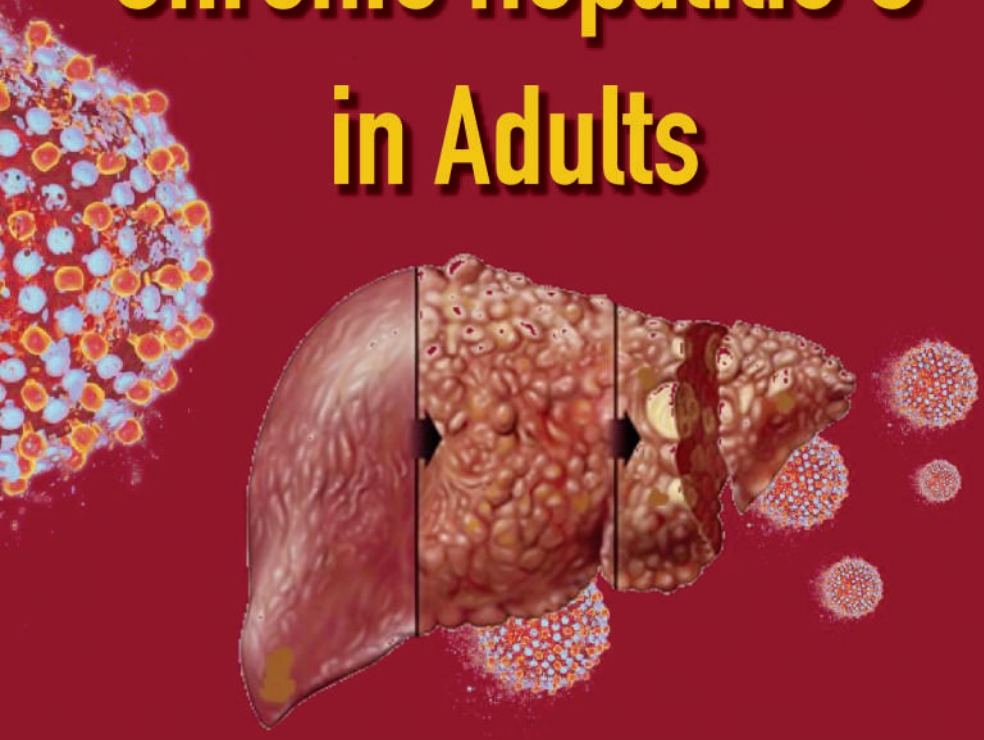
CLINICAL PRACTICE GUIDELINES

2019

MOH/P/PAK/433.19(GU)-e

Management of Chronic Hepatitis C in Adults



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STATEMENT OF INTENT

These clinical practice guidelines (CPG) are meant to be guides for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every healthcare provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

UPDATING THE CPG

These guidelines were issued in 2019 and will be reviewed in a minimum period of four years (2023) or sooner if new evidence becomes available. When it is due for updating, the Chairman of the CPG or National Advisor of the related specialty will be informed about it. A discussion will be done on the need for a revision including the scope of the revised CPG. A multidisciplinary team will be formed and the latest systematic review methodology used by MaHTAS will be employed.

Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found on the websites mentioned above.

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KEY RECOMMENDATIONS

The following recommendations were highlighted by the CPG Development Group as the key clinical recommendations that should be prioritised for implementation.

A. Screening, Diagnosis and Investigation

- Hepatitis C screening should be targeted for populations with increased risk of hepatitis C virus (HCV) infection or exposure.
- Screening for HCV infection should be based on the detection of antibodies to HCV by rapid diagnostic test or laboratory-based immunoassay.
- Confirmation of active viraemia or ongoing chronic HCV infection should be based on the detection of HCV ribonucleic acid (RNA) or HCV core antigen (HCVcAg).
- Non-invasive measures may be used to assess the degree of liver fibrosis in hepatitis C.

B. Treatment, Monitoring and Follow-up

- Prior to initiation of direct acting antivirals (DAAs) for hepatitis C,
  - identify presence of co-morbidity and perform baseline investigations
  - assess for cirrhosis status
  - evaluate for drug-drug interactions
  - counsel to avoid pregnancy for female patient and female partner of male patient during and six months after completion of treatment
- All hepatitis C patients (confirmed viraemia) should be initiated with DAAs within a year.
- In patients with hepatitis C and non-cirrhotic liver disease, the combination of sofosbuvir and daclatasvir may be prescribed for treatment.
- Routine laboratory monitoring shall be limited at week 4 of treatment and 12 weeks post-DAA treatment for hepatitis C.
  - Additional monitoring for full blood count should be done for hepatitis C patients treated with ribavirin.
- HCV RNA should be used to assess sustained virological response (SVR) 12 weeks post-DAAs.
  - HCVcAg at 24 weeks (SVR24) may be used as an alternative.
- Screening for early detection of hepatocellular carcinoma should be continued 6-monthly for all cirrhotic hepatitis C patients.

LEVELS OF EVIDENCE

Level	Study design
I	Evidence from at least one properly randomised controlled trial
II-1	Evidence obtained from well-designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group
II-3	Evidence from multiple time series with or without intervention; dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees

SOURCE: US / CANADIAN PREVENTIVE SERVICES TASK FORCE 2001

FORMULATION OF RECOMMENDATION

In line with new development in CPG methodology, the CPG Unit of MaHTAS is adapting **Grading Recommendations, Assessment, Development and Evaluation (GRADE)** in its work process. The quality of each retrieved evidence and its effect size are carefully assessed/reviewed by the CPG Development Group. In formulating the recommendations, overall balances of the following aspects are considered in determining the strength of the recommendations:-

- overall quality of evidence
- balance of benefits versus harms
- values and preferences
- resource implications
- equity, feasibility and acceptability

GUIDELINES DEVELOPMENT AND OBJECTIVES

GUIDELINES DEVELOPMENT

The members of the Development Group (DG) for these Clinical Practice Guidelines (CPG) were from the Ministry of Health (MoH), Ministry of Education and private sector. There was active involvement of a multidisciplinary Review Committee (RC) during the process of the CPG development.

A literature search was carried out using the following electronic databases: mainly Medline via Ovid and Cochrane Database of Systemic Reviews and others e.g. Pubmed and Guidelines International Network (refer to **Appendix 1** for **Example of Search Strategy**). The search was limited to literature published in the last ten years, on humans, adults and in English. In addition, the reference lists of all retrieved literature and guidelines were searched to further identify relevant studies. Experts in the field were also contacted to identify further studies. All searches were conducted from 3 January 2018 to 9 January 2019. Literature searches were repeated for all clinical questions at the end of the CPG development process allowing any relevant papers published before 31 July 2019 to be included. Future CPG updates will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

References were made to other guidelines on hepatitis C e.g.

- Guidelines for The Care and Treatment of Persons Diagnosed with Chronic Hepatitis C Virus Infection (World Health Organization, 2018)
- EASL Recommendations on Treatment of Hepatitis C (European Association for the Study of the Liver, 2016 and 2018)
- Hepatitis C Guidance 2018 Update: AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection (American Association for the Study of Liver Diseases and Infectious Diseases Society of America, 2018)

A total of 11 main clinical questions were developed under five different sections. Members of the DG were assigned individual questions within five sections (refer to **Appendix 2** for **Clinical Questions**). The DG members met 18 times throughout the development of these guidelines. All literature retrieved were appraised by at least two DG members using Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed in DG meetings. All statements and recommendations subsequently formulated were agreed upon by both the DG and RC. Where evidence was insufficient, the recommendations were made by consensus of the DG and RC.

This CPG is based largely on the findings of systematic reviews, meta-analyses and clinical trials, with local practices taken into consideration.

The literature used in these guidelines were graded using the US/ Canadian Preventive Services Task Force Level of Evidence (2001), while the grading of recommendation was done using the principles of GRADE (refer to the preceding page). The writing of the CPG strictly follows the requirement of AGREE II.

On completion, the draft of the CPG was reviewed by external reviewers. It was also posted on the MoH Malaysia official websitefor feedback from any interested parties. The draft was finally presented to the Technical Advisory Committee for CPG, and the HTA and CPG Council MoH Malaysia for review and approval. Details on the CPG development methodology by MaHTAS can be obtained from Manual on Development and Implementation of Evidence-based Clinical Practice Guidelines published in 2015 (available at http://www.moh.gov.my/moh/resources/CPG_MANUAL_MAHTAS.pdf?mid=634).

OBJECTIVES

The objectives of the CPG are to provide evidence-based recommendations on the management of hepatitis C in adults on the following aspects:

- screening and diagnosis
- treatment
- special groups
- monitoring and follow-up
- referral

CLINICAL QUESTIONS

Refer to **Appendix 2**.

