, 26% in Oman, and 80% in Egypt. Although CKD is widespread in Saudi Arabia, infection rates have significantly declined during the past 20 years.[164]

According to one study, patients with HCV have a two-fold increased risk of membranoproliferative disease and a 17-fold increased risk of acquiring cryoglobulinemia.[165] In individuals with eGFR >15 ml/min, treating HCV and achieving SVR12 reduces the incidence of end-stage renal disease.[166] Following DAA therapy, renal function improves in patients with chronic kidney disease (CKD), but there is a delay in cryoglobulinemia resolution after achieving SVR.[167] All-cause mortality, including liver-related mortality, is higher among patients who need hemodialysis, but cardiovascular-related mortality remains the leading cause of death regardless of HCV.[168]

For approved DAA combinations, no dose modifications are required. Effective pan-genotypic regimens with high SVR rates, including those for hemodialysis patients, include GLE/PIB for 12 weeks. EXPEDITION-5 is an open-label phase III study that assessed the efficacy and safety of 8–16 weeks of GLE/PIB in adults with compensated cirrhosis and with stage 3b, 4, or 5 CKD, genotypes 1–6. The SVR12 rate was 97% (98/101). No patients experienced virologic failure, and there were no safety signals.[169] In EXPEDITION-4, this multi-center, open-label, phase III study evaluated GLE/PIB for 12 weeks in adults who had genotype 1–6 infection with or without cirrhosis with CKD stage 4 or 5. Patients either were treatment-naive or had received previous treatment with IFN, RBV, SOF, or a combination of these medications. The SVR12 rate was 98% (102/104), and no patients had virologic failure. Serious adverse events were reported in 24% of the patients. Four patients discontinued the treatment prematurely because of adverse events; three of these patients had SVR12.[170]

Similarly, MAGELLAN-2 was a phase III, open-label study conducted in patients who were ≥3 months post-transplant. Patients without cirrhosis who were HCV treatment-naive (genotypes 1–6) or treatment-experienced (genotypes 1, 2, 4–6; with IFN-based therapy with or without SOF, or SOF plus RBV) received GLE/PIB for 12 weeks. The overall SVR12 was 98% (98/100).[115,171,172]

Sofosbuvir raises safety concerns in patients with significant renal dysfunction (eGFR <30 ml/min/1.73m²) as it is largely excreted by the kidneys.[173] However, in this patient population, it has been reported to be safe and effective.[174-178] In a phase IIb, open-label, non-randomized, multi-center study, SOF-based therapy (n = 38) for 12 weeks was safe and effective in patients with stage 4–5 CKD who were not on dialysis. Adverse events were mostly mild or moderate in severity.[174] In another phase II study, HCV-infected patients with genotypes 1–6 (n = 59) undergoing hemodialysis or peritoneal dialysis received open-label SOF/VEL (400 mg/100 mg) once daily for 12 weeks. Patients were HCV treatment-naive or treatment-experienced without cirrhosis or with compensated cirrhosis. SVR12 was achieved in 95% (56/59) of patients.[175] In an observational, multi-center, real-world analysis from Taiwan, 3,480 HCV patients (genotypes 1–6), of whom 15.8% had CKD, were treated with SOF/VEL with or without RBV for 12 weeks. The SVR12 in CKD patients was 100%. The eGFR remained stable throughout treatment and follow-up, and there were no serious adverse events.[74]

In circumstances where no other treatment options are available, SOF/VEL therapy can be used without dose adjustments, according to limited safety evidence.[175,179,180] While there is a lack of data supporting the use of the SOF/VEL/VOX combination in kidney transplant settings, there is a wealth of information for the non-transplant population.[47,50,135,177,181] In the C-SURFER trial, grazoprevir and elbasvir treatment for 12 weeks in patients with genotype 1b with stage 4 or 5 CKD, including 75% on hemodialysis, resulted in a 92% SVR12 rate. However, this regimen is no longer employed in Saudi Arabia and has been omitted from this guidelines document.[182]

