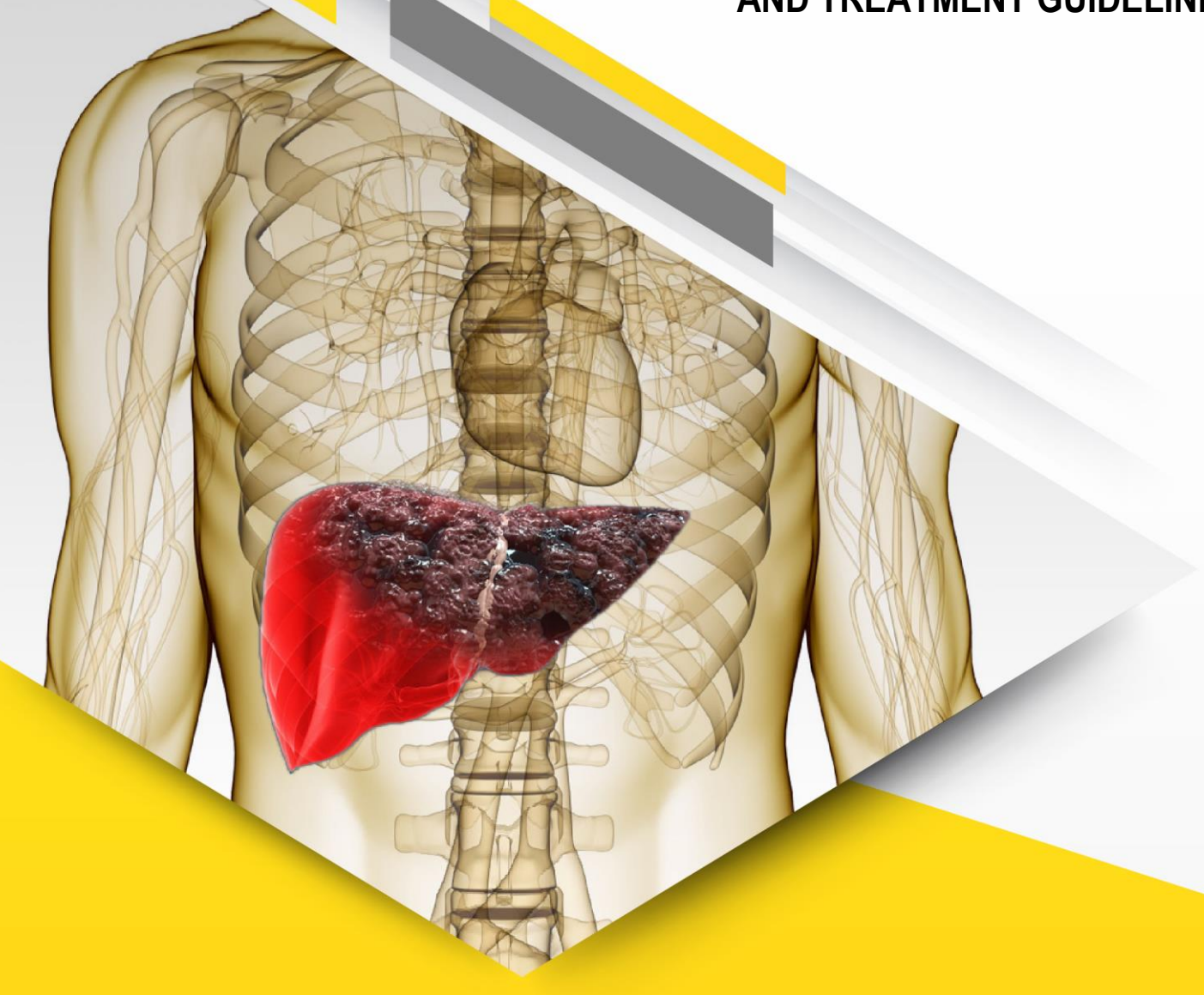
HEPATITIS C

SCREENING, TESTING AND TREATMENT GUIDELINES



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This document is developed as a guideline to all health care providers involved in the screening, care and treatment of HCV infected person. It will also be used as a training reference in educating and upgrading the knowledge among health care providers.

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ABBREVIATIONS AND ACRONYMS

AASLD	American Association for the Study of Liver Diseases
ALT	Alanine Aminotransferase
APRI	AST (aspartate aminotransferase) to Platelet Ratio Index
CPS	Child Pugh Score
DAA	Direct Acting Antiviral
EASL	Europan Association for the Study of Liver
HAART	Highly Active Antiretroviral Therapy
HCC	Hepatocecullar Carcinoma
HCV	Hepatitis C Virus
HIV	Human Deficiency Virus
IFN	Interferon
IMR	Institute of Medical Research
LFT	Liver Function Test
MoH	Ministry of Health
MELD	Model for End Stage of Liver Disease
Peg-IFN	Pegylated Interferon
PHC	Primary Health Care
PWID	People Who Inject Drugs
RBV	Ribavirin
RDTs	Rapid diagnostic tests
RNA	Ribonucleic acid
SVR	Sustained virological response

GLOSSARY AND TERM

Acute HCV	Presence of HCV within six months of acquiring infection
Chronic HCV	Continued presence of HCV six months or more after acquiring Infection
Cirrhosis	An advanced stage of liver disease characterized by extensive hepatic fibrosis, nodularity of the liver, alteration of liver architecture and disrupted hepatic circulation.
Decompensated Cirrhosis	Clinical features are portal hypertension (ascites, variceal haemorrhage and hepatic encephalopathy), coagulopathy or liver insuffiency (jaundice). Other clinical features of advanced liver disease/cirrhosis may include : hepatomegaly, splenomegaly, pruritus, fatique, arthralgia, palmer erythema and oedema.
Hepatocelluar Carcinoma (HCC)	Primary cance of the liver arising from the hepatocytes and may be a complication of chronic hepatitis B or C infection.
Liver Fuction Test	These tests provide a gauge of how damaged the liver cells are. For people with hepatitis C, the enzyme Alanine Aminotransferase (ALT) is one of the most relevant enzymes measured by an LFT. ALT is released into the blood when liver cells are inflamed.
Rapid Diagnostic Test (RDT)	Immunoassays that detect antibodies or antigens and can give a result in less than 30 minutes. Most RDTs can be performed with capillary whole blood collected by finger-prick sampling.
Serological Assays	Assays that detect the presence of either antigens or antibodies, typically in serum or plasma but also in capillary / venous whole blood and oral fluid. These include rapid diagnostic tests (RDTs), and laboratory-based immunoassays e.g enzyme immunoassays (EIAs), chemiluminescence immunoassays (CLIAs) and electro-chemiluminescence immunoassays (ECLs)
Sustained virological response (SVR)	Undetectable HCV RNA three or six months after the end of treatment
Viramic infection	Hepatitis C infection associated with presence of virus in the blood (as measured by HCV RNA) and often referred to as active, ongoing or current infection

1.0
INTRODUCTION

1.0 INTRODUCTION

Hepatitis C (HCV) infection is one of major public health challenge, comparable with other major communicable disease such as HIV, Tuberculosis, and Malaria. Globally, it is reported that 71 milion people were living with chronic hepatitis C in 2015 with prevalence of 1.0%. In Malaysia, it was estimated that 453,700 people living with HCV infection in 2009. Malaysia is on the verge of treating more people living with HCV in the near future aligned with WHO's Global Strategy on Viral Hepatitis targets to end HCV by 2030. A guideline is developed to be used as reference to all health care providers involved in the screening, care and treatment of HCV infected person.

1.1 HEPATITIS C INFECTION

For the past decades, Hepatitis C virus (HCV) has become one of the major public health concerns due to its long-term consequences. With the availability of direct- acting antivirals (DAAs) curing at faster and higher rates, they set the scene for elimination of HCV as a major public health threat. It is estimated that 2.5% of population aged 15-64 years were living with HCV infection of which 59% (95% CI: 50%; 68%) acquired their infection through injecting drugs. The most common genotypes found are genotype 3 and 1.