TARGET POPULATION (Inclusion Criteria)

- Adults at risk and with HCV infection

TARGET GROUP/USERS

This document is intended to guide health professionals and relevant stakeholders in primary and secondary/tertiary care in the management of hepatitis C in adults including:

i. doctors
ii. allied health professionals
iii. trainees and medical students
iv. policy makers
v. patients and their advocates
vi. professional societies

HEALTHCARE SETTINGS

Primary and secondary/tertiary care settings

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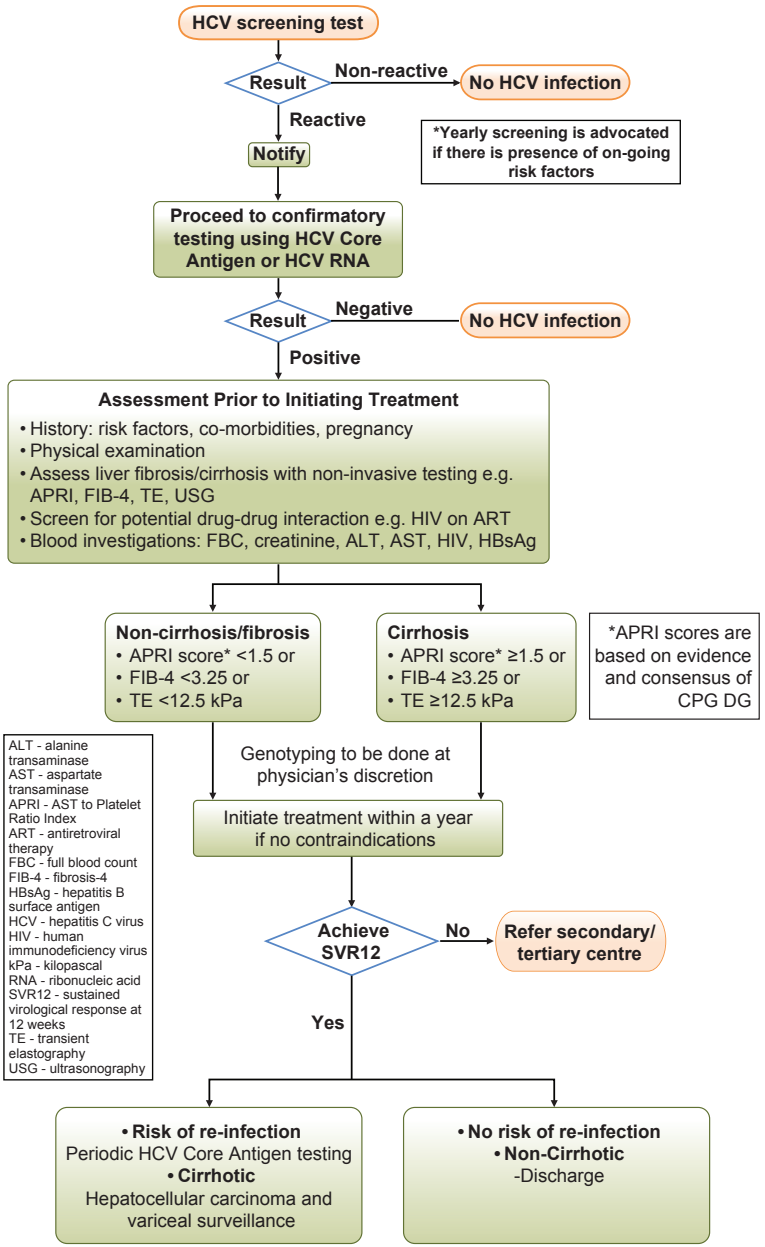
ALGORITHM ON MANAGEMENT OFCHRONIC HEPATITIS C IN ADULTS



1. INTRODUCTION

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease infection with worldwide approximation of 71 million people being infected.[1] In Malaysia, it is estimated that there are 453,700 people with anti-HCV positivity in 2009. The prevalence rate of people living with HCV infection among those aged 15 - 64 years is 2.5%.[2; 3]

Many of the estimated 380,000 people living with hepatitis C remain undiagnosed.[4] Screening and access to care of HCV is crucial to reduce the transmission and address the increasing disease burden in the country.[2] With the initiatives by the Ministry of Health (MoH) Malaysia, in-line with World Health Organization (WHO)'s strategy towards elimination of hepatitis C by 2030, screening and treatment of hepatitis C has expanded tremendously. At present, MoH is focussing on screening the high risk populations in particular people who inject drugs (PWID). The landscape of treatment for hepatitis C has evolved with the accessibility of direct-acting antivirals (DAAs) which are generally effective, well tolerated and given for 12 - 24 weeks.

Locally, the common genotypes found are genotype 3 (61.9%) and 1 (35.9%) which may give variation in treatment regime.[5] People who are HCV-infected are at risk of developing advanced liver disease, contributing to the continuous rise in HCV-related morbidity and mortality. Approximately 60 - 70% of chronically infected person will eventually develop chronic liver disease of which 5 - 20% will have cirrhosis of the liver and 1 - 5% will die of cirrhosis or hepatocellular carcinoma (HCC).[2]

The primary goal of HCV treatment is to cure the infection i.e. to achieve a sustained virological response (SVR). In view of high disease burden and variation in practice, an evidence-based CPG is required to guide healthcare providers locally in the management of hepatitis C.

2. SCREENING

Most chronic HCV infected individuals are asymptomatic and thus unaware of their infection. Failure to identify them prevents linkage to care and successful control of HCV. Therefore, screening of hepatitis C is an important step towards improving detection and ultimately treatment and cure of infected individuals.

- Hepatitis C screening is recommended for the following target populations that have increased risk of HCV infection or exposure:[6, 7]
  - current or past intravenous drug users
  - healthcare providers, emergency medical and public safety workers after needle sticks, sharps or mucosal exposures to HCV-infected blood
  - recipients of blood/blood products/clotting factor concentrates/ organ transplant before 1994
  - unexplained chronic liver disease and/or chronic hepatitis including elevated alanine aminotransferase (ALT) levels
  - people who have exchanged sex for money, goods or favours
  - men who have sex with men who have additional risk factors including human immunodeficiency virus (HIV) infection, report of traumatic sexual practice (e.g. fisting), diagnosis of lymphogranuloma venereum or syphilis, previous resolved or treated hepatitis C infection, engaging in 'chemsex'
  - people with HIV infection
  - current and past prisoners (incarceration)
  - people on long-term haemodialysis (HD)
  - children born to HCV-infected women
  - intranasal illicit drug users - non-injecting drug users

In intermediate to high HCV-prevalence (>2%) countries, programmes with pre-screening selection based on HCV risk profile or migrant status and programmes in psychiatric clinics are associated with high HCV prevalence.[8, level III] In contrast, programmes targeting healthcare workers (Asian population involved in liver transplantation) and pregnant women (obstetric/antenatal clinics in United Kingdom, US and Brazil) have low HCV prevalence.[9, level I]

Increase in screening uptake for hepatitis C in primary care can be achieved through targeted case finding, support and training of primary care practitioners, alternative HCV testing methods and provision of outreach testing. However, careful attention needs to be given to resource implications and potentials for intervention to improve outcomes once a positive diagnosis has been made in primary care.[10, level I]

Recommendation 1

- Hepatitis C screening should be targeted for populations with increased risk of hepatitis C virus infection or exposure.*

*Refer to the preceding yellow box.

3. INVESTIGATION

3.1 Laboratory Test

Diagnosis of HCV infection is based on two categories of laboratory tests:

- serological assays which detect antibody (anti-HCV) and antigen (HCV core antigen/ HCVcAg)
- molecular assays that can detect and quantify HCV ribonucleic acid (RNA)

These tests play a role in the diagnosis of infection, therapeutic decision-making and assessment of virological response to therapy.

3.1.1 Screening Test

Screening for hepatitis C infection (to determine serological evidence of past or present infection) in adults, adolescents and children (>18 months of age) is initiated by detection of a single test for anti-HCV antibodies using either a rapid diagnostic test (RDT) or laboratory-based immunoassay formats. Quality-assured RDT can be used in setting where there is limited access to laboratory infrastructure and testing, and/or in population where access to rapid testing would facilitate linkage to care and treatment.[11]

- RDT
  - Point-of-care testing
  - Effective and affordable diagnostic tool
- Laboratory-based Immunoassays
  - include enzyme immunoassay (EIA), chemiluminescence immunoassay (CIA) and electrochemoluminescence assay
- Screening tests should meet minimum acceptance criteria of either WHO's prequalification of in vitro diagnostics (IVDs) or a stringent regulatory review for IVDs. All IVDs should be used in accordance with manufacturers' instructions and where possible at testing sites enrolled in a national or international external quality assessment scheme.

A diagnostic study evaluating the performance characteristics of five anti-HCV RDTs showed that only Alere Truline, SD Bioline and OraQuick RDTs had high sensitivity of >99% and specificity >98% and, excellent inter-observer agreement and operational characteristics.[12, level III]

SD Bioline and OraQuick HCV RDT, immunochromatographic assays for the detection of antibodies to HCV in human serum, plasma and venous whole blood, have been accepted for the WHO list of prequalified in vitro diagnostics. SD Bioline has a sensitivity of 100% (95% CI 97.76 to 100) and specificity of 100% (95% CI 98.85 to 100) while OraQuick has a sensitivity of 100% (95% CI 97.8 to 100) and specificity of 99.7% (95% CI 98.3 to 100).[13, level III]

Flowchart for serological testing is illustrated in **Appendix 3**.

Recommendation 2
- Screening for hepatitis C virus (HCV) infection should be based on the detection of antibodies to HCV by rapid diagnostic test or laboratory-based immunoassay.

3.1.2 Confirmatory Test

The diagnosis of chronic hepatitis C is based on the detection of both anti-HCV antibody and HCV RNA or HCVcAg.[14]

- **HCV core antigen**

In acute hepatitis C, HCVcAg (a viral protein) is found in the blood two weeks after infection. It becomes detectable in blood a few days after HCV RNA.

HCVcAg, which uses enzyme-linked immunosorbent assay, is a lower-cost option than molecular test. However, it is less sensitive than HCV RNA assay (lower limit of detection equivalent to approximately 500 to 3,000 HCV RNA IU/mL).[14]

Using a threshold of quantifiable HCV RNA (≥15 IU/mL), HCVcAg demonstrates consistently high specificity (98 - 100%) at all time-points but a wide range of sensitivity (31 - 100%). Among baseline samples, there is a strong correlation between HCVcAg levels and HCV RNA levels (r_s 0.767 - 0.89, p ≤0.0001).[15 - 16, level III]

WHO has suggested that HCVcAg is too limited to recommend for its use as a substitute for HCV RNA as assessment of test of cure, known as SVR.[17] However, EASL allows this as an alternative if the latter is not available and/or not affordable to be done at SVR 24.[14]

- **HCV molecular**

HCV RNA polymerase chain reaction (PCR) is used to detect the presence of the virus, determine if the infection is active and if the individual would benefit from antiviral treatment. This assay detects the presence of viral RNA through targeting a specific segment of the virus.