Antiviral therapy should be considered for all hemodialysis patients. Several criteria, such as the type of donor, length of the waiting list, policies of the particular center, HCV genotype, and degree of liver fibrosis, must be taken into account when treating HCV-infected patients awaiting kidney transplantation. DAAs are extremely safe, highly effective, and likely to cure kidney transplant recipients.[183-185] Moreover, if a patient receives a kidney from an HCV-positive donor, they may be treated with DAAs after the transplant.[186,187] THINKER was an open-label, single-group, pilot study that sought to determine the safety and efficacy of transplantation of kidneys from HCV genotype 1–viremic donors into HCV-negative patients, followed by elbasvir–grazoprevir treatment (n = 10). SVR12 was 100% (10/10) along with

potentially excellent allograft function post treatment.[149] In a systematic review that included 16 studies (n = 557), SVR12 was achieved in 97.7%, serious adverse events from DAA treatment occurred rarely [0.4% (95% CI, 0.1–2.8%)], and ≥1 year after transplantation, recipient death occurred in 2.1% (95% CI, 0.9–3.7) and allograft survival was 97.6% (95% CI, 95.7–98.9%).[188]

Recommendations:

1. Patients with end-stage renal disease who are receiving hemodialysis and those with severe renal impairment should be treated in a center with close monitoring (Grade B1).
2. Patients with renal disease can be treated for HCV infection according to the general recommendations without dose adjustment of HCV DAAs (Grade A1).
3. For HCV patients with severe end-stage renal disease requiring hemodialysis, the preferred treatment is the fixed-dose combination of glecaprevir (300 mg) and pibrentasvir (120 mg), administered once daily with food (Grade B1).
4. Patients with decompensated cirrhosis should be treated with the fixed-dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) in a single tablet administered once daily with RBV for 12 weeks in patients with mild to moderate renal impairment (eGFR >30 ml/min/1.73 m²). The recommended starting dose of RBV is 600 mg per day, and the dose can be adjusted based on tolerance and hemoglobin levels (Grade B1).
5. Patients with decompensated cirrhosis with significant renal impairment (eGFR <30 ml/min/1.73 m²) should be treated with the fixed-dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) in a single tablet administered once daily for 24 weeks without ribavirin (Grade B1).
6. Prior to kidney transplantation and the treatment of HCV-positive individuals, risks and benefits must be evaluated (Grade B1).
7. It is recommended to treat post-kidney-transplanted, treatment-naïve HCV patients, with and without compensated cirrhosis, using a daily combined fixed dose of glecaprevir and pibrentasvir for 12 weeks (Grade A1).
8. It is recommended to treat post-kidney-transplanted, treatment-naïve HCV patients, with and without compensated cirrhosis, using a daily combined fixed dose of sofosbuvir and velpatasvir for 12 weeks (Grade C2).
9. Post-kidney-transplanted, DAA-experienced HCV patients, with and without compensated cirrhosis, can be treated with a daily fixed dose of sofosbuvir, velpatasvir, and voxilaprevir, either with or without ribavirin, for 12 weeks (Grade C2).

## Patients with HIV co-infection

The prevalence of HIV in Saudi Arabia is 3 instances per 10,000 people. Globally, about 25% of patients with HIV also have chronic HCV infection.[189] Compared to the general population, HIV-infected patients have a prevalence of hepatitis C and B infections that is 10 and 20 times greater, respectively.[190] The advancement of liver fibrosis and cirrhosis is accelerated independently by HIV–HCV co-infection.[31,191,192] Similar to HCV mono-infection, DAAs are safe and effective for individuals who are co-infected.[193,194] Both co-infected and non-co-infected groups exhibit a similar response rate to the SOF/VEL combination therapy. However, due to potential interactions between DAAs and anti-retroviral drugs, careful monitoring for DDIs is necessary in co-infected individuals.

While most anti-retrovirals can be administered with daily fixed-dose combinations of SOF/VEL or LDV/SOF, other regimens, such as elbasvir-grazoprevir and GLE/PIB, require attention to a wider range of DDIs. Although there is a paucity of information on SOF/VEL/VOX in patients with HIV-HCV co-infection, recent studies found that the SVR12 rate was similar to that of HCV mono-infected populations. The RESOLVE study was a multi-center, open-label, phase IIb study investigating the safety, tolerability, and efficacy of SOF/VEL/VOX in patients with genotype 1 HCV infection who had relapsed following DAA therapy. SVR12 was 93% based on per-protocol analysis.[195] In another study, consecutive HIV-HCV-co-infected patients on dolutegravir-based anti-retroviral therapy were treated with SOF/VEL for 12 weeks. The SVR12 rate was 97.7% by per protocol analysis, and no grade 3/4 adverse events were reported.[196] These results have been extended to generic versions of SOF/VEL in a study where after 12 weeks of therapy SVR12 was achieved in 97% HIV-HCV-co-infected (67/69) and 98% (156/159) of mono-infected patients.[197]