The number of HCV infection captured in the Ministry of Health's (MoH) database shows an upward trend for the past 10 years due to the increased awareness among health care workers in notifying the disease and public especially those from high risk groups. Parenteral exposure via blood or blood products leads to infection in the majority cases, and many of the intravenous drug users become infected by repetitive exposure to contaminated injection equipment. There are some well- documented instances of acute HCV occurring after a defined sexual exposure with person with HCV infection. People who have received blood/ blood product transfusion are no doubt at high risk of HCV infection but the good practice of blood donor screening and blood donation deferral program established since 1992 has managed to curb HCV transmission through the parenteral route.

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% to 70% of chronically infected person will eventually develop chronic liver disease; 5% to 20% will develop cirrhosis of the liver, and 1% to 5% will die of cirrhosis or hepatocellular carcinoma.

The HCV-related disease burden is already high and is forecasted to rise steeply over the coming decades under the current intervention. Scaling up screening, care and treatment of HCV is crucial to address the high HCV disease burden in the country and reduce transmission.

1.2 DRUGS AVAILABLE IN MALAYSIA FOR HEPATITIS C

Direct Acting Antivirals
• Sofosbuvir
• Sofosbuvir / Ledipasvir
• Paritaprevir / Ombitasvir / Ritonavir
• Dasabuvir
• Daclatasvir
• Elbasvir/ grazoprevir

Interferons
• Pegylated interferon alpha-2a
• Pegylated interferon alpha-2b

Other
• Ribavirin

2.0 SCREENING AND TESTING

2.0 SCREENING AND TESTING

Screening for HCV infection requires an initial serologic screening test followed by an HCV RNA (Quantitative) to confirm the presence of viraemia and therefore chronic infection, as 15–45% of those initially infected will spontaneously clear the virus, usually within six months of acquiring the infection. Persons who do not clear HCV within six months are defined as having chronic HCV infection and are diagnosed either during routine screening or when they develop symptoms of HCV-associated liver disease.

2.1 SCREENING

2.1.1 Who to screen for HCV

Target person / population who have increased risk of HCV infection or exposure are strongly recommended to be screened.

Targeted person / Populations at increased risk of HCV infection	
a) People who inject drugs (PWID)	PWID have the highest risk of infection. Globally, the prevalence of HCV is 67% among PWID. In Malaysia, 59% HCV infection acquired through injecting drugs.
b) Intranasal illicit drug use	Non-injecting drug use (e.g. through sharing of inhalation equipment for cocaine) is associated with a higher risk of HCV infection. The present of blood and HCV RNA in the nasal secretions of HCV-positive long-term drug sniffers can be transferred onto sniffing implements (i.e., straws) during simulated intranasal drug use.
c) Recipients of blood / blood products / clotting factor concentrates / organ transplant before July 1992	There is a high risk of HCV infection via transfusion of unscreened blood and blood products. In 1992, Ministry of Health Malaysia has outlined that all donated blood and blood products are to be screened for HCV.

Targeted person / Populations at increased risk of HCV infection	
d) persons on long-term hemodialysis (ever)	Risk of HCV infection among dialysis patient is high in condition where level of infection-control practices is low / ignored. Risk of HCV infection also varies depending upon the frequency of medical procedures (i.e. number of injections/person/year). A study reported that 53.9% of patient on dialysis from 1985 and September 1991 were positive for anti-HCV.
e) healthcare, emergency medical, and public safety workers after needle sticks,sharps, or mucosal exposures to HCV-infected blood	Risk of HCV infection varies depending upon the frequency of medical procedures (i.e. number of injections/person/year) and level of infection-control practices. High frequency of injections and low level of infection control can result in high prevalence of HCV in the general population
f) persons with percutaneous / parenteral exposures in an unregulated setting	Tattoo recipients have higher prevalence of HCV compared with persons without tattoos (odds ratio = 2.24, 95%CI 2.01,2.50)
g) children born to HCV-infected women	HCV transmission risk is estimated as 4–8% among mothers without HIV infection Transmission risk is estimated as 17-25% among mothers with HIV infection.
h) persons who were ever incarcerated	persons who were incarcerated are at risk for Hepatitis C because many people in jails or prisons already have Hepatitis C.
i) People with HIV infection	Persons with HIV infection, in particular MSM, are at increased risk of HCV infection through unprotected sex.
j) People with sexual partners who are HCV-infected	There is low or no risk of sexual transmission of HCV among HIV-uninfected heterosexual couples and HIV-uninfected men who have sex with men (MSM). The risk of sexual transmission is strongly linked to pre-existing HIV infection.
k) Unexplained chronic liver disease and/or chronic hepatitis including elevated alanine amino-transferase levels	Approximately 60% to 70% of chronically (HCV) infected person will eventually develop chronic liver disease.
l) Solid organ donors (deceased and living)	There is a risk of HCV infection in unscreened organ donors.

2.1.2 HCV Screening Test

Screening test	• HCV serological testing • Marker: anti HCV (HCV Antibody) • Interpretation: positive HCV antibody indicates evidence of past or present infection. • Antibody-based assays are unable to detect infection soon after acquisition of HCV infection, as antibodies may not be detected for 2–3 months in an individual who has been recently infected.

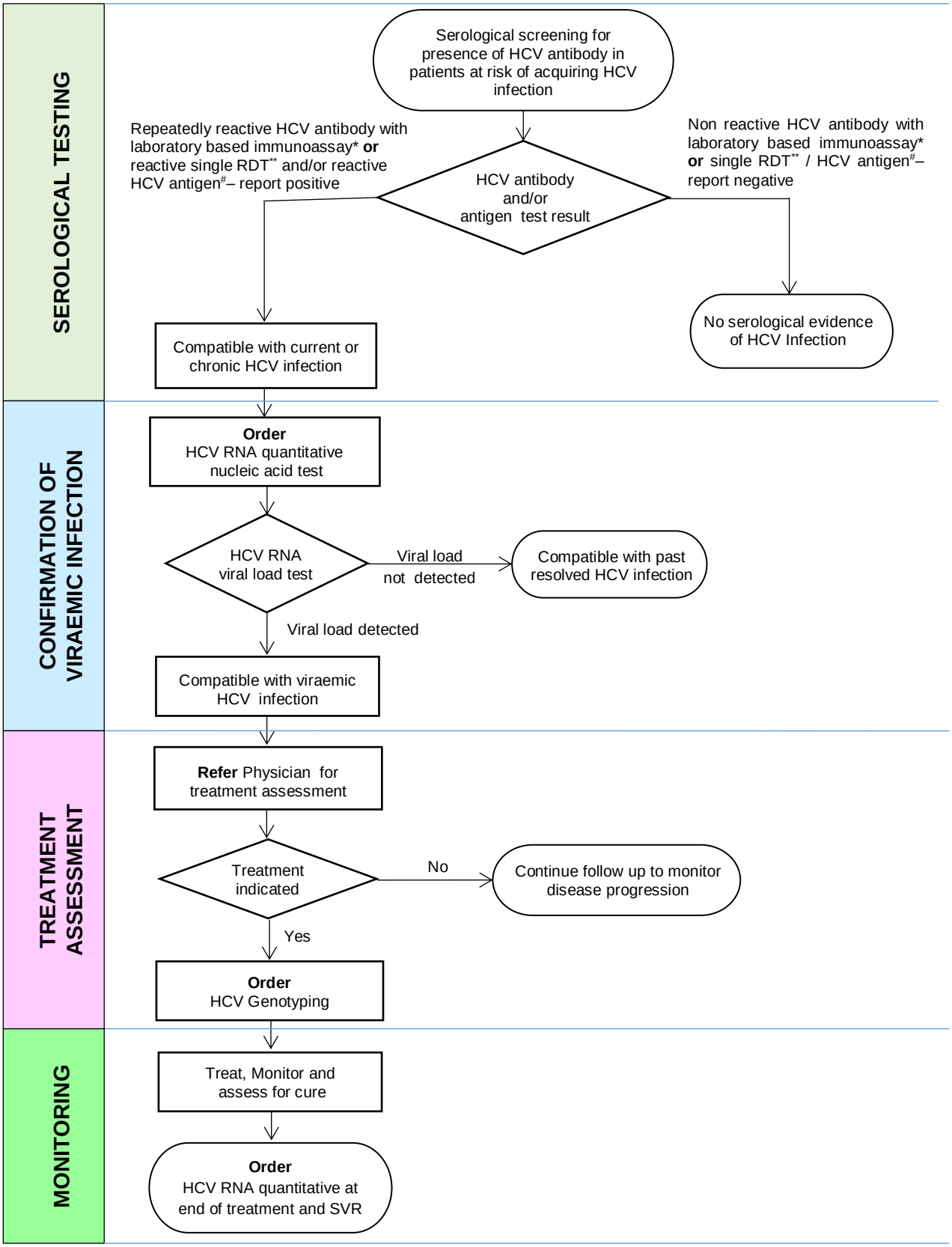
Where to do HCV screening	• HCV screening to be carried out by hospital / central regional laboratories
	• Suspected HCV case who have been identified at primary health care or hospital without screening facilities will send blood to the respective hospital / central regional laboratories
	• Rapid diagnostic tests (RDTs)
	  • Can be considered to be used as a screening tool provided it comply with the specification requirement and validated by Institue of Medical Reasearch (IMR) / National Public Health Laboratory (MKAK) and preferable certified by WHO.
	  • RDTs are single-use disposable assays that are provided in simple-to-use formats that generally require no additional reagents except those supplied in the test kit.
	  • They can also be used in primary health cares facilities and outreach programmes (e.g. prison services, prevention and treatment services for people who use drugs).

