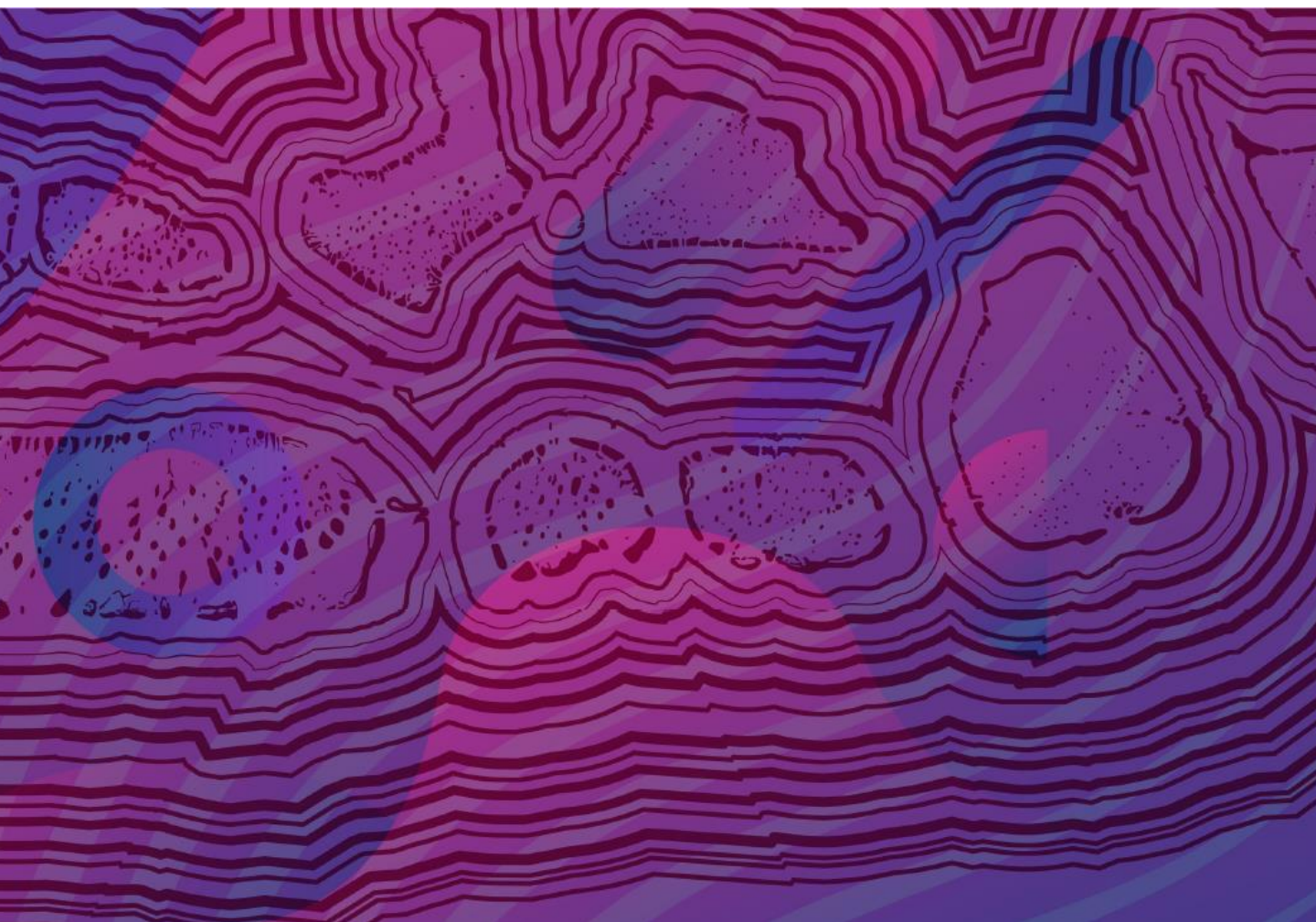


NATIONAL GUIDELINE FOR THE DIAGNOSIS AND MANAGEMENT OF HEPATITIS C



Contents

3	Abbreviations
5	Introduction
6	Background
7	Screening
10	Diagnosis
12	Assessment of patients with HCV infection
16	Treatment
21	Special situations
25	Monitoring during treatment
27	Acknowledgements
28	References

Abbreviations

AASLD	American Association for the study of Liver disease
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
Anti- HBc	Antibody to hepatitis B core antigen
Anti-HBe	Antibody to hepatitis B envelope antigen
Anti-HBs	Antibody to hepatitis B surface antigen
APRI	Aspartate aminotransferase-to-platelet ratio index
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
CHB	Chronic hepatitis B
CKD	Chronic kidney disease
DAA	Direct-acting antiviral
DNA	Deoxyribonucleic acid
EASL	European Association for the Study of the Liver
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
FIB-4	Fibrosis-4 score
GGT	Gamma-glutamyl transferase
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCP	Health care personnel
HCV	Hepatitis C virus

Abbreviations

HIV	Human Immunodeficiency virus
IGMH	Indira Gandhi Memorial Hospital
INR	International normalized ratio
LAM	Lamivudine
MSM	Men who have sex with men
NA	Nucleos(t)ide analogue
NS5B	Non-structural protein 5B (of HCV)
NS3/NS4A	Non-structural protein 3/ non-structural protein 4A (of HCV)
PegINF-a	Pegylated interferon alpha
PWID	Persons who inject drugs
RBV	Ribavirin
RNA	Ribonucleic acid
STI	Sexually transmitted infection
SVR12	Sustained virological response at 12 weeks post-treatment
TB	Tuberculosis
WHO	World Health Organization

Introduction

Worldwide, viral hepatitis caused 1.34 million deaths in the year 2015. Most viral hepatitis deaths were due to chronic liver disease and primary liver cancer (1). In May 2016, the World Health Assembly endorsed the Global Health Sector Strategy (GHSS) on viral hepatitis, which proposes to eliminate viral hepatitis as a public health threat by 2030. Elimination of chronic hepatitis infection as a public health threat requires 90% reduction in new infections and 65% reduction in mortality.