EXPEDITION-2 was a phase III, multi-center, open-label study that evaluated GLE/PIB in HIV/HCV genotype 1–6-coinfected adults without and with compensated cirrhosis for 8 and 12 weeks, respectively. Patients were either HCV treatment-naive or -experienced with SOF, RBV, or IFN. The SVR12 rate was 98% (50/153), with no virologic failures in 137 patients treated for 8 weeks.[194] Real-world evidence from the HEPAVIR-DAA and GEHEP-MONO multi-center cohorts analyzed data in HIV-HCV-co-infected and mono-infected patients, respectively, treated with GLE/PIB. The overall SVR rates were 95.1% (487/512) in HCV-mono-infected patients and 95.5% (126/132) in HIV/HCV-co-infected patients ($P$ = 1.00). SVR12 rates to 8 or 12 weeks of

treatment were similar in HIV/HCV-co-infected versus HCV-mono-infected patients. The main reason for not reaching SVR12 among HIV/HCV-co-infected patients was premature dropout linked to active drug use.[198]

Recommendations:
1. Patients co-infected with HIV-HCV should receive equivalent care to those with mono-infection during both initial treatment and retreatment. However, meticulous monitoring of potential anti-retroviral drug interactions is essential (Grade B1).
2. The same medications can be used similar to patients without HIV, but special attention must be directed toward managing drug–drug interactions.

### Patients with chronic hepatitis B co-infection

HCV patients have a dismal prognosis if they also have HBV or HIV co-infection. Both infections should be screened in patients.[199] Between 5% and 10% of people worldwide are affected by HBV or HCV.[200] The risk of disease progression, liver decompensation, and HCC is increased in the presence of detectable viremia for both viruses. Variable and frequently low or undetectable DNA levels are observed in HBV-co-infected patients, with chronic inflammatory activity primarily driven by HCV. Potential co-infection with hepatitis D virus (triple infection) should be taken seriously. While cases of HBV re-activation have been documented, the risk remains uncertain during HCV treatment or after clearance.[36,201-204] In one study, two-thirds of co-infected patients receiving LDV/SOF treatment for 12 weeks exhibited higher HBV DNA levels without experiencing clinical consequences. Only 5% of patients had an increase in ALT (2 × ULN) that required the institution of HBV treatment.[38,205]

Routine monitoring of HBV DNA and HCV RNA levels is advised during or after treatment. Testing for HBV is recommended before initiating HCV treatment, and a positive HBsAg result indicates the need for concurrent nucleoside/nucleotide analogue treatment for HBV. Additionally, it is important to monitor ALT levels if HBsAg is negative but anti-core antibodies are positive. Testing for HBsAg and HBV DNA should be undertaken if ALT does not normalize or rises during or after treatment.[206]

Recommendations:
1. If a patient has co-infection of HCV and HBV and the HIV status is unknown, testing for HIV should be undertaken (Grade A1).
2. Patients co-infected with HCV and HBV should receive the same anti-HCV treatments and adhere to the same guidelines as patients with HCV mono-infection (Grade A1).
3. Patients who test positive for HBsAg should undergo an evaluation to determine whether their HBV DNA meets the SASLT criteria for HBV treatment and to consider the initiation of antiviral therapy for HBV (Grade B1).
4. Nucleoside/nucleotide analogue prophylaxis should be administered to patients with positive HBsAg and can be discontinued 12 weeks after anti-HCV treatment. Patients need to be monitored monthly after stopping HBV treatment (Grade B1).
5. Patients with anti-HBc antibody-positive status and negative HBsAg need periodic monitoring of serum ALT levels to detect potential re-activation (Grade B1).

### Patients with recently acquired hepatitis C virus

The first 6 months after infection are referred to as acute hepatitis C, and most individuals are asymptomatic during this time. Recent seroconversion can confirm recent hepatitis C acquisition. Approximately 15–45% of those infected naturally eliminate the virus within 6 months without treatment. The remaining 55–85% develop chronic HCV infection. IL28B gene polymorphism, younger age, female gender, and symptomatic disease, are all factors linked to spontaneous clearance.[207]

Given that late relapses after spontaneous recovery from acute HCV have been documented, negative findings at 12 and 24 weeks are necessary to demonstrate final clearance. In the absence of confirmed transmission, post-exposure prophylactic therapy is not advisable. Early treatment in high-risk groups reduces transmission and is cost-effective. The test-and-treat approach is encouraged. A low likelihood of spontaneous clearance in HIV-infected patients is predicted by the absence of a significant decrease in HCV RNA levels after 4 weeks.[208,209]