2.2 CONFIRMATION AND MONITORING

Confirmation and monitoring test for HCV is to be carried out by hospital / central regional laboratories.

Algorithm for detection, treatment, and monitoring for HCV as in Figure 1.

FIGURE 1 : TESTING ALGORITHM FOR DETECTION, TREATMENT AND MONITORING OF VIRAEMIC HCV INFECTION



Notes :

* Laboratory-based Immunoassays include Enzyme Immunoassay (EIA), chemoluminescence immunoassay (CLIAs), and electrochemoluminescence assay (ECL)

** Once locally evaluated and reliable rapid test kit is recommended for use nationwide

\# may include 4th generation combined antibody/antigen assays, if available

3.0
TREATMENT

3.0 TREATMENT

Treatment for HCV infection will differ in regime and duration depending on the status of infection, genotype and complication of the disease.

About 20% of those exposed to HCV will develop acute hepatitis and recovered without requiring treatment. In these cases, acute hepatitis C can be suspected if the clinical signs and symptoms are compatible with acute hepatitis (alanine aminotransferase [ALT] >10 times the upper limit of normal, and jaundice) in the absence of a history of chronic liver disease or other causes of acute hepatitis, and/or if a likely recent source of infection is identifiable. Most patients with acute hepatitis C are asymptomatic, but a high rate of chronicity is expected (50–90%).

Patients with acute hepatitis C, delay in treatment initiation is acceptable as monitoring for spontaneous clearance is recommended for a minimum of 6 months. When the decision is made to initiate treatment after 6 months, treating as chronic hepatitis C is recommended owing to high safety and efficacy. There is currently no indication for antiviral therapy as post-exposure prophylaxis in the absence of documented HCV transmission.

Up to 85% of those exposed to HCV will develop chronic hepatitis and require treatment. Genotyping of the virus that the infected person had is warranted before any initiation of therapy. The most common genotypes in Malaysia are genotype 3 (56%) and genotype 1 (39%) where as the less common are genotype 2 (4%) and genotype 4 (1%). It was found the genotype 2 or 3 have a better prognosis than those with genotype 1 or 4.

3.1 FACTORS TO BE CONSIDERED IN PRIORITISING TREATMENT

i. Patient's willingness to start and adhere strictly to treatment and follow up

ii. Increased risk of death (e.g. advanced fibrosis and cirrhosis, post-liver transplantation)

iii. Risk of accelerated fibrosis (e.g. HIV or HBV co-infection, metabolic syndrome)

iv. Extrahepatic manifestations and evidence of end-organ damage (e.g. debilitating fatigue, vasculitis and lymphoproliferative disorders)

v. DAA options that are available

vi. Patient with no drug-drug interaction with current treatment (eg HAART, amiodarone)

3.2 INDICATIONS FOR TREATMENT: WHO SHOULD BE TREATED?

i. All treatment-naive and treatment-experienced patients with compensated or decompensated chronic liver disease due to HCV must be considered for therapy

ii. Treatment should be considered without delay in:

- patients with including decompensated (Child-Pugh B or C) cirrhosis,
- patients with HCV related conditions (e.g. symptomatic vasculitis associated with HCV-related mixed cryoglobulinaemia, HCV immune complex-related nephropathy and non-Hodgkin B cell lymphoma),
- patients with HCV recurrence after liver transplantation, and
- individuals at risk of transmitting HCV (active PWID, men who have sex with men with high risk sexual practices, women of child-bearing age who wish to get pregnant, haemodialysis patients and incarcerated individuals)

iii. Treatment is not recommended in patients with limited life expectancy due to non-liver-related comorbidities.

iv. All treatment-naive and treatment-experienced patients with compensated or decompensated chronic liver disease related to HCV, who are willing to be treated and who have no contraindications to treatment, must be considered for therapy.

v. Treatment must be considered without delay in:

- patients with significant fibrosis (METAVIR score F2 or F3) or cirrhosis (METAVIR score F4), including decompensated cirrhosis
- patients with clinically significant extrahepatic manifestations (e.g. symptomatic vasculitis associated with HCV-related mixed cryoglobulinaemia, HCV immune complex-related nephropathy and non-Hodgkin B cell lymphoma)
- patients with HCV recurrence after liver transplantation
- patients at risk of a rapid evolution of liver disease due to concurrent comorbidities (non-liver solid organ or stem cell transplant recipients, diabetes); and
- individuals at risk of transmitting HCV (active PWID, men who have sex with men with high-risk sexual practices, women of childbearing age who wish to get pregnant, haemodialysis patients, incarcerated individuals).

PWID and men who have sex with men with high-risk sexual practices should be made aware of the risk of reinfection and should take preventive measures after successful treatment.

Patients with decompensated cirrhosis and an indication for liver transplantation with a MELD score of 18–20 will benefit from transplantation first and antiviral treatment after transplantation, because the probability of significant liver function improvement and delisting is low. However, patients with a MELD score of 18–20 with a waiting time before transplantation expected to be more than six months can be treated for their HCV infection.

3.3 RECOMMENDATION FOR WHEN AND IN WHOM TO INITIATE TREATMENT

i. Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. Patients with short life expectancies owing to liver disease should be managed in consultation with an expert.

ii. Person with cirrhosis (including those who achieved SVR) should be screened for HCC with 6 monthly USG examination and AFP estimation, and should have endoscopy every one or two years to exclude varices.

3.4 RECOMMENDED TREATMENT REGIME

Recommended preferred regime with treatment durations for

i. person without cirrhosis (Table 1)

ii. person compensated cirrhosis CPS A (Table 2)

iii. person decompensated cirrhosis CPS B & C (Table 3)

Table 1 : Summary of recommended preferred regimes with treatment durations, person without cirrhosis