Currently, hepatitis C screening by anti-HCV antibody test is available in many of the islands in Maldives. Confirmatory HCV RNA testing will soon be available in Maldives itself.

Highly effective directly acting antiviral drugs has made hepatitis C a completely curable disease with a definitive short course of treatment. Since 2016, pan-genotypic directly acting anti-virals (DAAs) have been approved for the treatment of hepatitis C, reducing the need for genotyping in resource limited settings such as Maldives.

In line with the viral hepatitis elimination target, the WHO country office provided technical support to the HPA, Ministry of Health to develop national guidelines for diagnosis and management of Hepatitis B and Hepatitis C and a national action plan for viral hepatitis.

A consultation was held with WHO SEARO technical unit for advice regarding developing the national guideline for diagnosis and management of Hepatitis C. Taking in to consideration the limited facilities available, a practical, feasible and evidence-based treatment approach was drafted based mainly on the 2018 WHO guideline for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. Other international treatment guidelines such as the AASLD and EASL guidelines were also reviewed. The guideline was reviewed by a panel of internal reviewers and finalized after review by the WHO SEARO technical unit.

With the establishment of this guideline, DAAs will be launched in the country so that majority of patients with Hepatitis C can be treated in Maldives.

1 Background

WHO estimated that in 2015, 71 million persons were living with chronic hepatitis C virus (HCV) infection worldwide and that 399 000 died from cirrhosis or hepatocellular carcinoma caused by HCV infection (1). Among the WHO regions, the Eastern Mediterranean Region had the highest prevalence (2.3%) followed by the European Region (1.5%). Estimated prevalence of HCV in south east Asia region is 0.5%. Of the 71 million persons with HCV infection worldwide, 14 million (20%) had been diagnosed and of the 14 million diagnosed, 1.1 million (7%) had been started on treatment (1).

HCV is also found as a co-infection among the HIV population. About 2.3 million people (6.2%) of the estimated 36.7 million living with HIV globally have serological evidence of past or present HCV infection (Anti-HCV positive) (2).

Viral hepatitis screening data from IGMH, the main tertiary referral center in Maldives, for the period March 2017 to August 2019 showed that a total of 194 out of 36821 locals screened (0.5%) had evidence of past or current HCV infection (Anti-HCV positive). The 2008 behavioral and biological survey (BBS) on HIV/AIDS, found that 0.7% (85%CI: 0.018-3.66%) and 0.8% (95%CI: 0.028-4.28%) of the intravenous drug users in two cities in Maldives, Male' and Addu, respectively, had Hepatitis C infection (3).

1.1 Virology

HCV is a RNA virus belonging to the family Flaviviridae, genus Hepacivirus. HCV has 6 major genotypes with multiple subtypes. All the HCV genotypes are hepatotropic and pathogenic.

Within HCV genotype, several subtypes (designated as a, b, c, etc.) can be defined that differ in their nucleotide sequence. The prevalence of HCV genotypes and subtypes is geographically different. At present, genotype 1 is the most prevalent (46%) globally, followed by genotype 3, genotype 2 and genotype 4. HCV has a very high replicative rate with a high rate of mutations during replication. This leads to tremendous genetic diversity among HCV virus. This has led to challenges in developing pan genotypic drugs and vaccines against the HCV virus.

1.2 Transmission

Parenteral exposure is the most efficient means of hepatitis C transmission. Worldwide, **injection drug use** with shared needles has been the most common source of acute HCV infection. Worldwide 25 countries had reported that 60-80% of IDUs were anti-HCV positive and 12 countries had an anti-HCV prevalence rate of more than 80% among IDUs (4). **Health care associated** HCV transmission has been documented in several health care settings. Blood transfusions, fluid infusions, injections, organ transplantations and invasive medical and surgical interventions using contaminated equipment are potential sources of health care associated HCV infection. Unsafe blood transfusions leading to transmission of hepatitis C is still a concern in some low- and middle-income countries, where quality and coverage of blood screening are inadequate (1). In 2010, worldwide, 5% of health-care injections were given with unsterilized, reused injection devices which caused 315 000 new HCV infections worldwide (5). Since the year 2000, global efforts had reduced the risks associated with unsafe injections in health care practices. **Sexual transmission** of HCV can occur, although the risk appears to be low particularly among monogamous heterosexual partners (6).

The seroprevalence of anti-HCV is increased among heterosexuals with multiple sexual partners, men who have sex with men (MSM), and sexual partners of HIV coinfecting individuals. Perinatal transmission of HCV occurs at the time of birth in about 5 to 6 percent of infants born to anti-HCV positive women. Transmission occurs almost exclusively from mothers who are HCV-RNA positive (7). The risk of infection is approximately twofold higher in infants born to women coinfecting with HCV and HIV (8). Some procedures involved in traditional medicine such as cupping as well as tattooing and body piercing may also transmit HCV infection.