It is currently unknown how long this group of patients should receive treatment. Various methods have been explored using different DAAs, resulting in varying SVR rates. In the multi-center, open-label, randomized REACT study, the SVR12 rates for fixed-dose combinations of SOF/VEL (n = 188) were 89.4% (76/85) for the 6-week regimen and 97.7% (86/88) for the 12-week regimen, in

per-protocol analysis.[210] However, in the smaller HepNet acute HCV-V study, SOF/VEL was administered for 8 weeks in adult patients with acute HCV (n = 20), and SVR12 was achieved in 100% (n = 18/18) per protocol analysis.[211] Data for GLE/PIB treatment in acute HCV remain limited. In a pilot study, 30 adults with recent HCV infection (duration of infection <12 months) and 77% (n = 23) with HIV co-infection received GLE/PIB daily for 6 weeks. SVR12 in the per-protocol population was 96% (27/28).[212] In the TARGET3D multi-center international study, 23 adults with recent HCV (duration of infection <12 months; median duration 17 weeks) received GLE/PIB for 4 weeks. Although SVR12 was achieved by 78% (18/23), this was lower than observed with longer treatment durations.[213] The combination of 200 mg SOF (when it was off-label) and 60 mg DCV daily for 8 weeks, was conducted in 31 patients regardless of the genotype in patients with acute hepatitis C and an estimated glomerular filtration rate (eGFR) below 30 mL/min. All patients completed the treatment, and 26/27 (96.2%) achieved SVR12. These findings suggest that the 8-week DCV plus SOF regimen is effective for acute hepatitis C.[214]

Recommendations:
1. When acute HCV infection is suspected due to exposure, clinical presentation, or elevated aminotransferase levels, it is advisable to conduct HCV antibody and HCV RNA testing (Grade A1).
2. In cases where there is a strong suspicion, patients exhibiting positive anti-HCV antibodies but negative HCV-RNA or HCV-core antigen should undergo a second HCV-RNA test at 12 and 24 weeks (Grade A1).
3. Patients with recently acquired HCV should undergo an 8-week treatment course with either the combination of sofosbuvir and daclatasvir regimen, glecaprevir and pibrentasvir regimen or sofosbuvir and velpatasvir regimen (Grade B1).
4. In the absence of documented HCV transmission, there is no indication for the use of antiviral therapy as post-exposure prophylaxis (Grade B1).

## Patients with bleeding disorders and hemoglobinopathies

The prevalent hemoglobinopathy associated with chronic hepatitis C is thalassemia major, a condition more frequently observed in nations lacking adequate blood screening protocols. Additionally, HCV is common in patients with sickle cell anemia. Iron overload resulting from hemoglobinopathy accelerates the risk of liver disease.[215] Inherited bleeding disorders such as hemophilia A and B result from deficiencies in Factor VIII or IX. Prior to 1985, non-virally inactivated concentrates posed a significant risk of HCV transmission among hemophiliacs. Bleeding disorders like Von Willebrand disease, fibrinogen deficiency, and deficiencies in coagulation factors II, VII, X, XI, and XIII can be effectively managed with concentrates. The progression to end-stage liver disease in hemophiliacs with HCV is similar to that in HCV-positive individuals in the general population, and the treatment is similar to that in the non-hemophilic population. Monitoring the progression of the illness involves non-invasive techniques and transjugular liver biopsies.

Antiviral therapy trials have been conducted in individuals with inherited bleeding disorders, including the use of SOF/VEL in those with thalassemia or grazoprevir and elbasvir in those with various hemoglobinopathies. These studies achieved high rates of SVR.[216,217] Liver transplantation is a viable option for patients with hemophilia and can result in the production of factor VIII, leading to a phenotypic cure. Co-infection of HIV-HCV in patients with hemophilia does not preclude liver transplantation.

Recommendations:
1. The indications for HCV therapy remain the same for patients, regardless of the presence of hemoglobinopathies or bleeding disorders (Grade A1).
2. Individuals with hemoglobinopathies or bleeding disorders should undergo treatment with the same anti-HCV regimens, adhering to the same guidelines as patients with HCV mono-infection (Grade B1).