The use of quantitative or qualitative molecular test for detection of HCV RNA is recommended as the preferred strategy to diagnose viraemic infection following a reactive HCV antibody serological test. The new generation of quantitative and qualitative assays have the same lower detection limit (around 15 IU/mL). However, quantitative assays are a reproducible method to detect and quantify HCV RNA in plasma or serum. Although quantitative RNA assays are considered the “gold standard” assays for the diagnosis and monitoring of HCV, the high

cost of these assays and laboratory requirements means that they are not readily available in resource-limited settings.[17]

- Both HCV RNA and HCVcAg are confirmatory tests indicating current infection.
- The sensitivity and specificity of HCVcAg are 96.3 - 99.3% and 100% respectively against HCV RNA (gold standard). HCVcAg can be used instead of HCV RNA to diagnose acute or chronic HCV infection when HCV RNA assays are not available and/or not affordable.[17; 18 - 19, level III]

- Hepatitis C is mandatory to be notified under the Prevention and Control on Infectious Disease Act 1988 to the nearest District Health Office within seven days of diagnosis.[20, level III]

- **HCV genotype**

HCV strains are classified into six major genotypes and 67 subtypes. The genotype of HCV for diagnosis is mostly determined by sequencing of genomic nucleotide sequence or by kit-based assays which employ complementary probes to report genotype present in a specimen. Sequencing of highly conserved regions such as NS5, core, E1 and 5'UTR is the most recommended method used for genotyping of HCV.

Most of the laboratory are using in vitro reverse transcription-PCR in plasma and serum from HCV-infected individuals. The limit of detection of HCV genotype is 500 - 1000 IU/mL (depends on the type of reagents used) to get an accurate HCV genotype result.

Testing for HCV resistance prior to treatment is not recommended.[14]

- In local setting where the choice of DAAs is limited, genotyping is still recommended to determine the optimal regime in cirrhotic population.
- Where new pangenotypic regimes are available, treatment can be initiated without knowledge of the genotype and subtype.[14]

Recommendation 3

- The diagnosis of chronic hepatitis C should be based on the detection of both anti-hepatitis C virus (HCV) antibody and HCV ribonucleic acid (RNA) or hepatitis C core antigen (HCVcAg).
- Confirmation of active viraemia or ongoing chronic HCV infection should be based on the detection of HCV RNA or HCVcAg.
- All hepatitis C patients (confirmed viraemia) should be initiated with direct-acting antivirals within a year.

3.2 Non-invasive Method of Liver Fibrosis Assessment

Accurate assessment on the severity of liver fibrosis is important for prognosticate and treatment planning in HCV patients.

Non-invasive methods of assessing fibrosis have been developed to reduce the need for liver biopsy.

A systematic review evaluates the ability of non-invasive measures in assessing hepatic inflammation and fibrosis among chronic HCV patients.[21, level II-2]

- A model using platelet count ≤140,000/mm^3, three spider nevi, aspartate aminotransferase (AST) >40 IU/L and male gender predicted cirrhosis with an AUC of 0.938.
- AST to platelet ratio index (APRI) is simple to be used in estimating fibrosis with AUC with a range of 0.87 - 0.89.
- For Fibrosis-4 (FIB-4) index, the AUC was 0.765 for differentiating Ishak 0 - 3 from 4 - 6. This was validated in a large cohort study which demonstrated AUC of 0.85 for severe fibrosis and 0.91 for cirrhosis.
- Transient elastography (TE) distinguished mild/moderate fibrosis from severe fibrosis/cirrhosis with AUC of 0.94.

Formula

$$\text{APRI} = \frac{\text{AST [IU/L]/AST (upper limit of normal) [IU/L]}}{\text{platelet [}10^9\text{/L]}} \times 100$$

$$\text{FIB-4 index} = \frac{\text{age ([year] x AST [IU/L])}}{\text{platelet [}10^9\text{/L] x ALT}^{1/2}\text{ [IU/L]}}$$

Although liver biopsy is the gold standard for detecting liver fibrosis and cirrhosis, it is an invasive test with increased risk of morbidity and mortality.

In two small diagnostic studies, the comparison of conventional ultrasonography (USG) to liver biopsy showed a PPV of 78 - 80%.[22 - 23, level III] The sensitivity was moderate at 68.18% but specificity was low at 14%.[23, level III]

TE has better sensitivity and specificity compared with conventional USG or doppler USG. The AUC increases from stage F1 to F4 liver fibrosis for both TE and US. However, the results are higher in TE.[24, level III] The diagnostic accuracy is much better in TE compared with doppler USG in F2 to F4 liver fibrosis. The AUC for TE in F2, F3 and F4 is 0.89, 0.96 and 1.0 respectively.[25, level III]

In a diagnostic study, TE and magnetic resonance elastography (MRE) had comparable accuracy in detecting all stages of liver fibrosis. However, the TE examiners were not blinded on the clinical data of the patients.[26, level III]

TE is available in limited centres whereas MRE is not available in Malaysia. However, once MRE is available, it can be incorporated into the MRI examination.

Recommendation 4
- Non-invasive measures* may be used to assess the degree of liver fibrosis in hepatitis C.
- Transient elastrography (TE) is the preferred non-invasive imaging modality for diagnosis of liver fibrosis and cirrhosis in hepatitis C.
  - Ultrasound abdomen is an alternative modality if TE is not available.

*Refer to the preceding text

Detection of cirrhosis using an APRI, FIB-4 and TEs is shown in the following table.

Table 1. Evaluation of APRI, FIB-4 and TE

Test	Non-cirrhotic/ fibrosis*	Cirrhotic*
APRI	<1.5	≥1.5
FIB-4	<3.25	≥3.25
TE	<12.5 kPa	≥12.5 kPa

Source:
1. World Health Organization. Guidelines for The Care and Treatment of Persons Diagnosed with Chronic Hepatitis C Virus Infection. Geneva: WHO; 2018
2. Castéra L, Le Bail B, Roudot-Thoraval F, et al. Early detection in routine clinical practice of cirrhosis and oesophageal varices in chronic hepatitis C: comparison of transient elastography (FibroScan) with standard laboratory tests and non-invasive scores. J Hepatol. 2009;50(1):59-68

*The values mentioned in **Table 1** are based on consensus of both CPG DG & RC.

3.3 Invasive Method of Liver Fibrosis Assessment

- Liver biopsy is the gold standard for detecting liver fibrosis and cirrhosis in hepatitis C. With the availability of non-invasive assessments, liver biopsy is not routinely done.

4. TREATMENT

4.1 Non-Pharmacological Treatment

HCV-infected patients should be counselled on the importance of strict adherence to attain high SVR. It is a multidisciplinary approach involving dedicated clinicians, pharmacists and nurses; it includes:

- HCV education
- monitoring services
- peer-based support

The following groups of patients will need additional support during DAAs treatment:

Group	Additional support
Ongoing alcohol consumption	Motivational enhancement therapy[27, level I]
Active drug abuse	Directly observed therapy (opioid users)[14] Behavioural modifications[14]
High risk sexual behaviours, particularly men who have sex with men	Behavioural modifications[14]

4.2 Pharmacological Treatment

- Untreated chronic hepatitis C infection may lead to liver cirrhosis and the risk of progression to cirrhosis varies according to the person's characteristics and behaviours.
- Alcohol use, hepatitis B virus (HBV) or HIV coinfection and immunosuppression due to any cause increase the risk of developing cirrhosis.[11]

4.2.1 Pre-treatment assessment

Prior to initiation of treatment, hepatitis C patients must be assessed to identify presence of co-morbidity and to determine cirrhosis status. The following baseline investigations need to be performed:

- full blood count (FBC)
- liver function test (LFT) including AST
- serum creatinine
- international normalised ratio/INR (for all cirrhotic patients)
- HIV and HBsAg screening

For those with cirrhosis, assessment for compensated and decompensated cirrhosis using Child-Turcotte-Pugh Score (CPS) as shown below.

Table 2. Child-Turcotte-Pugh Score for Grading Severity of Liver Disease

Variable	1	2	3
Ascites	None	Mild	Moderate/severe
Encephalopathy	None	Mild	Marked
Bilirubin (µmol/L)	<34	34 - 50	>50
Albumin (g/L)	>35	28 - 35	<28
Prothrombin time (seconds over normal)	<4	4 - 6	>6

Source: Kumar P, Clark M. Clinical Medicine Seventh Edition. Saunders Elsevier; 2009

- A total CPS of:
  - 5 - 6 is class A
  - 7 - 9 is class B
  - 10 - 15 is class C
- CPS classes B and C are considered decompensated stage.

Counselling to avoid pregnancy during and six months after completion of treatment should be given to both female patient and female partner of male patient who are taking DAAs regime containing ribavirin. There is lack of safety and efficacy data of DAAs in pregnancy.[28]

HCV-infected patients should be educated on the importance of adherence to treatment and report on the use of all other medications including recreational drugs.[14]

Pre-treatment assessment of concomitant medication should be done to avoid drug-drug interactions (DDIs).[EASL, 2018] About 30 - 44% of HCV patients on DAAs and concomitant medications are at risk of clinically significant DDIs. Potential DDIs are assigned to distinct risk categories according to the predicted level of significance as below:[29, level II-3]

- Category 0 : interaction has not been assessed
- Category 1 : no clinically significant interaction expected
- Category 2 : potential interaction that may require close monitoring, alteration of drug dosage or timing of administration
- Category 3 : co-administration either not recommended or contraindicated

Category 2 and 3 DDIs are considered as clinically significant. Higher number of elderly patients (≥ 65 years) have concomitant medications and clinically significant DDIs compared with non-elderly patients ($p<0.0001$).[30, level II-3] Prescribers may consult the University of Liverpool webpage on hepatitis drug interactions at https://www.hep-druginteractions.org/checker.