Genotype		Inteferon/ Ribavirin	Sofosbuvir/ Daclatasvir	Sofosbuvir/ Ledipasvir	Sofosbuvir/Ribavirin	Sofosbuvir/ Velpatasvir	Sofosbuvir/ Semiprevir	Ombitasvir/Paritaprevir/ Ritonavir/ Dasabuvir	Grazoprevir/Elbasvir
Genotype 1a	treatment naive	48 weeks	12 weeks	8-12 weeks	No	12 weeks	No	12 weeks with Ribavirin	12 wk, no Ribavirin ifHCV RNA≤800,000 (5.9log) IU/ml or 16 wk with Ribavirin if HCV RNA>800,000 (5.9log) IU/mlb
	treatment experience		12 wk with Ribavirin Or 24 wk, no Ribavirin	12 wk with Ribavirin or 24 wk, no Ribavirin					
Genotype 1b	treatment naive		12 weeks	8-12 weeks	No	12weeks	No	8-12 weeks	12 weeks
	treatment experience			12 weeks			No	12 weeks	
Genotype 2	treatment naive	24 weeks	12 weeks	No	12 weeks	12 weeks	No	No	No
	treatment experience								
Genotype 3	treatment naive	24 weeks	12 weeks	No	24 weeks	12 weeks	No	No	No
	treatment experience		12 wk with Ribavirin Or 24 wk, no Ribavirin			12 wk with Ribavirin Or 24 wk, no Ribavirin			
Genotype 4	treatment naive	48 weeks	12 weeks	12 weeks	No	12 week	12 weeks	No	12 weeks
	treatment experience		12 wk with Ribavirin or 24 wk, no ribavirin	12 wk with Ribavirin or 24 wk, no ribavirin			12 wk with Ribavirin or 24 wk, no ribavirin		12 wk, no Ribavirin if HCV RNA≤800,000 (5.9log) IU/ml or 16 wk with Ribavirin if HCV RNA>800,000 (5.9log) IU/mlb
Genotype 5	treatment naive		12 weeks	12 weeks	No	12 weeks	No	No	No
	treatment experience		12 wk with Ribavirin or 24 wk, no Ribavirin	12 wk with Ribavirin or 24 wk, no Ribavirin					
Genotype 6	treatment naive	48 weeks	12 weeks	12 weeks	No	12 weeks	No	No	No
	treatment experience		12 wk with Ribavirin or 24 wk, no Ribavirin	12 wk with Ribavirin or 24 wk, no Ribavirin					

Table 2 : Summary of recommended preferred regimes with treatment duration, person compensated cirrhosis CPS A

Genotype		Inteferon/ Ribavirin	Sofosbuvir/ Daclatasvir	Sofosbuvir/ Ledipasvir	Sofosbuvir/ Ribavirin	Sofosbuvir/ Velpatasvir	Sofosbuvir/ Semiprevir	Ombitasvir/Paritaprevir / Ritonavir/Dasabuvir	Grazoprevir/Elbasvir
Genotype 1a	treatment naive	48 weeks	12 weeks	8-12 weeks	No	12 weeks	No	12 weeks with Ribavirin	12 wk, no Ribavirin ifHCV RNA≤800,000 (5.9log) IU/mlor16 wk withribavirin if HCV RNA>800,000 (5.9log) IU/mlb
	treatment experience		12 wk with Ribavirin or 24 wk, no Ribavirin	12 wk with Ribavirin Or 24 wk, no Ribavirin					
Genotype 1b	treatment naive		12 weeks	12 weeks	No	12weeks	No	12 weeks	12 weeks
	treatment experience								
Genotype 2	treatment naive	24 weeks	12 weeks	No	12 weeks	12 weeks	No	No	No
	treatment experience								
Genotype 3	treatment naive	24 weeks	24 week with Ribavirin	No	24 weeks	12 wk with Ribavirina or 24 wk, no Ribavirin	No	No	No
	treatment experience								
Genotype 4	treatment naive	48 weeks	12 weeks	12 weeks	No	12 week	12 weeks	No	12 weeks
	treatment experience		12 wk with Ribavirin Or 24 wk, no Ribavirin	12 wk with Ribavirin Or 24 wk, no Ribavirin			12 wk with Ribavirin Or 24 wk, no Ribavirin		12 wk, no Ribavirin if HCV RNA ≤800,000 (5.9log) IU/ml or 16 wk with Ribavirin if HCV RNA>800,000 (5.9log) IU/mlb
Genotype 5	treatment naive		12 weeks	12 weeks	No	12 weeks	No	No	No
	treatment experience		12 wk with Ribavirin Or 24 wk, no Ribavirin	12 wk with Ribavirin or 24 wk, no Ribavirin					
Genotype 6	treatment naive	48 weeks	12 weeks	12 weeks	No	12 weeks	No	No	No
	treatment experience		12 wk with Ribavirin or 24 wk, no Ribavirin	12 wk with Ribavirin or 24 wk, no Ribavirin					

Table 3 : Summary of recommended preferred regimes with treatment durations, person decompensated cirrhosis CPS B & C

	Sofosbuvir / Daclatasvir	Sofosbuvir / Ledipasvir	Sofosbuvir / Velpatasvir
Genotype 1	12 weeks with Ribavirin	12 weeks with Ribavirin	12 weeks with Ribavirin
Genotype 2	12 weeks with Ribavirin	No	12 weeks with Ribavirin
Genotype 3	24 weeks with Ribavirin	No	24 weeks with Ribavirin
Genotype 4	12 weeks with Ribavirin	12 weeks with Ribavirin	12 weeks with Ribavirin
Genotype 5	12 weeks with Ribavirin	12 weeks with Ribavirin	12 weeks with Ribavirin
Genotype 6	12 weeks with Ribavirin	12 weeks with Ribavirin	12 weeks with Ribavirin

3.5 NOT RECOMMENDED REGIME

i. Not Recommended Regime for Patients with Decompensated Cirrhosis (Moderate or Severe Hepatic Impairment; CPS B or C)
• **Simeprevir-based regimes**
• **Paritaprevir-based regimes**
• **Elbasvir/Grazoprevir-based regimes**

ii . Regimes Not Recommended
• **Daily Sofosbuvir (400mg) and weight-based ribavirin for 24 weeks**
• **Peg-IFN/ribavirin with or without sofosbuvir, simeprevir, telaprevir or boceprevir**
• **Monotherapy with Peg-IFN , ribavirin or direct-acting antiviral**

3.6 MONITORING OF DRUG-DRUG INTERACTIONS :

i. The efficacy and toxicity of concurrent drugs given for comorbidities and potential drug-drug interactions should be monitored during treatment. Drug-drug interaction reference as in Appendix 13. (Also refer to Liverpool HEPi Chart (www.hep-druginteractions.org))

ii. When possible, an interacting co-medication should be stopped for the duration of HCV treatment or the interacting co-medication should be switched to an alternative drug with less interaction potential

3.7 HEPATITIS C THERAPY IN SPECIAL GROUPS

3.7.1 Hepatitis B co infection

i. Patients with HBV coinfection should be treated with the same regimens, following the same rules as HCV monoinfected patients.

ii. If chronic hepatitis B or “occult” HBV infection is detected, concurrent HBV nucleoside/nucleotide analogue therapy is indicated

3.7.2 Immune complex-mediated manifestations of chronic hepatitis C

i. Antiviral therapy should be considered for the treatment of mixed cryoglobulinemia and renal disease associated with chronic HCV infection, according to the above recommendations.

ii. Treatment of HCV-associated lymphoma should utilise IFN-free regimens as appropriate, but the effect of an SVR on the overall prognosis is not yet known

3.7.3 Patients With Co-morbidities

i. Patients with mild to moderate renal impairment (eGFR ≥30 ml/ min/1.73 m2) with HCV infection should be treated according to the general recommendations. No dose adjustments of HCV DAAs are needed, but these patients should be carefully monitored.

ii. Sofosbuvir should be used with caution in patients with an eGFR <30ml/min/1.73 m2 or with end-stage renal disease because no dose recommendation can currently be given for these patients.

iii. Patients with severe renal impairment (eGFR <30 ml/min/1.73 m2) or with end-stage renal disease on haemodialysis without an indication for kidney transplantation infected with HCV genotype 1a should be treated with the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir for 12 weeks or with the combination of grazoprevir and elbasvir for 12 weeks, with daily ribavirin (200 mg/day) if the haemoglobin level is >10 g/dl at baseline

iv. Patients with severe renal impairment (eGFR <30 ml/min/1.73 m2) or with end-stage renal disease on haemodialysis without an indication for kidney transplantation infected with HCV genotype 1b should be treated with the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir for 12 weeks or with the combination of grazoprevir and elbasvir for 12 weeks, without ribavirin

v. Patients with severe renal impairment (eGFR <30 ml/min/1.73 m2) or with end-stage renal disease on haemodialysis without an indication for kidney transplantation infected with HCV genotype 4 should be treated with the combination of ritonavir-boosted paritaprevir and ombitasvir for 12 weeks with daily ribavirin (200 mg/day) if the haemoglobin level is >10 g/dl at baseline, or with the combination of grazoprevir and elbasvir for 12 weeks without ribavirin.