1.3 Natural History

After acute infection the majority of patients (50 to 85%) who acquire HCV develop chronic infection. Of those patients who are able to spontaneously clear HCV, most do so within 12 weeks of seroconversion, although spontaneous clearance after a longer period of follow-up has been described. Chronic HCV infection is defined as persistence of HCV RNA for more than 6 months after acute infection. Chronic HCV infection is usually slowly progressive and may not result in clinically apparent liver disease in many patients.

During the course of chronic HCV, patients may experience exacerbations with significant elevations of serum aminotransferases. Exacerbations may be associated with more rapid progression of liver disease. Approximately 5 to 30 percent of chronically infected individuals develop cirrhosis over a 20- to 30-year period of time. Patients who develop cirrhosis are at risk of further complications such as variceal hemorrhage, ascites, and encephalopathy and hepatocellular carcinoma. Estimates of the risk of developing hepatocellular carcinoma once cirrhosis has developed have varied from 0 to 3 percent per year. HCV is also associated with a variety of extrahepatic manifestations which include diabetes mellitus, hematologic diseases, such as essential mixed cryoglobulinemia and lymphoma, renal disease, particularly membranoproliferative glomerulonephritis, autoimmune disorders, such as thyroiditis, dermatologic conditions, such as porphyria cutanea tarda and lichen planus.

2 Screening

2.1 One-time hepatitis C screening

One-time Hepatitis C screening should be offered to the following persons:

- Persons with high risk behaviors like injection-drug users (current or ever, including those who injected only once), intranasal illicit drug use (via sharing of implements such as straws which could be contaminated with nasal secretions and blood)
- Persons who had ever received hemodialysis
- Possible exposure to HCV in the health care setting
- Post exposure screening for healthcare, emergency medical and public safety workers (like police, fire fighters and paramedics) after needle-stick, sharps or mucosal exposures to HCV-infected blood
- Children born to HCV-infected mothers
- Prior recipients of transfusions or organ transplants
- Solid organ donors (deceased and living)
- Persons who were incarcerated
- Persons who have multiple sexual partners
- Persons who have HIV or HBV infection
- Sexually-active persons about to start pre-exposure prophylaxis for HIV
- Unexplained chronic liver disease and/or chronic hepatitis, including elevated ALT levels

2.2 Testing for persons with ongoing risk factors

Annual screening for hepatitis C is recommended for the following persons:

- Persons who continue to inject drugs
- Persons who are on long term hemodialysis
- Men who have sex with men

3 Diagnosis

Suspected cases of HCV infection should be initially tested with Anti-HCV antibodies detected by enzyme immunoassay. If Anti- HCV antibody is found to be positive, diagnosis of current HCV infection is confirmed by detection of HCV RNA. **(Figure 1)**

Anti-HCV antibody may be negative early in the course of acute HCV infection or in patients who are profoundly immunocompromised. Average time period for appearance of Anti-HCV antibody from the time of exposure is 8–9 weeks (9). Anti-HCV can be detected in 80% of patients within 15 weeks after exposure, in ≥90% within 5 months after exposure, and in ≥97% by 6 months after exposure (9).

Anti-HCV antibody test should be repeated at 4–6 months after exposure if the baseline Anti-HCV is negative. If earlier diagnosis of HCV infection is desired, testing for HCV RNA may be performed at 4–6 weeks (9).

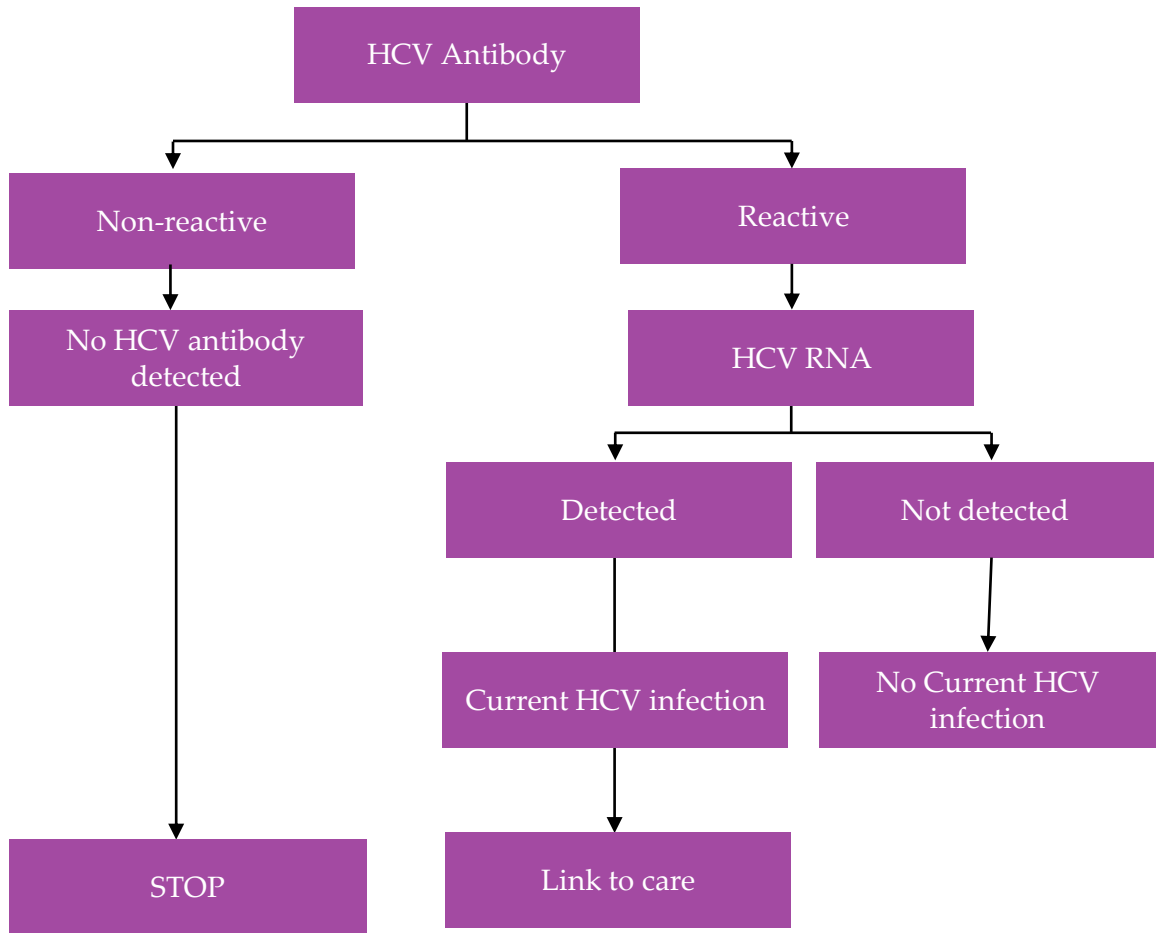
Among patients with negative HCV antibody if there is a high suspicion for HCV, consider doing HCV RNA if:

- Patient is immunocompromised
- Patient has history of exposure to HCV within the past 6months

In the setting where re infection with HCV is considered (e.g. after previous spontaneous or treatment-related viral clearance where HCV- antibody is expected to remain positive), initial screening should be done with HCV-RNA testing.

Persons who are found to have positive HCV antibody and a negative HCV RNA result should be informed that they do not have evidence of current (active) HCV infection.

All children born to HCV infected women should be tested for HCV infection. Testing is recommended with anti-HCV antibody at or after 18 months of age, as trans-placentally transferred maternal antibodies may persist for up to 18 months in the child. Testing with HCV RNA assay can be considered in the first year of life but the optimal timing of such testing is unknown (10).



Anti-HCV antibody test should be repeated if patient has history of exposure to HCV within the past 6months

Among patients with negative HCV antibody if there is a high suspicion for HCV, consider doing HCV RNA if patient is immunocompromised or has history of exposure to HCV within the past 6months.

Adapted from AASLD 2018

▲ **Figure 1:** Algorithm for diagnosis of Hepatitis C infection

4 Assessment of patients with HCV infection

Assessment of a patient with HCV infection is aimed at treating and achieving SVR. It should start with history taking, clinical examination and investigations.

Pretreatment evaluation of the risk of adverse events is based on the person's clinical information, concomitant medication and knowledge of treatment regimen to be administered.

All patients should undergo alcohol intake assessments before initiating treatment. Offer behavioral alcohol reduction intervention for persons with moderate to high alcohol intake.

All patients should receive assessment of liver fibrosis by Non-invasive tests like APRI or Fibroscan.

4.1 History and Examination

Symptomatic acute hepatitis C occurs in only about 15% of patients who are infected with hepatitis C virus (11). Symptomatic patients have nonspecific symptoms like fatigue, nausea, abdominal pain, loss of appetite, mild fever, itching, myalgia and jaundice.

Most patients with chronic hepatitis C are asymptomatic, however they often complain of fatigue or depression. Less common symptoms include arthralgias (chronic polyarthritides), paresthesia, myalgias, sicca syndrome, nausea, anorexia and difficulty with concentration.

It is also important to take history with regards to the mode of transmission and whether the patient has any high-risk factors mentioned in section 2 (Screening).

Patients with HCV may also present with extrahepatic manifestations like Autoimmune thyroiditis, B-cell non-Hodgkin's lymphoma, Lichen planus, Mixed cryoglobulinemia, Monoclonal gammopathies, Porphyria cutanea tarda.

Patients with HCV can develop cirrhosis of liver in 16% of cases over a 20-year period (12). Therefore, always look for signs of liver cirrhosis (**Table 1**).

4.2 Investigation

All patients who are investigated for Hepatitis C infection should receive the following tests:

- Complete Blood count (CBC)
- Prothrombin time / International normalized ratio (PT/INR)
- Liver Profile – Bilirubin (total /direct), liver enzymes AST/ALT/ALP/ GGT, serum Albumin
- Renal function tests – Serum Creatinine, eGFR
- Serum electrolytes
- Screening for other viruses (HBV, HIV)
- Ultrasound of abdomen
- Pregnancy test (Beta HCG)- for all women of child bearing age who are planned to be started on DAAs.