Recommendation 5

- Prior to initiation of direct acting antivirals for hepatitis C,
  - assess for cirrhosis status
  - identify presence of co-morbidity and perform baseline investigations as below:
    - full blood count
    - liver function test including aspartate aminotransferase
    - serum creatinine
    - international normalised ratio (for all cirrhotic patients)
    - HBsAg screening
    - HIV screening
  - evaluate for drug-drug interactions
  - counsel to avoid pregnancy for female patient and female partner of male patient during and six months after completion of treatment

4.2.2 Direct-acting antivirals

Treatment for chronic hepatitis C has evolved from using pegylated-interferon (PEG-IFN) with low cure rates and many side effects to various regimes of oral DAAs. The aim is to provide high cure rate or SVR by using drugs that are effective with short duration treatment and minimal side effects. Hepatitis C patients (confirmed viraemia) should be considered for DAA treatment except in those with limited life expectancy or significant non-liver-related co-morbidities. Treatment should be initiated without delay in those with significant fibrosis or cirrhosis, including those with decompensated cirrhosis and clinically significant extra-hepatic manifestations due to HCV infection.[14]

- In local setting, all hepatitis C patients (confirmed viraemia) should be initiated with DAAs within a year.
- SVR12 is defined as undetectable HCV RNA at 12 weeks post-treatment. It is considered equivalent to cure for hepatitis C infection.[11]
- SVR24 is defined as undetectable HCVcAg at 24 weeks post-treatment. It can be used as an alternative endpoint of treatment if HCV RNA assays are not available and/or not affordable.[14]

The available DAAs are:

Direct-Acting Antivirals (DAAs)	Pharmacological Class	Available in Malaysia
Sofosbuvir (SOF)	NS5B polymerase inhibitor (nucleotide analogue)	✔
Daclatasvir (DCV)	NS5A inhibitors	✔
Sofosbuvir/ledipasvir (SOF/LDV)	NS5B polymerase inhibitor/NS5A inhibitors	✔
Sofosbuvir/velpatasvir (SOF/VEL)	NS5B polymerase inhibitor/NS5A inhibitors	✔
Grazoprevir/elbasvir (GZR/EBR)*	NS3/4A polymerase inhibitor/NS5A inhibitors	✘
Glecaprevir/pibrentasvir (GLE/PIB)	NS3/4A (protease) inhibitor/NS5A inhibitor	✘
Ombitasvir/ritonavir/ Paritaprevir and Dasabuvir (OrPD)*	NS3/4A (protease) inhibitor/NS5A inhibitor/NS5B polymerase inhibitor (non-nucleoside analogue)	✘
Sofosbuvir/velpatasvir/ voxilaprevir (SOF/VEL/VOX)	NS5B polymerase inhibitor/NS5A inhibitors/NS3/4A (protease) inhibitors	✘
Sofosbuvir/ravidasvir	NS5B polymerase inhibitor (nucleotide analogue)/NS5A inhibitors	✔ (on-going clinical trial)

Ribavirin (RBV) is used in some combinations.
*Discontinued since 2019

- The choice of DAAs and treatment duration depends on stage of liver disease.
- HCV genotype (GT) should be considered in cirrhosis.

Recommendation 6
- All hepatitis C patients (confirmed viraemia) should be initiated with direct-acting antivirals within a year.

Refer to **Appendix 4** on **DAAs Regime and Duration in Non-Cirrhotic/ Compensated Cirrhotic Patients**.

Refer to **Appendix 5** on **Dosage Form, Administration and Side Effects of DAAs**.

a. Treatment of non-cirrhotic liver disease

In a systematic review of 42 low-moderate quality primary papers, various DAAs regimes showed high SVR12 rates in non-cirrhotic chronic hepatitis C as summarised in **Table 3**. In the review, combination of DCV and SOF showed high SVR rates with 12- and 24-week treatment (96% to 100%).[31, level I]

In the relatively new combination of GLE/PIB, randomised controlled trials (RCTs) had shown that non-inferiority or comparable results between eight weeks and 12 weeks regime on non-cirrhotic HCV patients.[32 - 33, level I] Both evidence are pharmaceutically-funded. The fixed combination is yet to be made available in Malaysia. The findings are also summarised in **Table 3**.

Table 3. Effectiveness of DAAs in Non-Cirrhotic Liver Disease

Genotype	Treatment-experience	Addition of ribavirin	GZV/EBR (SVR%)	OrPD (SVR%)	SOF/DCV (SVR%)	SOF/LDV (SVR%)	SOF/VEL (SVR%)	GLE/PIB (SVR%)	SOF/VEL/VOX (SVR%)
1a	Naïve	Yes		12 wk (95%)	24 wk (100%)	8 wk (92%) 12 wk (100%) 24 wk (100%)		8 wk (99.1%) 12 wk (99.7%)	
		No	12 wk (92%)		24 wk (100%)	8 wk (93%) 12 wk (95-99%) 24 wk (100%)	12 wk (97%)		8 wk (92%)
	Experienced	Yes		12 wk (96-97%)	12 wk (100%)	12 wk (95%) 24 wk (99%)			
		No		12 wk (90%)	12 wk (95%)	12 wk (95%) 24 wk (99%)	12 wk (97%)		12 wk (96%)
1b	Naïve	Yes		24 wk (95%) w/o DSV 12 wk (98-99%)	24 wk (100%)	12 wk (100%) 24 wk (100%) 8 wk (95%)		8 wk (99.1%) 12 wk (99.7%)	
		No	12 wk (99%)	12 wk (99%)	24 wk (100%)	12 wk (98-100%) 24 wk (97%) 8 wk (98%)	12 wk (100%)		8 wk (97%)
	Experienced	Yes		24 wk (90%) w/o DSV 12 wk (97%)	12 wk (100%)	12 wk (100%) 24 wk (100%)			
		No		12 wk (100%)	12 wk (95%)	12 wk (87%) 24 wk (100%)	12 wk (100%)		12 wk (100%)
2	Naïve	Yes			12/24 wk (92-100%)			8 wk (98%) 12 wk (99.5%)	
		No					12 wk (99-100%)		
	Experienced	Yes							
		No					12 wk (99-100%)		12 wk (100%)
3	Naïve	Yes				12 wk (100%)		8/12 wk (95%)	
		No			12 wk (94-97%)	12 wk (64%)	12 wk (97%)		8 wk (99%)
	Experienced	Yes							
		No			12 wk (94-97%)	12 wk (82%)	12 wk (97%)		12 wk (95%)

Genotype	Treatment-experience	Addition of ribavirin	GZV/EBR (SVR%)	OrPD (SVR%)	SOF/DCV (SVR%)	SOF/LDV (SVR%)	SOF/VEL (SVR%)	GLE/PIB (SVR%)	SOF/VEL/VOX (SVR%)
4	Naïve	Yes		12 wk (100%) w/o DSV				8 wk (93%) 12 wk (99%)	
		No	12 wk (100%)	12 wk (91%) w/o DSV		12 wk (95%)	12 wk (100%)		8 wk (92%)
	Experienced	Yes		12 wk (100%) w/o DSV					
		No				12 wk (91-95%)	12 wk (100%)		12 wk (91%)
5	Naïve	Yes						8 wk (93%) 12 wk (99%)	
		No				12 wk (95%)	12 wk (97%)		8 wk (94%)
	Experienced	Yes							
		No				12 wk (95%)	12 wk (97%)		
6	Naïve	Yes						8 wk (93%) 12 wk (99%)	
		No	12 wk (80%)			12 wk (96%)	12 wk (100%)		8 wk (100%)
	Experienced	Yes							
		No					12 wk (100%)		

wk=weeks, w/o DSV=without dasabuvir

Recommendation 7
- In patients with hepatitis C and non-cirrhotic liver disease, the combination of sofosbuvir and daclatasvir may be prescribed for treatment. Other combination of direct acting antiviral may also be considered*.

*Refer to **Appendix 4**.

b. Treatment of cirrhotic liver disease

- **Compensated liver disease**

Patients with cirrhosis are at increased risk for development of HCC and the need for liver transplantation. The risk of cirrhosis at 20 years after the infection with HCV ranges from 15% to 30%.[34 - 35, level II-2] The 1-year mortality is 5.4% in compensated patients; those in stage 1 (no varices) have longer survival than stage 2 patients (varices present).[36, level II-2] Cirrhosis can remain compensated for many years and it has been reported that the median survival of patients with this condition is more than 12 years.[37, level II-2]

In a systematic review, various DAAs regimes showed high SVR12 rates in cirrhotic chronic hepatitis C.[31, level I] All-oral, once-daily (GLE/PIB) is effective for most patients with HCV (GT1, 2, 4, 5 or 6) and compensated cirrhosis.[38, level II-3] SOF/VEL/VOX (eight weeks) is not non-inferior to SOF/VEL (12 weeks), but the two regimes have similar SVR rates in patients with HCV GT 3 and cirrhosis.[39, level I] The above findings are summarised in **Table 4**.

Table 4. Effectiveness of DAAs in Compensated Cirrhotic Liver Disease of HCV Patients

Genotype	Treatment-experience	Addition of ribavirin	GZV/EBR (SVR%)	OrPD (SVR%)	SOF/DCV (SVR%)	SOF/LDV (SVR%)	SOF/VEL (SVR%)	GLE/PIB (SVR%)	SOF/VEL/VOX (SVR%)
1a	Naïve	Yes			24 wk (100%)	12/24 wk (100%)			
		No	12 wk (92%)		24 wk (100%)	12 wk (99%) 24 wk (100%)	12 wk (100%)	12 wk (99%)	
	Experienced	Yes			12 wk (100%)	12 wk (95%) 24 wk (99%)			
		No			12 wk (95%)	12 wk (95%) 24 wk (99%)	12 wk (100%)	12 wk (99%)	12 wk (98%)
1b	Naïve	Yes		24 wk (98%) w/o DSV	24 wk (100%)	12 wk (100%) 24 wk (100%)			
		No	12 wk (99%)		24 wk (100%)	12 wk (100%) 24 wk (97%)	12 wk (97%)	12 wk (99%)	
	Experienced	Yes		24 wk (96%) w/o DSV	12 wk (100%)	12 wk (100%) 24 wk (100%)			
		No			12 wk (95%)	12 wk (87%) 24 wk (100%)	12 wk (96%)	12 wk (99%)	12 wk (98%)
2	Naïve	Yes					12 wk (100%)		
		No					12 wk (99-100%)	12 wk (100%)	
	Experienced	Yes					12 wk (100%)		
		No					12 wk (99-100%)	12 wk (100%)	12 wk (98%)
3	Naïve	Yes			12 wk (88%) 16 wk (92%)	12 wk (100%)			
		No			12 wk (90%)	12 wk (64%)	12 wk (91%)		8 wk (96%)
	Experienced	Yes			12 wk (88%) 16 wk (92%)				
		No			12 wk (86%)	12 wk (82%)	12 wk (91%)		12 wk (98%)
4	Naïve	Yes							
		No	12 wk (100%)			12 wk (95%)	12 wk (100%)	12 wk (100%)	
	Experienced	Yes							
		No				12 wk (91 - 95%)	12 wk (100%)	12 wk (100%)	

Genotype	Treatment-experience	Addition of ribavirin	GZV/EBR (SVR%)	OrPD (SVR%)	SOF/DCV (SVR%)	SOF/LDV (SVR%)	SOF/VEL (SVR%)	GLE/PIB (SVR%)	SOF/VEL/VOX (SVR%)
5	Naïve	Yes							
		No				12 wk (95%)	12 wk (100%)	12 wk (100%)	
	Experienced	Yes							
		No				12 wk (95%)	12 wk (100%)	12 wk (100%)	
6	Naïve	Yes							
		No	12 wk (80%)			12 wk (96%)	12 wk (100%)	12 wk (100%)	
	Experienced	Yes							
		No					12 wk (100%)	12 wk (100%)	

wk=weeks, w/o DSV=without dasabuvir

Studies on combination of SOF + ravidasvir that shows promising results in both non-cirrhotic and cirrhotic hepatitis C-infected patients are yet to be published.

