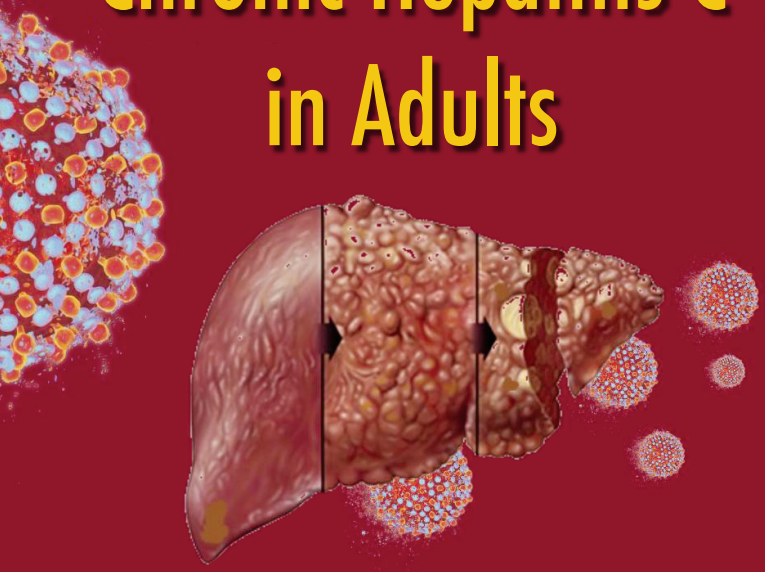
QUICK REFERENCE
FOR HEALTHCARE PROVIDERS

Management of Chronic Hepatitis C in Adults



Ministry of Health
Malaysia

Academy of
Medicine Malaysia

KEY MESSAGES

1. Hepatitis C virus (HCV) infection is a major cause of chronic liver disease infection worldwide.
2. Hepatitis C screening should be targeted for populations with increased risk of HCV infection or exposure.
3. Screening for HCV infection should be based on the detection of antibodies to HCV by rapid diagnostic test or laboratory-based immunoassay.
4. 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).
5. HCV infection is curable with direct acting antivirals (DAAs).
6. Prior to initiation of DAAs for hepatitis C,
   - identify presence of co-morbidity & perform baseline investigations
   - assess liver fibrosis/cirrhosis using aspartate transaminase (AST) to platelet ratio index (APRI) score or/and fibrosis-4 (Fib-4) or/and transient elastrography
   - evaluate for drug-drug interactions (refer to https://www.hep-druginteractions.org/checker)
   - counsel to avoid pregnancy for female patient & female partner of male patient during & 6 months after completion of treatment
7. DAAs are effective with minimal side effects, therefore routine laboratory monitoring should be limited at week 4 of treatment & 12 weeks post-DAA treatment for hepatitis C.
8. Cure is considered equivalent to sustained virological response 12 (SVR12), which is defined as undetectable HCV RNA at 12 weeks post-treatment or HCVcAg at 24 weeks (SVR24).
9. Screening for early detection of hepatocellular carcinoma (HCC) should be continued 6-monthly for all cirrhotic hepatitis C patients.
10. DAAs used in special groups, e.g. hepatitis B co-infection, human immunodeficiency virus (HIV) co-infection, chronic kidney disease & haemoglobinopathies, are equally effective.

- Hepatitis C is mandatory to be notified under the Prevention and Control on Infectious Disease Act 1988 to the nearest District Health Office within 7 days of diagnosis.