Skin, Nails and Hands

Spider naevi – small telangiectatic superficial blood vessels with a central feeding vessel

Clubbing of the hands

Leuconychia – expansion of the paler half-moon at the base of the nail

Palmar erythema – seen on the thenar and hypothenar eminence – often with blotchy appearance

Bruising

Dupuytren's contracture

Scratch marks – particularly in cholestatic liver disease

Endocrine

Gynaecomastia

Testicular atrophy

Loss of axillary and pubic hair

Others

Parotid swelling – particularly in alcohol-related liver disease

Hepatic foetor – characteristic sweet-smelling breath

Hepatic flap – a sign of encephalopathy and advanced disease

◀ **Table 1:**
Peripheral stigmata of chronic liver disease

4.3 Staging of liver fibrosis

Assessing the degree of liver fibrosis (presence or absence of cirrhosis) is an important step in the clinical management of persons with HCV infection.

Liver Biopsy is the gold standard to ascertain the degree of necroinflammation and fibrosis, and to help guide the decisions to treat. Table 2 shows the METAVIR liver-biopsy scoring system to determine the level of fibrosis. However, as this test is invasive, associated with risks of complications and due to lack of availability, we recommend using non-invasive tests to determine liver fibrosis in patients with chronic HCV infection.

METAVIR STAGE	F0	F1	F2	F3	F4
Definition	No Fibrosis	Portal fibrosis without septa	Portal fibrosis with few thin septa	Numerous septa without cirrhosis	Cirrhosis

◀ **Table 2:** METAVIR liver-biopsy scoring system

There are numerous non-invasive tests for liver fibrosis that have been validated in adults. These include tests that uses blood and serum markers for fibrosis, including APRI, FIB-4 scores and FibroTest (commercially available blood markers).

Transient elastography (FibroScan) is an ultrasound-based technique to measure liver stiffness (as a surrogate for fibrosis) and is based on the propagation of a shear wave through the liver.

APRI Score is easy to calculate using readily available laboratory investigations. Using the formula below APRI can be easily calculated.

$$\text{APRI} = \frac{\frac{\text{AST level}}{\text{AST (Upper Limit of Normal)}}}{\text{Platelet Count (10}^9\text{/L)}} \times 100$$

There are no validated exact cut-offs for specific stages of fibrosis with FibroScan. Table 3 shows the most commonly used cut-offs for F4 and ≥ F2 stages of fibrosis.

	APRI (Low cut-off)	APRI (High cut-off)	Transient Elastography (FibroScan)
Cirrhosis (METAVIR F4)	1.0	2.0	> 11-14 kPa
Significant Fibrosis (METAVIR ≥ F2)	0.5	1.5	> 7 – 8.5 kPa

◀ **Table 3: Commonly used cut-off values for detection of significant fibrosis and cirrhosis**

FibroScan is recommended where available to assess the degree of liver fibrosis, however, in places where FibroScan is not available APRI Score should be used.

Liver stiffness mean cut-off of 12.5 kPa (on FibroScan) or APRI score > 2 can be used to diagnose cirrhosis (13).

For diagnosis of cirrhosis Fibroscan has a better sensitivity (86%) than the APRI low or high cut-off (65% and 35%, respectively). FibroScan had similar specificity (87%) to the APRI high cut-off (89%).

5 Treatment

5.1 Who should be treated ?

Treatment should be offered to all patients with chronic HCV who are of age ≥ 12 years, with the exception of pregnant women.

The main goal of hepatitis C treatment is to achieve cure. Sustained virological response (SVR) 12 or SVR at 12 weeks after completion of treatment is considered a cure for HCV infection. SVR is defined as the continued absence of detectable HCV RNA for at least 12 weeks after completion of therapy (10).

Various studies have demonstrated that by achieving SVR, there is a significant reduction in incidence of HCC, liver related and all-cause mortality (14,15). Availability of highly active DAAs has revolutionized the treatment of HCV infection by achieving high rate of SVR with shorter duration of treatment. Achieving SVR not only decreases risk of HCC and mortality, it is also associated with improvement in extra-hepatic manifestations (16).

In addition, by treating all patients it reduces the risk of transmission.

5.2 Treatment counselling

Prior to initiation of treatment, patients should be counselled and educated about the goal of therapy, importance of treatment adherence, potential adverse effects and drug-drug interactions. Though SVR rates are high with DAAs, possibility of treatment failure with poor adherence should be emphasized along with limited options in case of failure. It is also important to check for treatment adherence during each follow up visit.