- **Decompensated liver disease**

The number of decompensated cirrhosis caused by chronic HCV infection is projected to rise. Infected patients with advanced fibrosis or cirrhosis are at increased risk of both liver-related and all-cause mortality, e.g. liver failure and HCC, and the need for liver transplantation.

Optimising HCV treatment outcomes for patients with advanced liver disease remains an important objective because of the reduced therapeutic responses often observed in this group and the potentially life-threatening consequences of treatment failure.

The pan-genotypic combination of SOF, DCV and RBV achieves SVR12 rates of 78 - 92% in the advanced cirrhosis cohort.[40, level II-1]

Rates of SVR are 83% (95% CI 74 to 90) in patients receiving SOF/VEL for 12 weeks, 94% (95% CI, 87 to 98) among those on SOF/VEL + RBV for 12 weeks and 86% (95% CI 77 to 92) in those having SOF/VEL for 24 weeks.[41, level I]

Treatment with SOF + DCV and SOF/VEL for genotype 2 or 3 who are ribavirin ineligible is recommended for 24 weeks.[28]

SOF/LDV + RBV provide high rates of SVR12 for patients with advanced liver disease in genotype (GT) 1 and 4, including those with decompensated cirrhosis before or after liver transplantation.[42, level I]

The above findings are summarised in **Table 5**.

Table 5. Effectiveness of DAAs in Decompensated Cirrhosis of HCV Patients

Treatment regime	Genotype	Child-Turcotte-Pugh class (CPS)	Duration	SVR	SVR + RBV
SOF + DCV	1, 2, 3, 4, 5	B, C	12 weeks	89%	92%
	3	B	24 weeks	80%	86%
		C	24 weeks	78%	-
SOF/VEL	1, 2, 3, 4, 6	-	12 weeks	83%	94%
		-	24 weeks	86%	-
SOF/LDV	1, 4	B	12 weeks	87%	-
			24 weeks	96%	-
		C	12 weeks	85%	-
			24 weeks	78%	-

Recommendation 8
- In patients with hepatitis C and decompensated cirrhosis, the following combination of direct-acting antivirals may be used for 12 weeks:
  - sofosbuvir (SOF) + daclatasvir (DCV) + ribavirin (RBV)
  - sofosbuvir/velpatasvir (SOF/VEL) + RBV
  - sofosbuvir/ledipasvir + RBV (for genotype 1 and 4)
- In patients with hepatitis C and decompensated cirrhosis with genotype 2 or 3 and are ribavirin ineligible, SOF + DCV and SOF/VEL may be given for 24 weeks.

c. Liver transplantation

HCV infection with advance cirrhosis or recurrence after liver transplantation (LT) is associated with poor outcomes. Decompensated liver cirrhosis due to hepatitis C infection is an indication for LT because of its risk of HCC. Reinfection of the grafted liver has increased risk of progressive disease and graft loss.

An open label study assessed the safety and effectiveness of SOF, DCV and RBV on patients with chronic HCV infection of any genotype and either compensated/decompensated cirrhosis or post-LT recurrence. In patients with cirrhosis, SVR12 rates were higher in patients with CPS A or B (93%) vs CPS C (56%). In transplant recipients, SVR12 was achieved by 95%. There were no treatment-related serious adverse events. In post-LT patients, dose adjustment of immunosuppression was needed but there was no graft rejection.[43, level II-3]

Another study on HCV recurrence after LT using combination of LDV and SOF had shown an overall SVR12 of 96%. A total of 32% of patients underwent adjustment in immunosuppression and one episode of mild rejection was observed. However, there was no graft loss attributed to HCV treatment.[44, level II-3]

A multicentre open label trial evaluated the effectiveness and safety of GLE/PIB in chronic HCV treatment naive GT1 - 6 or treatment experience GT1, 2, 4 - 6 infection, without cirrhosis and who had received liver or kidney transplants for 12 weeks duration. The overall SVR12 was 98% and the adverse events were mostly mild and rarely of laboratory abnormalities.[45, level II-3]

The above findings are summarised in **Table 6**.

Table 6. Effectiveness of DAAs in Liver Transplant of HCV Patients

Treatment regime	Treatment naïve/experienced	Genotype	Rivabirin	Duration	SVR
SOF + DCV		1, 3	-	12 weeks	94%
SOF/LDV		1	-	12 weeks	94%
			+	12 weeks	97%
			-	24 weeks	95%
			+	24 weeks	100%
GLE/PIB	Naïve	1 - 6	-	12 weeks	98%
	Experienced	1, 2, 4 - 6	-		

5. SPECIAL GROUPS

5.1 Hepatitis B Co-infection

HBV/HCV co-infection is more common among PWID or in areas where these two viruses are endemic. Co-infection of HBV/HCV increases risk for HCC by 13.3%.[46] HBV/HCV co-infected patients should be treated similar to HCV mono-infected once HBV status has been assessed.

In a meta-analysis of 17 cohort studies on HBV/HCV co-infection receiving DAAs treatment, HBV reactivation occurred more frequently in patients with chronic [hepatitis B surface antigen (HBsAg)] than resolved [HBsAg-negative/hepatitis B core antibody (HBcAb)-positive] infection. The pooled proportion of patients who had HBV reactivation was 24% (95% CI 19 to 30) in the former and 1.4% (95% CI 0.8 to 2.4) in the latter. In those with chronic HBV infection, the risk of HBV-reactivation-related hepatitis was significantly lower in patients with HBV DNA below the lower limit of quantification at baseline than in those with quantifiable HBV DNA (RR=0.17, 95% CI 0.06 to 0.50). Thus, the use of antiviral prophylaxis might be warranted in HBsAg positive patients, particularly those with quantifiable HBV deoxyribonucleic acid (DNA).[47, level II-2]

Antibody and Antigen Biomarkers for Hepatitis B Infection are shown in **Table 7**.

Table 7. Antibody and Antigen Biomarkers for Hepatitis B Infection

Clinical state	HBsAg	Total HBsAb	Total HBcAb
Chronic infection	Positive	Negative	Positive
Acute	Positive	Negative	Positive (HBc immunoglobulin M)
Resolved infection	Negative	Positive	Positive
Immune (immunisation)	Negative	Positive	Negative
Susceptible (never infected and no evidence of immunisation)	Negative	Negative	Negative
Isolated core antibody	Negative	Negative	Positive

Source: Centres for Disease Control and Prevention. Hepatitis B Questions and Answers for Health Professionals. Available at: https://www.cdc.gov/hepatitis/hbv/hbvfaq.htm

5.2 Human Immunodeficiency Virus Co-infection

HIV/HCV co-infected patients are at higher risk to develop liver-related morbidity and mortality than HCV mono-infected patients. Fewer HIV/HCV co-infected patients have been treated in DAAs trials; however, the effectiveness rates among these groups have been remarkably similar to the HCV mono-infected groups in the evidence discussed below.

Treatment of HIV/HCV co-infected patients requires special attention due to the complexity of DDIs that can occur between DAAs and antiretroviral medications.

- CPG DG suggests that antiretroviral therapy (ART) should be initiated first and DAAs should be delayed in patients with HIV/HCV co-infection. This is to allow viral suppression and to avoid the difficulty in recognising ADR.
- If patients are not ready for ART, DAAs shall be considered if there are no contraindications.

The DDIs are summarised in **Appendix 6**.

i. Sofosbuvir + Daclatasvir

Two studies looked at the effectiveness of SOF+DCV in HIV/HCV co-infections. In ALLY-2 study, the combination of SOF+DCV once daily for 12 weeks achieved SVR12 in 97% of treatment-naïve and 98% of treatment-experienced HIV/HCV co-infected GT1 - 4 patients. The combination was safe and well tolerated.[48. level II-3] In another study, various combinations of DAAs which includes SOF+DCV (25% of patients) for 12 weeks were associated with 91% of SVR12 in GT1, 3 or 4 HIV/HCV co-infections.[49, level II-2]

The dose of DCV should be increased from 60 mg to 90 mg when used with potent inducer of cytochrome P450 (CYP) 3A4 e.g. efavirenz (EFV), etravirine (ETV) or nevirapine (NVP). Meanwhile it should be decreased from 60 mg to 30 mg when used with CYP 3A4 inhibitor e.g. ritonavir-boosted atazanavir, cobicistat-boosted atazanavir or elvitegravir/cobicistat. The usual dose of 60 mg should be used with ritonavir-boosted darunavir and ritonavir-boosted lopinavir.[28]

ii. Sofosbuvir/Ledipasvir

Studies had shown that SOF/LDV for 12 weeks were associated with high SVR12 rates of 96 - 100% in HIV/HCV co-infections.[49 - 50, level II-2; 51 - 52, level II-3] The patients included those who had previous treatment failure while receiving regimes that included DAAs and those with cirrhosis.[51, level II-3] None of the studies reported clinically significant changes in HIV RNA levels, cluster of differentiation 4 (CD4) cell counts

or change in estimated Glomerular Filtration Rate (eGFR). These findings suggested that SOF/LDV was safe and effective regime for HIV/HCV co-infected patients of all GTs (even though majority of the participants were in GT1 infection).