SCREENING

- Hepatitis C screening is recommended for the following target populations that have increased risk of HCV infection or exposure:
  - current or past intravenous drug users
  - healthcare providers, emergency medical & 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 levels
  - people who have exchanged sex for money, goods or favours
  - men who have sex with men who have additional risk factors including 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 & past prisoners (incarceration)
  - people on long-term haemodialysis
  - children born to HCV-infected women
  - intranasal illicit drug users - non-injecting drug users

DIAGNOSIS

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

- serological assays which detect antibody (anti-HCV) & antigen (HCVcAg)
- molecular assays that can detect & quantify HCV RNA

PRE-TREATMENT ASSESSMENT

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

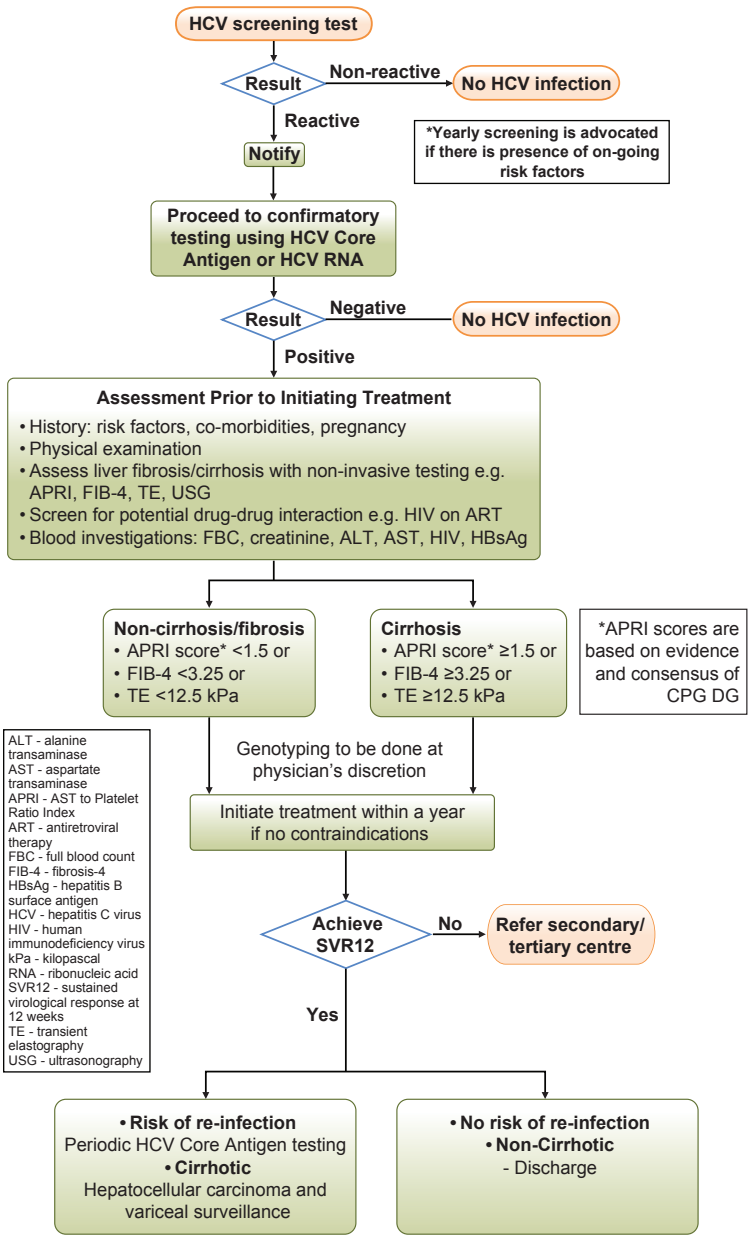
- full blood count
- liver function test (LFT) including AST
- serum creatinine
- international normalised ratio (for all cirrhotic patients)
- HIV & hepatitis B surface antigen screening
- APRI and/or FIB-4 score

Formula

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

$$\text{FIB-4 index} = \frac{\text{age ([year] x AST [IU/L])}}{\text{platelet [}10^9\text{/L] x ALT1/2 [IU/L]}} \times 100$$