5.3 HCV treatment regimen

5.3.1 Treatment in Adults

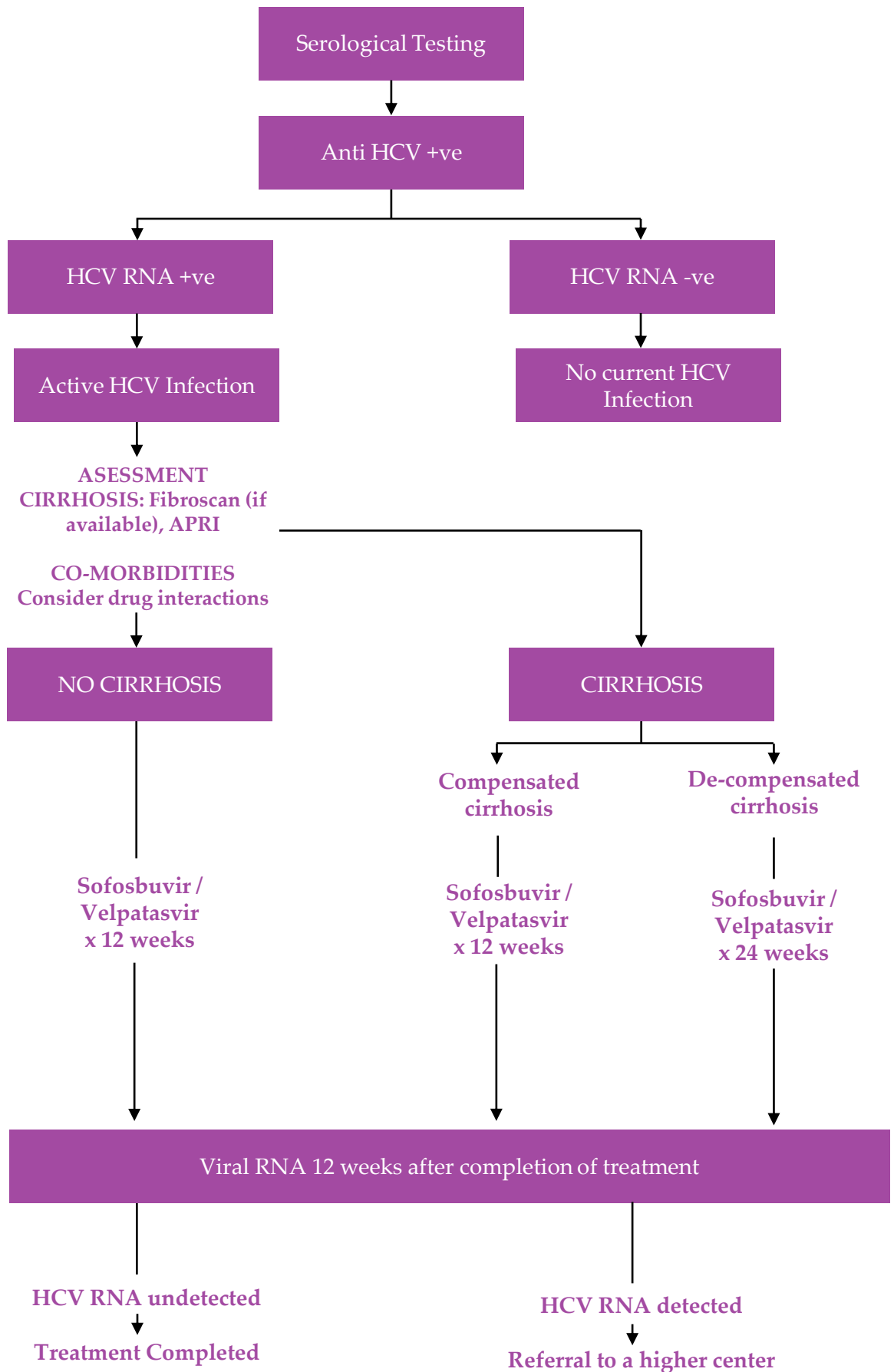
With the introduction of highly efficacious direct-acting antivirals (DAAs), treatment of HCV has been revolutionized. There are various direct-acting antivirals from four classes. **Table 4** shows currently available DAAs according to class. Currently there are 4 pangenotypic regimens recommended by WHO to treat HCV infection. These include:

- Sofosbuvir/Velpatasvir
- Glecaprevir/Pibrentasvir
- Sofosbuvir/Daclatasvir
- Sofosbuvir/Velpatasvir/voxilaprevir

NS3/4A (protease) inhibitors	NS5A inhibitors	NS5B polymerase inhibitor (nucleotide analogue)	NS5B polymerase inhibitor (non-nucleotide analogue)
Glecaprevir	Daclatasvir	Sofosbuvir	Dasabuvir
Voxilaprevir	Velpatasvir		
Grazoprevir	Ledipasvir		
Paritaprevir	Ombitasvir		
Simeprevir	Pibrentasvir		
	Elbasvir		

▲ **Table 4:** Direct-acting antivirals (DAAs) according to class

We recommend using pangenotypic DAA regimens for the treatment of adults with HCV. The patient should be assessed to determine the presence of cirrhosis to decide on the combination of DAAs and the duration. The following algorithm will guide on choosing the combination of DAAs (**Figure 2**). The HCV drugs recommended for treatment of HCV in the Maldives are listed in **Table 5**.



▲ **Figure 2:** Algorithm for management of HCV in adults

5.3.2 Treatment of adolescents (12-17 years)

Genotypic testing is recommended in adolescents with HCV (<18 years)

In adolescents aged 12- 17 years or weighing at least 35 kg, a genotype specific regimen for treatment of chronic HCV is recommended.

- In genotypes 1, 4, 5 and 6:
 - Sofosbuvir/ledipasvir for 12 weeks (in treatment-naive patients)
 - Sofosbuvir/ledipasvir for 24 weeks (in treatment-experienced and with compensated cirrhosis)
- In genotype 2: Sofosbuvir/ribavirin for 12 weeks
- In genotype 3; sofosbuvir/ribavirin for 24 weeks

Traditionally, standard of care for treating adolescents and children with HCV was using pegylated-interferon and ribavirin. These were associated with significant side-effects and the rate of achieving SVR was low. Though currently available pangenotype DAAs are effective in treating adults with HCV infection, there are no data available on use of these DAAs on individuals younger than 18 years. At the moment trials are ongoing to evaluate the use of these pangenotypic DAAs in adolescents (>12 years) and even younger children. There are few DAA regimens (sofosbuvir/ledipasvir and sofosbuvir/ribavirin) available for treatment of HCV in adolescents (≥ 12 years) (17,18). As these regimens are not pangenotypic, genotypic testing is required to decide on the regimen of DAA.