LDV's AUC decreases by 34% when co-administered with EFV-containing regimes and increases by 96% when co-administered with ritonavir-boosted atazanavir. Although no dose adjustments of LDV are recommended to account for these interactions, the combinations should be used with cautions and frequent renal monitoring.[28]

SOF/LDV increases tenofovir levels when given as tenofovir disoproxil fumarate (TDF), which may increase the risk of tenofovir-associated renal toxicity. This combination should be avoided in patients with an eGFR <60 ml/min/1.73 m^2.[28]

iii. Grazoprevir/Elbasvir (GZR/EBR)

In HIV/HCV co-infections, GZR/EBR for 12 weeks:

- ± RBV achieve SVR12 of 93 - 98% in GT1[53, level I]
- achieve SVR12 of 96% in GT 1, 4 and 6 including those with cirrhosis[54, level II-3]

GZR/EBR is not compatible with any ritonavir- or cobicistat-boosted HIV protease inhibitor (PI), elvitegravir/cobicistat, EFV or etravirine.[28]

iv. Ombitasvir/ritonavir/Paritaprevir + Dasabuvir (OrPD)

OrPD with or without ribavirin for 12 weeks are associated with SVR12 between 91 - 94% in HIV/HCV GT1, 3 or 4 co-infections. No treatment-related serious AEs occur.[49 - 50, level II-2; 53, level I]

OrPD should not be given to patients:[28]

- not on ART due to the potential risk for HIV PI resistance
- on rilpivirine and EFV due to potential risk of toxicity

OrPD is not recommended to be given together with ritonavir-boosted lopinavir due to high cumulative dosage of ritonavir which may induce severe gastrointestinal (GI) side effects.

v. Sofosbuvir/Velpatasvir (SOF/VEL)

SOF/VEL for 12 weeks is safe and achieves overall SVR12 of 95% including in compensated cirrhosis and treatment-experienced HIV/HCV co-infections.[55, level II-3]

SOF/VEL is not recommended to be used in patients on EFV or etravirine. SOF/VEL increases tenofovir levels when given as TDF, which may increase the risk of tenofovir-associated renal toxicity. This combination should be used with caution with close monitoring of renal profile in patients with an eGFR <60 ml/min/1.73 m^2.[28]

vi. Sofosbuvir/Velpatasvir/Voxilaprevir (SOF/VEL/VOX)
The SOF/VEL/VOX regime has not been studied in HIV/HCV co-infected patients. Despite lack of data, it is highly likely that response rates in the patients will be similar to those of HCV mono-infected patients.[28]

Recommendation 9
- HIV/HCV co-infections should be treated as HCV mono-infection.
  - Potential drug-drug interaction should be assessed prior to initiation and during treatment period.

5.3 Haemoglobinopathy

The prevalence of chronic HCV infection among thalassemia patients varies widely and can reach up to 85%.[56, level II-2] HCV was transmitted mainly through blood transfusion before screening of blood donors was introduced.[57, level II-2]

The EASL guidelines recommend DAAs for HCV infection in patients with hemoglobinopathies. However, data regarding their use are limited.[14]

In a cohort study among various hemoglobinopathies (mainly thalassemia major, HCV GT1b with previous PEG-IFN + RBV treatment failure and cirrhosis) using DAAs including SOF-based regimes mainly SOF + DCV and SOF + LDV ± RBV, high SVR12 of 93.5% had been reported, similar to patients without hemoglobinopathies.[57, level II-2]

The blood unit transfused in the three months before, during and three months after treatment did not increase in DAAs without RBV (mean unit transfused 3.8 vs 3.7 vs 3.8 respectively); however, it was significantly increased in the RBV group (3.6 vs 5.5 vs 4.0 respectively).[57, level II-2]

5.4 Immune-Complex Mediated Manifestations

HCV patients are at risk of developing extrahepatic manifestations that include cryoglobulinaemic vasculitis (CV). Mixed cryoglobulinaemia (MC) is a clonal disorder of B cells with a strong association to HCV infection. HCV can lead to systemic vasculitis with immune complex formation and deposition. Current therapeutic approaches are aimed at elimination of HCV infection, removal of cryoglobulins and expansion of B-cell clonal.

Patients with HCV-associated cryoglobulinemia treated with DAAs show significant improvement in:
- virological response[58, level II-3]
- biochemical response[58, level II-3; 59 - 61, level II-2]
- clinical response[59 - 60, level II-2]

- immune response[58, level II-3; 59 - 61, level II-2]
- complete response[58, level II-3]
- Model for End-Stage Liver Disease (MELD) score[59, level II-2]

DAAs are safe in HCV-related mixed cryoglobulinaemia[60, level II-2] with mild adverse events (AEs).[58, level II-3; 59, level II-2]

Recommendation 10
- Patients with hepatitis C virus-associated cryoglobulinemia should be treated with direct-acting antivirals.

5.5 Chronic Kidney Disease/End-Stage Renal Disease

HCV infection in chronic kidney disease (CKD) is associated with increased liver-related morbidity and mortality rates, accelerated progression to end-stage renal disease and risk of cardiovascular events.

A meta-analysis of 21 cohort studies of moderate quality showed that regime including SOF could be proposed for HCV-infected CKD patients with or without HD and should be associated with close clinical, biological, cardiovascular and therapeutic drug monitoring.[62, level II-2]

Studies showed that a once-daily oral regime of GZV/EBR for 12 weeks achieved high rates of SVR 97.4 - 99 % and had an acceptable safety profile in patients with HCV genotype 1 infection and advanced CKD with or without dialysis.[63 - 64, level I]

Treatment with GLE/PIB for 12 weeks resulted in an SVR of 98% (95% 95 to 100) in patients with stage 4 or 5 CKD and HCV infection.[65, level II-3]

- Patients with renal impairment (eGFR <30 ml/min/1.73 m^2) or those with ESRD on dialysis, SOF-free regime should be preferred. If there is no other choice, SOF-based regime may be used with close monitoring and treatment should be rapidly interrupted if renal function deteriorates.[14]

5.6 Pregnancy

Treatment of hepatitis C should not be initiated until pregnancy has been excluded due to the lack of safety and efficacy data.[28]

5.7 Acute Hepatitis C

Most patients with acute hepatitis C are asymptomatic. Spontaneous viral clearance varies from 14% to 50%. A minimum of six months of monitoring for spontaneous clearance is recommended before deciding to initiate treatment. If decision is to initiate treatment during the acute infection period, HCV RNA monitoring for at least 12 to 16 weeks before starting treatment is recommended. Patients who spontaneously clear after acute hepatitis C, antiviral treatment is not recommended.[28]

Treatment recommendation is as described for chronic hepatitis C treatment.

Recommendation 11

- Patients with acute hepatitis C should be monitored for six months for spontaneous viral clearance before initiating treatment.
  - Those who achieve spontaneous clearance should not be treated with antiviral.

5.8 Hepatitis C in Children and Adolescents

The United Nations Convention on the Rights of the Child defines a child as an individual below the age of 18 years; WHO defines an adolescent as a person between the ages of 10 and 19. Mother-to-infant transmission is the major route of infection in children while the adolescents are at risk of infection via injecting drug use.

There are numerous trials of PEG-IFN and RBV in children. However, current treatment options with DAAs are limited. The use of SOF/LDV for 12 weeks in children ages 12 - 17, weighing greater than 35 kg (genotype 1, 4, 5 and 6) have resulted in SVR rate of 98%. Combination of SOF and RBV has also been proposed for genotypes 2 and 3 for adolescents.[11; 14]

Adolescents aged ≥12 years, infected with genotype 2 or 3, who are treatment-naïve or treatment-experienced, without cirrhosis or with compensated cirrhosis (CPS A) can be treated with other regimens approved for adults, with caution pending on more safety data in this population.[11; 14]

In children younger than 12 years, treatment should be deferred until DAAs, including pangenotypic regimens, are approved for this age group.[11; 14]

6. MONITORING

The frequency of routine laboratory investigations and toxicity monitoring can be limited at the start and end of treatment since the DAAs are well tolerated.[11]

6.1 During and End of Treatment

The frequency of routine laboratory monitoring (LFT, serum creatinine) shall be limited at week 4 and 12 weeks post-DAAs treatment.11 Besides these clinic visits, regular review by treating team is highly recommended to ensure compliance.

More frequent monitoring e.g. FBC for drug-related AEs is necessary for those treated with RBV.[11; 28]

In patients who need RBV, the dose should be adjusted downward by 200 mg in decrement if the Hb level drops below 10 g/dL. RBV administration should be stopped if the level drops below 8.5 g/dL.[14]

A 10-fold increase in ALT activity at any time during DAAs treatment should prompt its discontinuation. An increase in ALT <10-fold that is accompanied by any clinical symptoms (e.g. weakness, nausea, vomiting, jaundice) or biochemical derangements (increased bilirubin, alkaline phosphatase or INR) should also prompt discontinuation of treatment. Asymptomatic increases in ALT <10-fold should be closely monitored with repeat ALT testing at 2-week intervals. If the levels remain persistently elevated, consideration should be given to discontinuation of treatment.[28]

HIV/HCV co-infection, HBV/HCV co-infection, cirrhosis, renal impairment, presence of potential DDIs and ill-health patients may also necessitate more frequent monitoring.[11] Increment of indirect bilirubin should be monitored in patients receiving OrPD. Renal function should be checked monthly in patients with reduced eGFR receiving SOF.[14]

HCV RNA should be tested at 12 weeks post-treatment to assess the effectiveness of the DAAs.