## Treatment of chronic hepatitis C in pregnant women

The Healthy Marriage Program, formerly known as the Premarital Screening Program, was established in 2004 in Saudi Arabia. It mandates individuals planning to marry in Saudi Arabia to undergo screening for conditions such as sickle cell disease, thalassemia, HIV, and hepatitis B and C. Upon completion of the screening, couples receive a pre-marital screening certificate, enabling them to proceed with their marriage plans. In cases where one partner is found to be affected by hepatitis B or C or HIV, the other prospective spouse is notified about the infection and advised to reconsider their decision to marry. However, the recommended course of action is to refer the individuals to a healthcare provider for further investigations, and typically, they are given top priority for treatment.[218] Therefore, it is extremely rare to find a Saudi pregnant woman with HCV because most patients discovered with HCV undergo treatment before marriage.

HCV infection has the potential to impact pregnancy outcomes, contributing to an increased occurrence of

pre-term delivery, intrahepatic cholestasis of pregnancy, and post-partum hemorrhage. There was an estimated 3.5% risk of mother-to-child transmission, and this risk increased with high viremia.[219,220] At present, there is a lack of extensive research regarding the safety and effectiveness of HCV DAAs in pregnant women, and none of these medications have been officially approved for use during pregnancy. In a prospective observational study involving pregnant patients with chronic HCV, treatment with LDV/SOF was initiated after the first trimester. The primary endpoints included SVR12, adverse drug reactions, and any congenital malformations in the infants. Additionally, the secondary endpoint was the transmission of HCV to the infants. A total of 26 patients were enrolled, with a mean age of 28 years. All patients were non-cirrhotic and treatment-naive. Among the participants, 19 (73%) were genotype 3, 5 (19%) were genotype 1, and 2 (8%) were genotype 4. All patients achieved SVR12, and no infants exhibited congenital malformations. Moreover, no child had detectable HCV RNA at 6 months of age.[221] An open-label, phase 1 study on pregnant participants underwent a 12-week course of oral LDV/SOF, with intensive pharmacokinetic visits at various gestational weeks, and was compared to non-pregnant women with HCV genotype 1 infection. The primary outcome, LDV/SOF area under the concentration–time curve of the dosing interval (AUCtau) during pregnancy, was compared to a non-pregnant reference group. Results showed similar exposures in pregnant and non-pregnant women [geometric mean ratio of AUCtau LDV 89·3% (90% CI 68·7–116·1); SOF 91·1% (78·0–106·3)]. The study concluded that LDV/SOF is safe and effective during pregnancy, with no clinically significant differences in drug exposure.[222] An international, phase 4, open-label, single-arm, multi-center study known as STORC is currently ongoing to examine the use of SOF/VEL for treating chronic HCV during pregnancy. Pregnant individuals in their 20$^{th}$ to 30$^{th}$ week of gestation receive a 12-week course of SOF/VEL. Preliminary results from July 2022 to September 2023 have shown promising outcomes, with 100% achieving SVR12. Adverse events related to SOF/VEL were mild, and none led to treatment discontinuation. Infants born to treated mothers tested negative for HCV RNA at 2 to 6 months of age. These findings provide early evidence supporting the safety and effectiveness of SOF/VEL in pregnant individuals after 20 weeks gestation.[223] Breastfeeding is considered safe for women with HCV, as existing data indicate that it does not elevate the risk of transmitting the virus from mother to child. However, if a mother experiences bleeding or cracked nipples, it is advisable to discontinue breastfeeding due to the potential risk of HCV transmission through blood exposure. In such cases, seeking specialized guidance is recommended for these individuals.[224]

Recommendations:

1. It is recommended that all couples with HCV be treated before marriage, according to the Saudi Healthy Marriage Program (Grade D2).
2. If a patient with HCV becomes pregnant while on treatment, she should be informed about the potential risks and benefits if she continues with the treatment, as some studies provide evidence supporting the safety of certain DAAs (Grade B2).
3. Breastfeeding is not contraindicated in women with HCV unless the nipples are cracked or bleeding (Grade B1).

## Financial support and sponsorship

Nil.

## Conflicts of interest

Drs. A. Alghamdi, M. Alghamdi, F. Abaalkhail, K. Alswat, A. AlQutub, M. Babatin, F. Sanai have been consultants for, and received speaker fees from AbbVie, and Gilead Sciences. Drs. F. Sanai and K. Alswat have received grants from AbbVie, and Bristol-Myers Squibb. Drs. F. Sanai and M. Alghamdi have been consultants for and received speaker fees from Spimaco. Others have nothing to disclose.

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