5.3.3 Treatment of Children aged less than 12 years

At present, the only licensed, treatment option for children younger than 12 years is interferon based treatment (13). As these regimens are associated with significant side-effects, and potentially irreversible post-therapy side-effects, such as thyroid disease, type 1 diabetes, ophthalmological complications and growth impairment (13), it is recommended that treatment be deferred until children either reach 12 years or until DAA regimens are approved for children less than 12 years.

	Pangenotypic regimen	Genotype specific regimen (for patients 12 to 17 years)	
DAA regimen	Sofosbuvir/Velpatasvir	Sofosbuvir/ledipasvir	Sofosbuvir/Ribavirin
Formulation	400mg of Sofosbuvir and 100mg of velpatasvir (fixed dose combination)	400 mg of sofosbuvir and 90mg of ledipasvir (fixed dose combination)	400mg of Sofosbuvir, 200mg of Ribavirin, individual drugs
Dosage	One tablet once daily	One tablet once daily	One tablet of sofosbuvir daily WITH dose of ribavirin based on weight: <75kg: 1g daily in divided doses, ≥75 kg: 1.2g daily in divided doses (ribavirin should be started with 600 mg daily and dose increased as tolerated)
Duration	Usually 12 weeks, 24 weeks in decompensated cirrhosis	12 weeks with HCV genotype 1, 4, 5 and 6	12 weeks in adolescents (12-17 years) with HCV genotype 2. 24 weeks in adolescents (12-17 years) with HCV genotype 3
Cirrhosis	Safe even in decompensated cirrhosis	Can be used in compensated cirrhosis	Can be used in compensated cirrhosis
CKD	Based on pharmacokinetic data obtained from studies involving HCV infected patients with ESRD requiring dialysis, Sofosbuvir and Velpatasvir may be used.		

▲ **Table 5:** Recommended pangenotypic and genotype specific regimens

5.3.2 Treatment of persons with treatment failure

The rate of SVR for highly efficacious DAAs are generally high with more than 90% achieving SVR across all genotypes (19). And those who do not achieve SVR following DAA treatment are considered to have treatment failure. Only limited treatment options are available to treat this group of patients (13). Hence, compliance should be ensured during treatment and potential drug-drug interactions that may impact the efficacy of DAAs should be considered. At present only one pan-genotypic regimen (combination of sofosbuvir, velpatasvir and voxilaprevir) is approved for the retreatment of patients with treatment failure who have been previously treated with any combination of DAAs (13). Patients with treatment failure should be referred to an expert with experience in managing patients with treatment failure.

6 Special situations

6.1 HIV/HCV Co-infection

Sofosbuvir/daclatasvir should be the preferred DAA regimen for treatment of HIV/HCV co-infection

HIV/HCV co-infected patients are usually more at risk of disease progression than HCV monoinfected patients (20). Even in those patients whose HIV viral load is suppressed with potent ART, their risk of hepatic decompensation is higher compared to HCV monoinfected patients (21). With the availability of highly active DAA, the treatment outcome of HIV/HCV co-infection is comparable to those with HCV monoinfection(22). There are important drug-drug interactions with pangenotypic DAAs and ART. Therefore, it is important to check for these drug-drug interactions before prescribing these medications. **(Table 6)**. Sofosbuvir/velpatasvir should not be used with efavirenz, nevirapine (10). Daclatasvir requires dose adjustments. Daclatasvir requires dose adjustment with increasing dose daclatasvir to 90mg in those taking efavirenz (10). Dose of daclatasvir decreased to 30mg in some other ARTs (ritonavir-boosted atazanavir, cobicistat-boosted atazanavir, elvitegravir/cobicistat) (10). The duration of sofosbuvir/daclatasvir is usually 12 weeks. In cases of decompensated cirrhosis, the duration of sofosbuvir/daclatasvir is prolonged to 24 weeks.

DAAAs	ABC	ATZ/r	DRV/r	DTG	EFV	LPV/r	NVP	RAL	TDF	TAF	ZDV	XTC
Daclatasvir		Adjust dose			Adjust dose							
Glecaprevir/ pibrentasvir												
Sofosbuvir												
Sofosbuvir/ ledipasvir		Monitor for renal toxicity when used with TDF	Monitor for renal toxicity when used with TDF		Monitor for renal toxicity when used with TDF	Monitor for renal toxicity when used with TDF			Monitor for renal toxicity when used with EFV or boosted protease inhibitor			
Sofosbuvir / Velpatasvir		Monitor for renal toxicity when used with TDF	Monitor for renal toxicity when used with TDF			Monitor for renal toxicity when used with TDF			Monitor for renal toxicity			

Red = Do not co-administer

Yellow = Possible toxicity / interaction / dose adjustment, as specified

Green = No interaction; can be co-administered

ABC: abacavir; ATZ/r: atazanavir/ritonavir; DRV/r: darunavir/ritonavir; DTG: dolutegravir; EFV: efavirenz; LPV/r: lopinavir/r; NVP: nevirapine; RAL: raltegravir; ZDV: zidovudine; TDF: tenofovir disoproxil fumarate; XTC: emtricitabine/lamivudine; TAF: tenofovir alafenamide

Source: *Guideline for the care and treatment of persons diagnosed with chronic hepatitis C infection. Geneva WHO; 2018. (13)*

Table 6: Drug–drug interactions between antiretrovirals and direct-acting antivirals.