vi. In patients receiving ribavirin, haemoglobin levels should be carefully and frequently monitored and ribavirin administration should be interrupted in case of severe anaemia (haemoglobin <8.5 g/dl). The use of erythropoietin and, eventually, blood transfusion, may be useful in patients with severe ribavirin-induced anaemia

vii. Patients with cirrhosis, and those with a contraindication or who do without ribavirin

viii. If treatment is urgently needed in patients with severe renal impairment (eGFR <30 ml/min/1.73 m2) or with end-stage renal disease on haemodialysis without an indication for kidney transplantation infected with HCV genotype 2, these patients should or the combination of sofosbuvir and daclatasvir for 12 weeks without ribavirin. Renal function may worsen and should be carefully monitored and treatment should be interrupted immediately in case of deterioration

ix. If treatment is urgently needed in patients with severe renal impairment (eGFR <30 ml/min/1.73 m2) or with end-stage renal disease on haemodialysis without an indication for kidney transplantation infected with HCV genotype 3, these patients should the combination of sofosbuvir and daclatasvir for 12 weeks with daily ribavirin (200 mg/day) if the haemoglobin level is >10 g/dl at baseline, or for 24 weeks without ribavirin. Renal function may worsen and should be carefully monitored and treatment should be interrupted immediately in case of deterioration

3.7.4 Patient who injected Drugs (PWIDs)

i. Evaluation of safety and efficacy of new IFN-containing and IFN-free regimens in PWIDs is needed

ii. The anti-HCV regimens that can be used in PWIDs are the same buprenorphine dose adjustment, but monitoring for signs of opioid toxicity or withdrawal should be undertaken

iii. A modest alteration in methadone dose may be appropriate for some patients. It may be necessary to increase the dosage of methadone during interferon treatment.

3.7.5 Haemoglobinopathies

i. The indications for HCV therapy are the same in patients with and without haemoglobinopathies

ii. Patients with haemoglobinopathies should be treated with an IFN free regimen, without ribavirin

iii. The anti-HCV regimens that can be used in patients with haemoglobinopathies are the same as in patients without haemoglobinopathies

iv. When the use of ribavirin is needed, careful monitoring is recommended, and blood transfusion support may be required

3.7.6 Bleeding disorders

i. The indications for HCV therapy are the same in patients with and without bleeding disorders

ii. Potential drug-drug interactions in HCV-HIV coinfected patients receiving antiretroviral agents requires careful selection of agents.

3.8 POST-TREATMENT FOLLOW-UP OF PATIENTS WHO ACHIEVE AN SVR

i. Non cirrhotic patients with SVR should be retested for ALT and HCV RNA (or HCV core antigen) at 48 weeks post-treatment, then discharged if ALT is normal and HCV RNA is negative

ii. Patients with advances fibrosis (F3) and cirrhosis patients with SVR should undergo surveillance for HCC every 6 months by means of ultrasound.

iii. Guidelines for management of portal hypertension and oesophageal and fundal varices should be implemented, though index variceal bleed is seldom seen in low-risk patients after the achievement of SVR (unless additional causes for on-going liver damage are present and persist).

iv. Following SVR, monitoring for HCV reinfection through annual HCV RNA assessment should be undertaken in people who inject drugs or men who have sex with men with on-going risk behaviour

3.9 FOLLOW-UP OF UNTREATED PATIENTS AND OF PATIENTS WITH TREATMENT FAILURE

i. Untreated patients with chronic hepatitis C and those who failed prior treatment should be regularly followed up.

ii. Non-invasive methods for staging fibrosis are best suited for follow-up assessment at intervals of 1 to 2 years.

iii. Non-invasive methods for staging fibrosis are best suited for follow-up HCC surveillance every 6 months must be continued indefinitely in patients with advanced fibrosis (F3) and cirrhosis.

4.0 MANAGEMENT HCV AT PRIMARY HEALTH CARE (PHC)

4.0 MANAGEMENT HCV AT PRIMARY HEALTH CARE (PHC)

Snap Shot Management at Primary Health Care	
Identify	• Identify people with sign and symptom of HCV infection or suspected HCV infection.
HCV Screening	• Send blood to nearby hospital / central regional laboratories • If HCV RDTs kit is available, HCV screening can be done at PHC
HCV Confirmation Test	• Done at hospital/central regional laboratories • 2nd sample may be required for verification by clinician.

Assessment Prior to Treatment	• Can be carried at PHC as well as hospital
	• Types of testings:
	  • FBC, LFT, APRI Score,
	  • Alpha feto protein
	  • HCV Genotyping (for suitable patients)
	  - Sampel sent to designated hospital
	  • Fibro scan
	  - If required, refer to designated hospital where the service is available.

Treatment	• Refer to hospital for treatment • If drugs are available at PHC, treatment can be initiated by trained FMS • Treatment as in Section 3.0
Referral	• HCV case where drugs are not available at PHC • All Hepatitis C with co-morbidities • Designated mentor hospital for Hepatitis C patients
Monitoring	• Phyical examination • Laboratory monitoring (as in Section 3.6)

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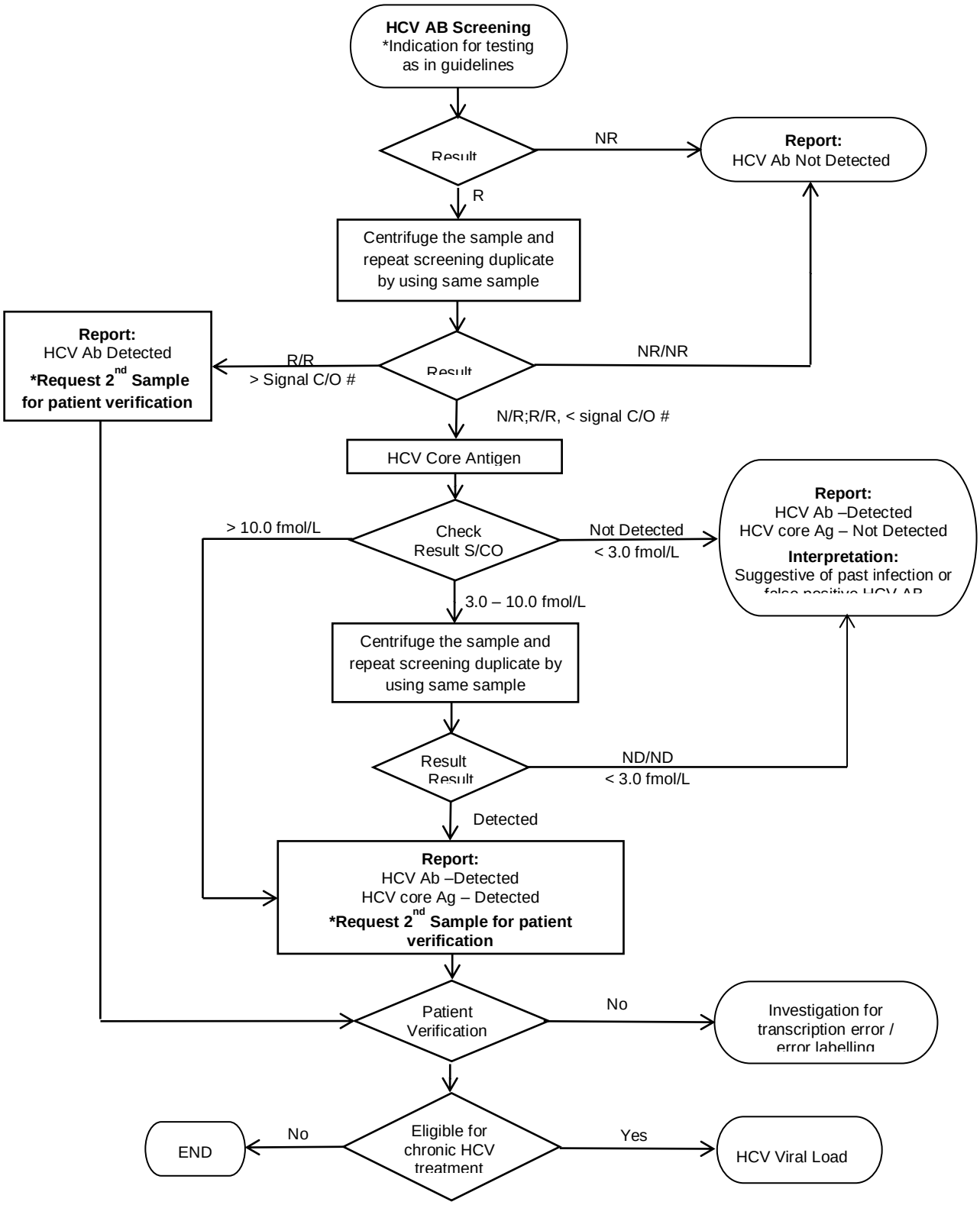
APPENDIX