- Caution on risk of decompensation (first or worsening) in the following group of patients during DAAs treatment:[66, level II-3]
  - GT3 cirrhosis
  - CPS of B or C
  - albumin level <35 g/L
- Nucleic acid testing for qualitative or quantitative detection of HCV RNA should be used as test of cure at 12 or 24 weeks (i.e. SVR12 or SVR24) after completion of antiviral treatment.[17]
- Undetectable HCVcAg at 24 weeks (SVR24) after the end of treatment can be used as an alternative endpoint of therapy, if HCV RNA assays are not available and/or not affordable.[14]

Recommendation 10
- Routine laboratory monitoring* shall be limited at week 4 of treatment and 12 weeks post-direct-acting antiviral treatment for hepatitis C.
  - Additional monitoring for full blood count should be done for hepatitis C patients treated with ribavirin.

*LFT and serum creatinine

6.2 Post-Treatment

Following DAAs completion, treatment effectiveness should be determined by SVR12. However, periodic viraemia testing is recommended for patients with ongoing risk of re-infection.[39, level III]

Patients who have achieved SVR should be discharged if they have all of the following:
- no cirrhosis
- no ongoing risk behaviour
- no other co-morbidities

Advanced fibrosis and cirrhosis significantly increase the risk of HCC by 5- and 27-fold respectively, regardless of treatment status.[67, level II-2] Patients with cirrhosis with SVR should undergo surveillance for HCC 6-monthly by ultrasound.[14] In local setting, alpha-fetoprotein is also done routinely for the same surveillance.

Patients who have achieved SVR should also be counselled regarding sources of liver injury (e.g. alcohol, fatty liver, other potential hepatotoxins), which can independently contribute to liver fibrosis progression. They should be evaluated if serum levels of liver enzymes are raised.[39, level III]

In patients with cirrhosis, surveillance for oesophageal varices should be performed if varices are present at pre-treatment endoscopy.[14]

In PWID, the incidence of persistent re-infection is 1.7/100 person-years (95% CI 0.8 to 3.1) among individuals with injecting drug use (IDU) prior to treatment and 4.9/100 person-years (95% CI 2.3 to 8.9) among those who has relapsed to IDU after treatment. Low education level (OR=3.64, 95% CI 1.44 to 9.18) and lower age (<30 years) at treatment (OR=7.03, 95% CI 1.78 to 27.8) are associated with relapse to IDU.[68, level II-2] Thus, special consideration, e.g. harm reduction programme, should be made available following successful HCV treatment in PWID as re-infection is possible with ongoing risk exposure.

Recommendation 11

- Hepatitis C virus (HCV) RNA should be used to assess the sustained virological response (SVR) 12 weeks post-direct-acting antivirals.
  - HCV core antigen (HCVcAg) at 24 weeks (SVR24) may be used as an alternative.
- Screening for early detection of hepatocellular carcinoma should be continued 6-monthly for all cirrhotic hepatitis C patients.

6.3 Treatment Failure

For patients who have failed to achieve SVR12 (treatment failure) and those who have not received treatment, regular follow-up should be offered. Non-invasive methods for staging fibrosis are best suited in the assessment at intervals of one to two years. HCC surveillance 6-monthly must be continued indefinitely in patients with advanced fibrosis (F3) and cirrhosis.[14]

7. REFERRAL CRITERIA

There is no retrievable evidence on referral criteria for patients with HCV. Based on the consensus of CPG DG, patients with the following features should be referred to centres with Gastroenterologists and Hepatologists for further management:

- cirrhosis
- treatment failure
- hepatitis B co-infection
- CKD stage 4 and 5
- extrahepatic manifestation
- haemoglobinopathies
- solid organ transplantation

8. IMPLEMENTING THE GUDELINES

Hepatitis C treatment with DAAs is new in Malaysia and experience on it is limited. It is important to implement this CPG as a guidance in providing quality healthcare services based on best available evidence applied to local scenario and expertise.

8.1 Facilitating and Limiting Factors

The facilitating factors in implementing the CPG are:

i. availability of CPG to healthcare providers (hardcopies and softcopies)
ii. conferences and updates on management of hepatitis C which may involve professional societies e.g. Malaysian Society of Gastroenterology & Hepatology, Malaysian Association of HIV Medicine, Malaysian Family Medicine Specialist Association, Malaysian Pharmaceutical Society, etc.
iii. public awareness hepatitis campaign which may involve other government agencies and non-governmental organisations e.g. World Hepatitis Day

Limiting factors in the CPG implementation include:

i. limited awareness and knowledge in the management of hepatitis C among healthcare providers
ii. different levels of hepatitis C care due to expertise, drugs, laboratory and radiology facilities
iii. challenges in managing hepatitis C with/in:
    - renal failure
    - thalassemia
    - on-going risk factors
    - incarcerated population
    - DAAs resistance

8.2 Potential Resource Implications

To implement the CPG, there must be strong commitments to:

i. ensure widespread distribution of CPG to healthcare providers via printed copies and online accessibility
ii. reinforce training of healthcare providers via regular seminars and workshops
iii. involve multidisciplinary team at all levels of health care
iv. improve the diagnostic and therapeutic facilities
v. train more experts in the field of hepatitis C
vi. strengthen the hepatitis C registry

To assist in the implementation of the CPG, the following are proposed as clinical audit indicators for quality management:

- Percentage of hepatitis C patients (confirmed viraemia) initiated with DAAs within a year* = $\frac{\text{Number of hepatitis C patients (confirmed viraemia) initiated with DAAs within a year in a period}}{\text{Total number of hepatitis C patients (confirmed viraemia) in the same period}}$ X 100%

*Target ≥70%

Implementation strategies will be developed following the approval of the CPG by MoH which include Quick Reference and Training Module.

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Appendix 1

EXAMPLE OF SEARCH STRATEGY

Clinical Question: What are the safe and effective pharmacological treatments for chronic hepatitis C?

1. HEPATITIS C, CHRONIC/
2. (hepatitis c adj2 chronic).tw.
3. 1 or 2
4. DRUG THERAPY/
5. chemoterap*.tw.
6. (drug adj1 therap*).tw.
7. English therap*.tw.
8. 4 or 5 or 6 or 7
9. ANTIVIRAL AGENTS/
10. (antiviral adj1 (agent* or drug*)).tw.
11. antiviral*.tw.
12. 9 or 10 or 11
13. direct.tw.
14. 12 and 13
15. RIBAVIRIN/
16. rebetol.tw.
17. ribavirin.tw.
18. copegus.tw.
19. 15 or 16 or 17 or 18
20. 8 or 14 or 19
21. 3 and 20
22. limit 21 to (“all adult (19 plus years)” and English and humans and last 10 years)
23. limit 22 to systematic reviews

Appendix 2

CLINICAL QUESTIONS

A. Screening and Diagnosis

- Who should be screened for hepatitis C?
- What are the accurate screening tests for hepatitis C?
- What are the accurate confirmatory tests for hepatitis C?
- What are the accurate tests to assess severity of liver disease in chronic hepatitis C?

B. Treatment

- What are the safe and effective non-pharmacological treatments for chronic hepatitis C?
- What are the safe and effective pharmacological treatments for chronic hepatitis C?
- What are the safe and effective pharmacological treatments for chronic hepatitis C with decompensated liver cirrhosis?

C. Special Groups

- What are the safe and effective treatments in special groups of chronic hepatitis C?
  - hepatitis B co-infection
  - HIV co-infection
  - chronic kidney disease/end-stage kidney disease
  - haemoglobinopathy
  - immune complex-mediated manifestations
  - transplant
  - pregnancy
- What are the safe and effective management in acute hepatitis C?

D. Monitoring and Follow-up

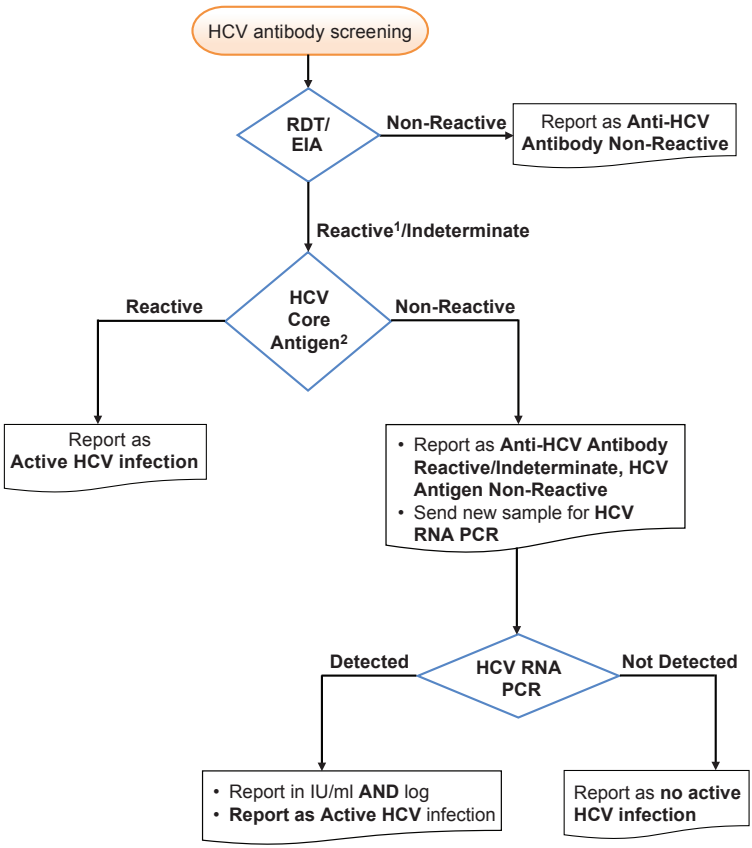
- What is the optimal monitoring and follow-up for chronic hepatitis C patients with the following conditions?
  - DAAs
  - Sustained virological response (SVR)
  - No SVR
  - Untreated

E. Referral

- What are the referral criteria for chronic hepatitis C patients?