6.2 HBV/HCV Co-infection

HBV/HCV co-infection may be common in certain populations especially among PWID. Prior to commencing on DAAs, patients with HCV should be tested for HBs antigen, anti-HBc antibodies and anti-HBs antibodies. When HBV-HCV co-infection is present, HCV infection should be treated following the same principles as applied to HCV monoinfected patients. There is a potential risk of HBV reactivation during or after treatment with DAAs. In HBV-HCV-coinfected patients with cirrhosis or those meeting recommended criteria for HBV treatment, HBV antiviral therapy should be started concurrently with DAA therapy.

In those who do not meet treatment criteria for HBV treatment, AST, ALT can be done at 3 monthly intervals from the start of DAA treatment until 3 months after completion of treatment. HBV DNA viral load should be done at the time of doing HCV viral load to assess SVR 12.

6.3 Chronic Kidney Disease

HCV infection is prevalent in those with CKD. In patients with mild to moderate renal impairment (eGFR > 30ml/min/1.73 m²), DAA combinations can be used without any dose adjustments. Glecaprevir/pibrentasvir is a pangenotypic DAA regimen that has safety and efficacy data in patients with chronic kidney disease and HCV infection (23). Its availability is however limited.

Sofosbuvir based regimens are generally avoided in patients with severe renal impairment (eGFR <30ml/min/1.73 m²). However, there are some evidence on use of sofosbuvir based regimens in patients with severe renal impairment (24,25). If there is no other choice than a sofosbuvir-based regimen, close monitoring is required and treatment should be interrupted if renal function deteriorates.

6.4 TB/HCV Co-infection

As persons at risk of HCV infection are also at risk of infection with TB, initial evaluation prior to commencing HCV treatment should include screening for active TB. Concurrent treatment of HCV and TB should be avoided as most DAAs interact with anti TB drugs and may lead to increased or decreased level of DAAs (13). As active TB may involve higher risk of secondary transmission and other complications in the short-term, TB should be treated before treating HCV. Monitoring of liver function test should be done closely as risk of anti-tuberculosis drug-induced liver injury is higher than those with TB mono-infection (26).

6.5 Persons with cirrhosis

The risk of cirrhosis is high in those with HBV and/or HIV coinfection and in those who consume excessive alcohol. Prior to initiation of HCV treatment, patients should be screened for cirrhosis. Person with cirrhosis including those who have achieved SVR should be considered for six-monthly HCC screening.

DAAs may cause severe complications in patients with decompensated cirrhosis (presence of ascites, jaundice, history of hepatic encephalopathy and variceal bleed or Child-Pugh score ≥ 7 [Class B and C]). Therefore, treatment of such patients should ideally take place in centres with expertise in managing complications. In cases of decompensated cirrhosis, the duration of is prolonged to 24 weeks.

6.6 Women of childbearing age

At present there are no data on safety of DAAs during pregnancy and lactation. Ribavirin is contraindicated in pregnancy due to its known teratogenicity. Its risk of teratogenicity persists for 6 months even after stopping it, for both men and women taking ribavirin (10). Hence effective contraception should be used during and for six months after completion of therapy.

All pregnant women with HCV infection should receive appropriate prenatal and intrapartum care based on their individual obstetric risk(s) and currently there is no known intervention to reduce mother to child transmission of HCV.

7 Monitoring during treatment

7.1 Monitoring for adherence and adverse effects of treatment

Patients should be followed up at monthly intervals during treatment to assess treatment adherence and adverse effects of drugs. DAA regimens are generally well tolerated with only minor adverse effects. Most common adverse effects of DAAs are fatigue, headache insomnia and nausea. Patients on Ribavirin should be monitored more closely as it is associated with dose dependent hemolytic anemia. Treatment adherence should be checked and reinforced at each follow up visit. Monitoring framework recommended for patients on DAA treatment is shown in (Table 7).

7.2 Monitoring of treatment response

Following completion of treatment with DAA, SVR should be assessed at 12 weeks after the end of therapy. Ideally, the same assay from the same laboratory, should be used in each patient to measure HCV RNA at different time points, in order to assure consistency of result.

Time	DAA alone			DAAs + Ribavirin		
	CBC, S.Creatinine, LFT	HCV viral load	adverse effects	CBC, S.Creatinine, LFT	HCV viral load	adverse effects
Baseline	√	√		√	√	
Week 2				√		√
Week 4	√		√	√		√
Week 8			√	√		√
Week 12	√		√	√		√
Week 12 after completion of treatment		√			√	

▲ **Table 7:** Monitoring schedule before and during DAA treatment

7.3 Drug-drug interaction

Drug-drug interaction for DAAs varied. Commonly prescribed drugs that may lead to drug-drug interactions include antiretrovirals (ARVs) for HIV, proton pump inhibitors, statins and antidepressants. For a comprehensive listing of drug-drug interactions, consult the University of Liverpool webpage on hepatitis drug interactions (<http://www.hep-druginteractions.org/>) prior to prescribing.

7.4 Post-treatment follow-up of patients who achieve SVR

Those patients without cirrhosis who achieve SVR are considered as cured (27). Those with advanced fibrosis and cirrhosis who achieve SVR should remain under surveillance for HCC and monitoring for complications of cirrhosis. Risk of re-infection should be emphasized to patients with ongoing risk.

Acknowledgements

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