APPENDIX 1

TESTING ALGORTIHM FOR DIAGNOSIS, TREATMENT AND MONITORING HCV INFECTION (LABORATORY REFERENCE ONLY)



NOTE

R	Reactive
NR	Non-Reactive
C/O	Cut Off Ratio
#	Depend on type of screening test kit use by the user. Please refer the table below.
*	Cases requiring 2nd sample verification to be determined by clinician

APPENDIX 2

SIGNAL-TO-CUT-OFF RATIOS FOR COMMERCIALLY AVAILABLE ASSAY

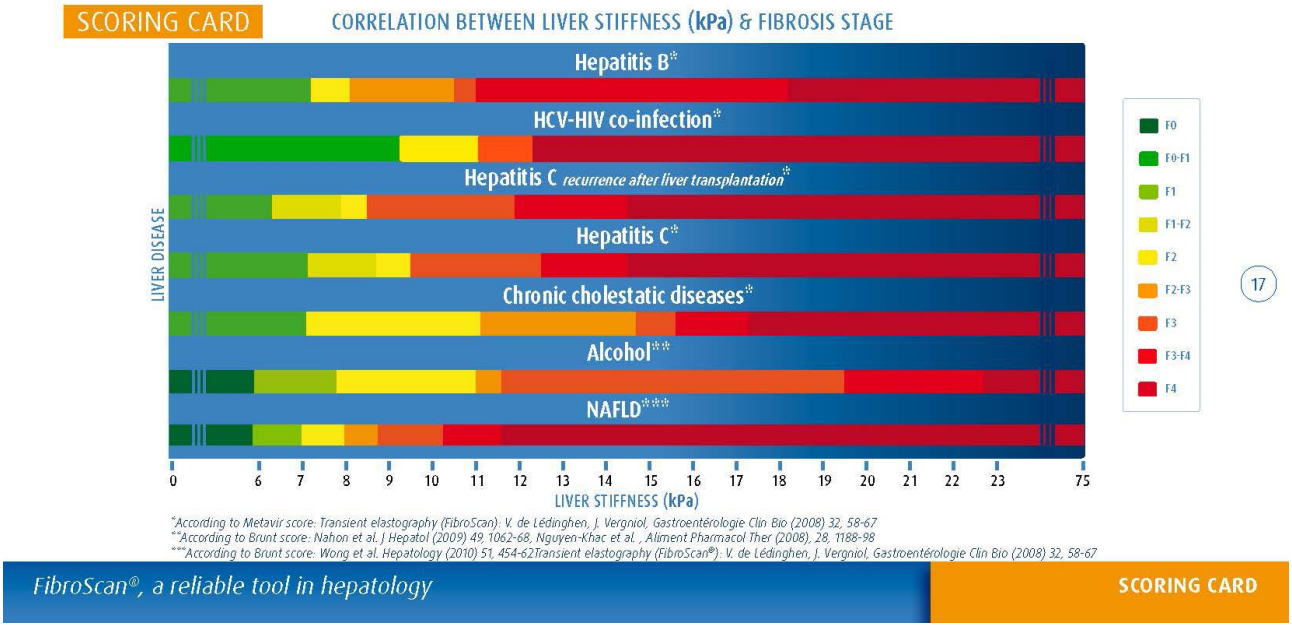
Screening Test Kit Name	Manufacturer	Assay Format	Signal-to-cut-off ratio predictive of a true positive ≥ 95% of the time
Ortho HCV Version 3.0 ELISA Test System	Ortho	EIA (Enzyme Immunoassay)	≥ 3.8
Abbott HCV EIA 2.0	Abbott	EIA (Enzyme Immunoassay)	≥ 3.8
VITROS Anti-HCV	Ortho	CIA (Chemiluminescent Immunoassay)	> 8.0
AxSYM Anti-HCV	Abbott	MEIA (Microparticle Immunoassay)	≥ 10.0
Architect Anti-HCV	Abbott	CIA (Chemiluminescent Immunoassay)	≥ 5.0
Advia Centaur HCV	Bayer	CIA (Chemiluminescent Immunoassay)	≥ 11.0

APPENDIX 3

SELECTED NON-INVASIVE TESTS TO ASSESS LIVER FIBROSIS

Test	Component	Requirements	Formula
APRI	AST , platelet	Simple serum and haematology tests	$\text{APRI} = \frac{\frac{\text{AST Level}}{\text{AST (Upper Limit of Normal)}}}{\text{Platelet Count } (10^9/\text{L})} \times 100$
FIB-4	Age , AST , ALT , platelets	Simple serum and haematology tests	$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Platelet Count } (10^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}}$
Fibrotest	gGT , haptoglubulin , bilirubin , A1 apolipoprotein , alpha2 macroglobulin	Specialized tests.Testing at designated laboratories	
Fibroscan	Transient Elastogtaphy	Dedicated equipment	

APPENDIX 4



APPENDIX 5

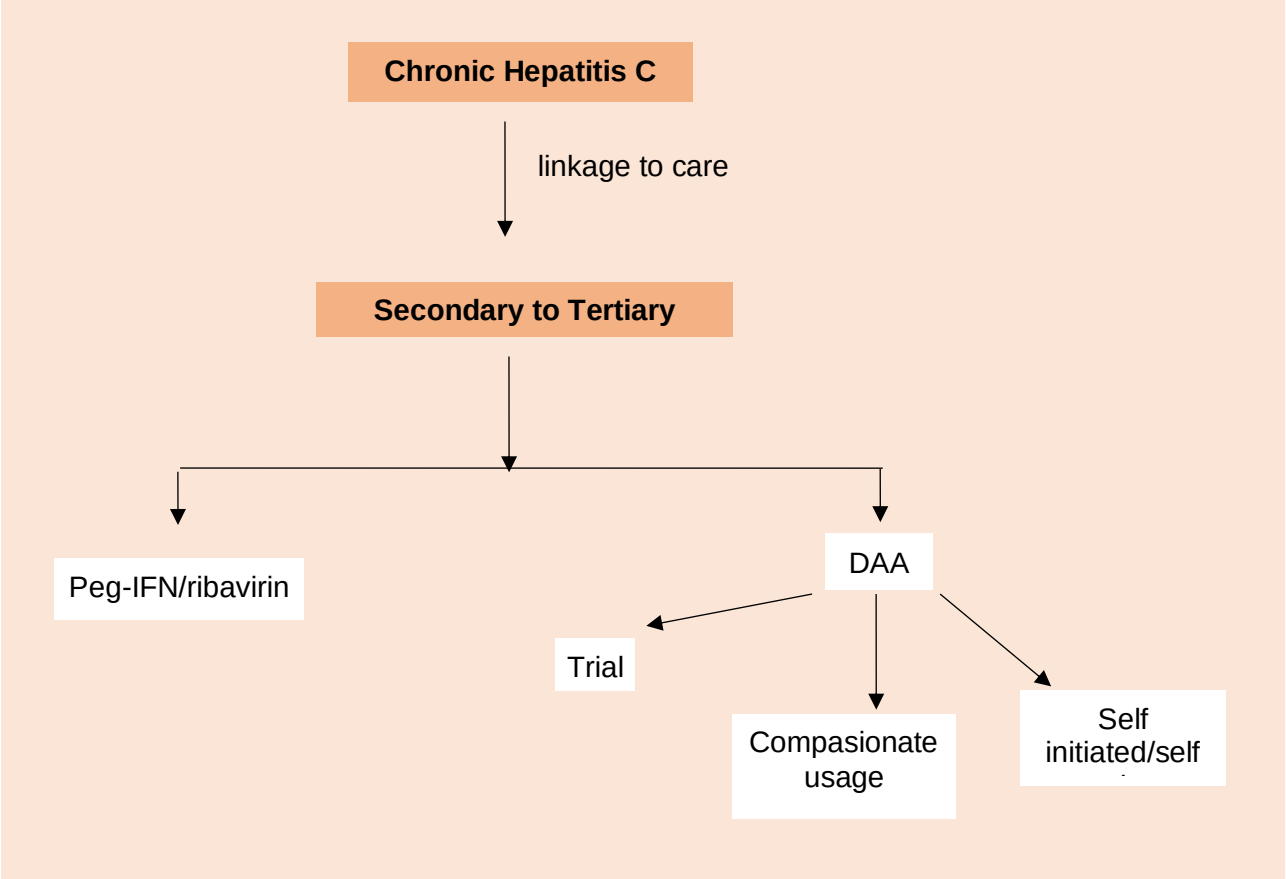
CHILD PUGH SCORE (CPS)