Appendix 3

LABORATORY WORK FLOW FOR DIAGNOSIS OF HCV INFECTION



Notes:
1. For previous known anti-HCV antibody reactive, proceed with HCV Ag
2. Follow manufacturer's recommendation

DIRECT-ACTING ANTIVIRALS REGIME AND DURATION IN NON-CIRRHOTIC/COMPENSATED CIRRHOTIC PATIENTS

Liver status	Non-cirrhotic													Cirrhotic (compensated)												
Prior treatment exposure	Treatment-naïve							Treatment-experienced~						Treatment-naïve							Treatment-experienced~						
Genotype	1a	1b	2	3	4	5	6	1a	1b	2	3	4	5	6	1a	1b	2	3	4	5	6	1a	1b	2	3	4	5	6
Treatment	Duration (weeks)																											
SOF/DCV	12	12	12	12	12	12		*12 /24	12	12	24	24	24		12	12	12	* 24	12	12		24	12	12 /16 /24	* 24	24	24	
SOF/LDV	^ 8/ 12	^ 8/ 12	-	-	12	12		12	12	-	-	12	12		12	12	-	-	12	12		* 12	12	-	-	* 12	-	
SOF/VEL	12	12	12	12	12	12		12	12	12	12	12	12		12	12	12	12	12	12		12	12	12	* 12	12	12	
GZR/EBR	12	12	-	-	12	-		12	12	-	-	@ 12	-		12	12	-	-	12	-		12	12	-	-	@ 12	-	
GLE /PIB	8	8	8	8	8	8		8	8	8	12 /16	8	8		12	12	12	12	12	12		12	12	12	16	12	12	
OrPD	* 12	$ 8/ 12	-	-	-	-		* 12	12	-	-	-	-		-	12	-	-	-	-		-	12	-	-	-	-	
SOF/VEL/VOX	-	-	-	-	-	-		-	-	12	-	-	-		-	-	-	12	-	-		-	-	-	12	-	-	

~Treatment- experienced: Only refer to PEG-IFN/ RBV- experienced patient
^Eight weeks treatment if patient is non-black, HIV-uninfected, and HCV RNA level is <6 million IU/mL
$Eight weeks treatment if METAVIR F0-2; 12 weeks treatment if METAVIR F3
*Use with RBV
@Only for virologic relapse patient

Source:

- AASLD-IDSA HCV Guidance Panel. Hepatitis C Guidance 2018 Update: AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. Clin Infect Dis. 2018;67(10):1477-1492
- European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2018. J Hepatol. 2018;69(2):461-511
- European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol. 2017;66(1):153-194

Appendix 5

DOSAGE FORM, ADMINISTRATION AND COMMON SIDE EFFECTS OF DIRECT-ACTING ANTIVIRALS IN MALAYSIA

Dosage Form	Administration	Common side effects
Sofosbuvir (400 mg)	One tablet once daily	Headache, fatigue, nausea, diarrhoea
Daclatasvir (60 mg)	One tablet once daily	
Fixed-dose sofosbuvir (400 mg)/ledipasvir (90 mg)	One tablet once daily	
Fixed-dose sofosbuvir (400 mg)/velpatasvir (100 mg)	One tablet once daily	
Fixed-dose elbasvir (50 mg)/grazoprevir (100 mg)	One tablet once daily	
Fixed-dose glecaprevir (300 mg)/pibrentasvir (120 mg)	Three tablets once daily	
Fixed-dose paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir mg)	Two tablets once daily	Pruritus, fatigue, nausea
Dasabuvir (250 mg)	One tablet twice daily	
Fixed-dose sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)	One tablet once daily	Headache, fatigue, diarrhoea, anaemia, insomnia, nausea
Ribavirin (200 mg)	Daily weight-based: (less if dose reduction needed) >75 kg: 1200 mg/day in 2 divided doses <75 kg: 1000 mg/day in 2 divided doses For decompensated cirrhosis: Recommended to start with 600 mg/day and titrate accordingly	Fatigue, nausea, anaemia, headache *Most of the side effects are reported during the combination treatment of PEG-IFN and ribavirin; thus, it is impossible to correlate frequency of side effects with ribavirin alone
Watch out risk of hepatic decompensation/failure in patients with evidence of advanced liver disease		

Source:

1. AASLD-IDSA HCV Guidance Panel. Hepatitis C Guidance 2018 Update: AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. Clin Infect Dis. 2018;67(10):1477-1492
2. European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol. 2017;66(1):153-194
3. European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2018. J Hepatol. 2018;69(2):461-511

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11. MAVYRET® US full prescribing information. North Chicago, IL: AbbVie Inc; Aug 2018
12. VOSEVI® package insert (Available at: https://www.gilead.com/-/media/files/pdfs/medicines/liver-disease/vosevi/vosevi_pi.pdf)
13. Copegus® package insert (Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021511s023lbl.pdf)

Appendix 6

DRUG-DRUG INTERACTION BETWEEN DIRECT-ACTING ANTIVIRALS AND HIGHLY ACTIVE ANTIRETROVIRAL THERAPY

HIV Antiviral Drugs	DCV	SOF	SOF/ LDV	SOF/ VEL	OBV/ PTV/r + DSV	GZR/ EBR	GLE/ PIB	RBV	SOF/ VEL/ VOX
Nucleoside reverse transcriptase inhibitors (NRTIs)									
Abacavir (ABC)	✓	✓	✓	✓	✓	✓	✓	-	✓
Emtricitabine (FTC)	✓	✓	✓	✓	✓	✓	✓	-	✓
Lamivudine (3TC)	✓	✓	✓	✓	✓	✓	✓	-	✓
Tenofovir (TDF)	✓	✓	-	-	✓	✓	✓	-	-
Tenofovir alafenamide (TAF)	✓	✓	✓	✓	-	✓	✓	✓	-
Zidovudine (AZT)	✓	✓	✓	✓	✓	✓	✓	×	✓
HIV entry/integrase inhibitor (IIs)									
Dolutegravir (DTG)	✓	✓	✓	✓	✓	✓	✓	✓	✓
Raltegravir	✓	✓	✓	✓	✓	✓	✓	✓	✓
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)									
Efavirenz (EFV)	-	✓	-	×	×	×	×	✓	×
Nevirapine (NVP)	-	✓	✓	×	×	×	×	✓	×
Protease inhibitors (PIs)									
Lopinavir	✓	✓	✓	✓	×	×	×	✓	×
Ritonavir	-	✓	✓	✓	×	×	×	✓	×

Symbols:
✓ No clinically significant interaction expected.
- Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring.
× Co-administration either not recommended or contraindicated.

Notes:
- Some drugs may require dose modifications depending on hepatic function. Refer to the product label of individual drugs for dosing advice.
- The symbol (✓, -, ×) used to rank the clinical significance of the DDI is based on www.hep-druginteractions.org
- For updated or additional DDIs and for a more extensive range of drugs, detailed pharmacokinetic interaction data and dosage adjustments, refer to the latest above-mentioned website.

Source:

- AASLD-IDSA HCV Guidance Panel. Hepatitis C Guidance 2018 Update: AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. Clin Infect Dis. 2018;67(10):1477-1492
- European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol. 2017;66(1):153-194
- European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2018. J Hepatol. 2018;69(2):461-511
- Interaction Checker (Available at: www.hep-druginteractions.org)

LIST OF ABBREVIATIONS

µmol/L	micromole/litre
AE	adverse event
ALT	alanine aminotransferase
Anti-HCV	antibody to HCV
APRI	AST to platelet ratio index
ART	antiretroviral therapy
AST	aspartate transaminase
AUC	area under the curve
BMI	body mass index
CD4	cluster of differentiation 4
CI	confidence interval
CIA	chemiluminescent immunoassay
CKD	chronic kidney disease
CPG	clinical practice guidelines
CPS	Child-Turcotte-Pugh score
CV	cryoglobulinaemic vasculitis
CYP	cytochrome P450
dL	desilitre
DNA	deoxyribonucleic acid
EBR	elbasvir
EFV	efavirenz
eGFR	(estimated) glomerular filtration rate
EIA	enzyme immunoassay
ESRD	end-stage renal disease
ETV	etravirine
DAAs	direct-acting antivirals
DCV	daclatasvir
DDI(s)	drug-drug interaction(s)
DG	Development Group
FBC	full blood count
FIB-4	fibrosis-4
g	gramme
GI	gastrointestinal
GT	genotype
HBc(Ab)	hepatitis B core (antibody)
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HCVcAg	HCV core antigen
HD	haemodialysis
HIV	human immunodeficiency virus
HR	hazard ratio
IDU	injecting drug user
INR	international normalised ratio
IU/L	international unit/litre
IU/mL	international unit/millilitre
IVDs	in vitro diagnostics
L	litre

LDV	ledipasvir
LFT	liver function test
LT	liver transplantation
MaHTAS	Malaysian Health Technology Assessment Section
MC	mixed cryoglobulinaemia
MD	mean difference
MEIA	microparticle enzyme immunoassay
mg	milligramme
MELD	Model for End-Stage Liver Disease
MoH	Ministry of Health
MRI	magnetic resonance imaging
MRE	magnetic resonance elastography
NICE	National Institute for Health and Clinical Excellence
NNRTI	non-nucleoside reverse transcriptase inhibitors
NVP	nevirapine
OR	odds ratio
OrPD	Ombitasvir/ritonavir/Paritaprevir and Dasabuvir
PCR	polymerase chain reaction
PEG-IFN	pegylated-interferon
PI	protease inhibitor
PIB	pibrentasvir
PPV	positive predictive value
PWID	people who inject drugs
RBV	ribavirin
RC	Review Committee
RCT(s)	randomised controlled trial(s)
RDT(s)	rapid diagnostic test(s)
RNA	ribonucleic acid
RR	relative risk
r_s	Spearman's Rho
SD	standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
SMD	standardised mean difference
SOF	sofosbuvir
SVR	sustained virological response
TDF	tenofovir disoproxil fumarate
TE	transient elastography
US	United States
USG	ultrasonography
VEL	velpatasvir
VOX	voxilaprevir
vs	versus
WHO	World Health Organization

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