ALGORITHM ON MANAGEMENT OF CHRONIC HEPATITIS C IN ADULTS



TREATMENT

DAAS 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 pegylated-interferon (PEG-IFN)/ribavirin (RBV)- experienced patient
^8 weeks treatment if patient is non-black, HIV-uninfected, & HCV RNA level is <6 million IU/mL
$8 weeks treatment if METAVIR F0-2; 12 weeks treatment if METAVIR F3
*Use with RBV
@Only for virologic relapse patient

Sofosbuvir = SOF
Ledipasvir = LDV
Grazoprevir = GZR
Elbasvir = EBR
Pibrentasvir = PIB
Voxilaprevir = VOX
Daclatasvir = DCV
Velpatasvir = VEL
Glecaprevir = GLE
Ombitasvir/ritonavir/Paritaprevir & Dasabuvir = OrPD

DOSAGE FORM, ADMINISTRATION & COMMON SIDE EFFECTS OF DAAS IN MALAYSIA

Dosage Form	Administration	Common side effects
SOF (400 mg)	1 tablet once daily	Headache, fatigue, nausea, diarrhoea
DCV (60 mg)	1 tablet once daily	
Fixed-dose SOF (400 mg)/LDV (90 mg)	1 tablet once daily	
Fixed-dose SOF (400 mg)/VEL (100 mg)	1 tablet once daily	
Fixed-dose EBR (50 mg)/GZR (100 mg)	1 tablet once daily	
Fixed-dose GLE (300 mg)/PIB (120 mg)	3 tablets once daily	
Fixed-dose paritaprevir (150 mg)/ ritonavir(100 mg)/ombitasvir (25 mg)	2 tablets once daily	Pruritus, fatigue, nausea
Dasabuvir (250 mg)	1 tablet twice daily	
Fixed-dose SOF (400 mg)/ VEL (100 mg)/VOX (100 mg)	1 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 & titrate accordingly	Fatigue, nausea, anaemia, headache *Most of the side effects are reported during the combination treatment of PEG-IFN & RBV; thus, it is impossible to correlate frequency of side effects with RBV alone
Watch out risk of hepatic decompensation/failure in patients with evidence of advanced liver disease		

- The choice of DAAs & treatment duration depends on stage of liver disease.
- HCV genotype should be considered in cirrhosis.
- SVR12 is defined as undetectable HCV RNA at 12 weeks post-treatment. It is considered equivalent to cure for hepatitis C infection.
- 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.

MONITORING

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

- More frequent monitoring e.g. FBC for drug-related adverse events is necessary for those treated with RBV.

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

FOLLOW-UP

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

For patients who have failed to achieve SVR12 (treatment failure) & those who have not received treatment, regular follow-up should be offered. HCC surveillance 6-monthly must be continued indefinitely in patients with advanced fibrosis (F3) & cirrhosis.

SPECIAL GROUPS

Human Immunodeficiency Virus Co-infection

- ART should be initiated first in patient with co-infection & DAAs should be delayed. This is to allow viral suppression & to avoid the difficulty in recognising adverse drug reaction.

- Dose increment of DCV to 90 mg when used with potent inducer of cytochrome P450 (CYP) 3A4 e.g. efavirenz, etravirine or nevirapine.
- Dose decrement of DCV to 30 mg when used with CYP 3A4 inhibitor e.g. ritonavir-boosted atazanavir, cobicistat-boosted atazanavir or elvitegravir/cobicistat.

Chronic Kidney Disease (CKD)/End-Stage Renal Disease (ESRD)

- 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 & treatment should be rapidly interrupted if renal function deteriorates.

REFERRAL

Patients with hepatitis C infection & the following features should be referred to centres with Gastroenterologist & Hepatologist for further management:

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

This Quick Reference provides key messages & a summary of the main recommendations in the Clinical Practice Guidelines (CPG) Management of Chronic Hepatitis C in Adults.

Details of the evidence supporting these recommendations can be found in the above CPG, available on the following websites:
Ministry of Health Malaysia: www.moh.gov.my
Academy of Medicine Malaysia: www.acadmed.org.my

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