	1	2	3
Encephalopathy	None	Grade 1-2	Grade 3-4
Ascites	Absent	Moderate or suppressed with medication	Severe or refractory to medication
Total Bilirubin (umol/L)	<34	34-51	>51
Albumin (g/dL)	>35	28-34	<28
INR	>1.7	1.7-2.3	>2.3

**CPS A (score 5-6)*
CPS B (score 7-9)
CPS C (score 10-15)

APPENDIX 6

HCV TREATMENT: LINKAGE TO CARE



APPENDIX 7

LIST OF HCV TEST IN HOSPITAL, MOH MALAYSIA 2017

NO	HOSPITAL	HCV Antibody	HCV core antigen	HCV immunoblot	HCV RNA (Quantitative)	HCV RNA (Qualitative)
1	H.TUANKU FAUZIAH	\				
2	H.SULTANAH BAHIYAH	\	Soon		\	
3	H.PULAU PINANG	\		\		
4	H.SEBERANG JAYA	\				
5	H.RAJA PERMAISURI BAINUN	\		\		
6	H.TAIPING	\				
7	H.TENGKU AMPUAN RAHIMAH	\				
8	H.SERDANG	\				
9	H KAJANG	\				
10	H.AMPANG	\	Soon			
11	H.SELAYANG	\			\	
12	H.SG BULOH	\		\	\	
13	H KUALA LUMPUR	\	\	\	\	
14	H.MELAKA	\	Soon		\	
15	H.TUANKU JA'AFAR	\	\			
16	H.SULTANAH AMINAH JB	\	\	\		
17	H.SULTAN ISMAIL JB	\				
18	H.BATU PAHAT	\				
19	H.PAKAR SULTANAH FATIMAH	\				
20	H.TENGKU AMPUAN AFZAN	\				
21	H.SULTANAH NUR ZAHIRAH	\				
22	H.RAJA PEREMPUAN ZAINAB II	\	Soon	\ kiv stop		
23	H.UMUM SARAWAK	\	\		\	\
24	H. SIBU	\				
25	H. BINTULU	\				
26	H. MIRI	\				
27	H. QUEEN ELIZABETH	\	Soon			
28	H. TAWAU	\				
29	H. DUTCHESS OF KENT	\				
30	H. KENINGAU	\				

APPENDIX 8

DRUG CLASSIFICATION

Drug category	Class	Drugs
Direct Acting Antivirals	Protease Inhibitor	simeprevir, boceprevir, paritaprevir, grazoprevir
	NS5A inhibitor	Ledipasvir, ombitasvir, daclatasvir, elbasvir
	NS5B Nucleoside Inhibitor	Sofobuvir
	NS5B Non- Nucleoside Inhibitor	Dasabuvir
Interferon	Pegylated interferon alpha-2a Pegylated interferon alpha-2b	Pegylated interferon alpha-2a Pegylated interferon alpha-2b
Other	Ribavirin	Ribavirin

APPENDIX 9

HEPATITIS C TREATMENT IN MALAYSIA

Drug Acting Antivirals

Medication	Brand Name	Dosage form & Strength	Dosage
Sofosbuvir	Sovaldi®	400 mg/ tab	One tablet once daily (morning)
Sofosbuvir/ledipasvir	Harvoni®	400 mg of sofosbuvir and 90 mg of Ledipasvir/ tab	One tablet once daily (morning)
Paritaprevir/ ombitasvir/ ritonavir	Viekirax®	75 mg of paritaprevir, 12.5 mg of ombitasvir and 50 mg of ritonavir/ tab	Two tablets once daily (morning)
Dasabuvir	Exviera®	250 mg of dasabuvir/ tab	One tablet twice daily (morning and evening)
Daclatasvir	Daklinza®	30 or 60 mg/ tab	One tablet once daily (morning)
Elbasvir/ Grazoprevir	Zepatier®	50mg of Elbasvir and 100mg of Grazoprevir/ tab	One tablet once daily (morning)

Treatment duration depends on genotypes, treatment naïve or experience, cirrhosis or without cirrhosis & etc.

Interferons

Medication	Brand Name	Dosage form & Strength	Dosage
Pegylated Interferon alpha-2a	Pegasys®	180 mcg prefilled syringe 135mcg prefilled syringe	Once weekly
Pegylated Interferon alpha-2b	Peg-intron®	150 mcg prefilled syringe 120mcg prefilled syringe 100 mcg prefilled syringe 80mcg prefilled syringe	Once weekly

Other

Medication	Brand Name	Dosage form & Strength	Dosage
Ribavirin	Copegus® Rebetol®	200mg/ tab	15mg/kg/day (in 2 divided doses)

APPENDIX 10

CONTRAINDICATION

i. Contraindication of Direct Acting Antivirals

Generally, it is contraindicated if hypersensitive to the active substances or to any of the excipients of DAA

Drug	Contraindication/ Warning
Ledipasvir/sofosbuvir	• Amiodarone co-administration • P-glycoprotein (gp) inducers • Renal failure (eGFR<30 mL/min/1.73 m2)
Daclatasvir	• Drugs inducing or inhibiting CYP3A
Sofosbuvir	• Amiodarone co-administration (caution also with beta-blockers) • Renalfailure (eGFR<30 mL/min/1.73 m2)
Ombitasvir/paritaprevir/ ritonavir — dasabuvir	• Child–Pugh Class B and C cirrhosis • Drugs inducing or inhibiting CYP3A or CYP2C8 • Use of ethinylestradiol-containing medicinal products • Untreated HIV-1 infection because ritonavir can lead to antiretroviral drug resistance

ii. Contraindications to Therapy with Ribavirin

If any regimen is administered with ribavirin, the contraindications to ribavirin also apply to this combination regimen.

Absolute contraindication	Relative contraindication
• **Pregnancy or unwillingness to use contraception** • **Breastfeeding women** • **Severe concurrent medical disease, including severe infections** • **Poorly controlled cardiac failure** • **Chronic obstructive pulmonary disease** • **Previous ribavirin hypersensitivity** • **Co-administration of didanosine**	• Abnormal haematological indices: - Hb<10 g/dL - Neutrophil count <1.5x109/L - Platelet count <90x109/L • Serum creatinine>1.5 mg/dL • Haemoglobinopathies (sickle cell disease or thalassaemia) • Significant coronary artery disease

iii. Contraindications to the Use of Pegylated Interferon

Absolute contraindication	Relative contraindication
• **Uncontrolled depression or psychosis** • **Uncontrolled epilepsy** • **Uncontrolled autoimmune disease** • **Decompensated cirrhosis (Child–Pugh ≥ B7 or B6 in HIV/HCV coinfection)** • **Pregnancy or unwillingness to use contraception** • **Breastfeeding women** • **Severe concurrent medical disease, including severe infections** • **Poorly controlled hypertension** • **Poorly controlled cardiac failure** • **Poorly controlled diabetes** • **Solid organ transplant (except liver transplant recipients)** • **Chronic obstructive pulmonary disease** • **Age less than 2 years** • **Previous interferon hypersensitivity** • **Co-administration of didanosine**	• Abnormal haematological indices: - Hb<10 g/dL - Neutrophil count <1.5x109/L - Platelet count <90x109/L • Serum creatinine>1.5 mg/dL • Haemoglobinopathies (sickle cell disease or thalassaemia) • Significant coronary artery disease • Untreated thyroid disease • Ophthalmological disease • Colitis • Pancreatitis

APPENDIX 11

SIDE EFFECTS OF PEGYLATED INTERFERON+ RIBAVIRIN

Category	Adverse effects	Percentage (%)
Gastrointestinal	Nausea	24
	Diarrhea	16
	Abdominal pain	15
	Nausea and Vomiting	5
General	Fatigue	49
	Rigors	30
	Pyrexia	35
	Injection site reaction	22
	Pain	11
	Asthenia	7
Metabolic and Nutritional	Anorexia	16
	Weight decrease	5
Musculoskeletal, connective tissue and bone	Myalgia	37
	Arthralgia	26
	Back pain	8
Neurological	Headache	52
	Insomnia	20
	Dizziness (exclude vertigo)	15
	Concentration impairment	9
Psychiatric	Depression	18
	Irritability	17
Skin and subcutaneous tissue	Alopecia	23
	Pruritus	13
Hematological	Anemia	13
	Thrombocytopenia	5 (PC < 50 $x10^9$/L)
	Neutropenia	5 (ANC < 0.5$x10^9$/L)

APPENDIX 12

SIDE EFFECTS OF DIRECT ACTING ANTIVIRALS

Treatment Regimen	Common Side Effects
sofosbuvir + ribavirin [4]	Fatigue and headache (>20%)
sofosbuvir + peg-interferon alpha + ribavirin [4]	Fatigue, headache, nausea, insomnia, anemia (>20%) Flu-like illness, decrease appetite, rash, chills (<10%)
Daclatasvir + sofosbuvir [5]	Headache and fatigue (>10%)
Daclatasvir + sofosbuvir + ribavirin [5]	Fatigue, nausea, anemia and headache (>10%)
Ledipasvir + sofosbuvir [6]	Fatigue and headache (>10%) Cough, myalgia, dizziness, dyspnea (<10%) depression, BUN elevation, Lipase elevation (5%)
Viekirax+ dasabuvir	Itching (>10%) Swelling or angioedema (<5%)
Viekirax+ dasabuvir + Ribavirin	Fatigue, nausea, asthenia, itching, insomnia, anemia (>10%) Swelling or angioedema (<5%)

APPENDIX 13

DRUG-DRUG INTERACTION

1) Ribavirin

Medication	Interaction
Zidovudine	Increase toxic effect of Ribavirin e.g. anemia
Influenza Virus Vaccine (Live/ Attenuated)	Reduce therapeutic effect of vaccine (avoid antivirals during the period beginning 48 hours prior and ending 2 weeks after vaccination)
Vitamin K Antagonist (e.g. Warfarin)	Reduce anticoagulant effect

2) Pegylated interferon

Medication	Interaction
Clozapine	Increase clozapine concentration & myelosuppressive effect
Deferiprone	Increase myelosuppressive effect
Telbivudine	Increase toxic effect of Telbivudine especially: peripheral neuropathy

3) Drug-Drug Interactions (DAA)

It is strongly recommended that prescribers consult the University of Liverpool webpage on hepatitis drug interactions (http://www.hep-druginteractions.org/) prior to prescribing, as details of interactions are frequently updated. It includes details of interactions with prescribed and non-prescribed drugs. [2]

4) Drug Interactions with Direct-Acting Antivirals and Selected Concomitant Medications [10]

Concomitant Medications	Daclatasvir	Ledispavir	Paritaprevir/ Ritonavir/ Ombitasvir + Dasabuvir	Sofosbuvir
Acid Reducing Agents*		x	x	
Alfuzosin/ tamsulosin			x	
Amiodarone	x	x	x	x
Anticonvulsants*	x	x	x	x
Antiretrovirals*	See HIV section			
Azole antifungals*	x		x	
Buprenophine/ noloxone			x	
Calcineurin inhibitors*			x	
Calcium channel blockers*	x		x	
Digoxin	x	x		
Ergot Deriatives			x	
Ethyl estradiol containing products			x	
Frusemide			x	
Gemfibrozil			x	
Glucocorticoids*	x		x	
St John wort	x	x	x	x
Statin groups*	x	x	x	
Macrolides antimicrobials*	x			
Others antiarrthymias*			x	
Phosphodiesterase inhibitors*			x	
Rifamycin antimicrobials*	x	x	x	x
Salmeterol			x	
Sedatives*			x	

x Assess potential drug interaction.

** Some drug interactions are not class specific: see product prescribing information for specific drugs within a class*

5) Drug–drug interactions between co-administered HCV and HIV treatmen

HIV Antiviral Drugs	Daclatasvir	Ledispavir/ Sofosbuvir	Paritaprevir/ Ritonavir/ Ombitasvir	Paritaprevir/ Ritonavir/ Ombitasvir+ Dasabuvir	Sofosbuvir	Pegylated Interferon	Ribavirin
Nucleoside reverse transcriptase inhibitors (NRTIs)							
Abacavir (ABC)	√	√	√	√	√	-	-
Emtricitabine (FTC)	√	√	√	√	√	-	-
Lamivudine (3TC)	√	√	√	√	√	-	-
Tenofovir (TDF)	√	-	√	√	√	-	-
Zidovudine (AZT)	√	√	√	√	√	x	x
HIV entry/ integrase inhibitor							
Dolutegravir (DTG)	√	√	√	√	√	√	√
Non- nucleoside reverse transcriptase inhibitors (NNRTIs)							
Efavirenz (EFV)	-	-	x	x	√	√	√
Nevirapine (NVP)	-	√	x	x	√	√	√
Protease Inhibitors (PIs)							
Lopinavir	√	√	x	x	√	√	√
Ritonavir	-	√	x	x	√	√	√

√ *No clinical signification interaction expected*
- *Potential interaction*
x *These drugs should not be co-administered*

i) Sofosbuvir (Sovaldi®)

Concomitant Drug	Effect on concentration	Clinical Comment
Antiarrhythmics: **Amiodarone**	Unknown	Co-administration not recommended. It may result in serious symptomatic bradycardia., fatal cardiac arrest (requiring pacemaker).
Anticonvulsants: **Carbamazepine** **Phenytoin** **Phenobarbital** **Oxcarbazepine**	↓ Sofosbuvir ↓ GS-331007	Coadministration is not recommended.
Antimycobacterials: **Rifabutin** **Rifampin** **Rifapentine**	↓ Sofosbuvir ↓ GS-331007	Coadministration is not recommended.
Herbal Supplements: **St. John's wort**	↓ Sofosbuvir ↓ GS-331007	Not recommended with (St. John's wort: intestinal P-gp inducer)
HIV Protease Inhibitors: **Tipranavir/Ritonavir**	↓ Sofosbuvir ↓ GS-331007	Coadministration is not recommended.

ii) Daclatasvir (Daklinza®)

Concomitant Drug	Clinical Comment
Anticonvulsants: **Carbamazepine** **Phenytoin**	Coadministration is contraindicated.
Antimycobacterials: **Rifampin**	Coadministration is contraindicated.
Herbal Supplements: **St. John's wort**	Coadministration is contraindicated.

iii) Ledipasvir 90mg/ Sofosbuvir 400mg (Harvoni®)

Concomitant Drug	Effect on Concentration	Clinical Comment
Antacids	↓Ledipasvir Ledipasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease concentration of ledipasvir.	It is recommended to separate antacid and HARVONI administration by 4 hours.
H2-receptor antagonists		H2 antagonists may be administered with or 12 hours apart from Harvoni at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
Proton-pump inhibitors		Proton-pump inhibitor doses comparable to omeprazole 20 mg or lower can be administered simultaneously with Harvoni under fasted conditions.
Antiarrhythmics: **Amiodarone**	Unknown	Serious symptomatic bradycardia: unknown mechanism. Coadministration is not recommended.
HIV Antiretrovirals: Tenofovir without an HIV protease inhibitor / ritonavir or cobicistat	↑ Tenofovir	Monitor tenofovir -associated adverse reactions in patients receiving HARVONI concomitantly with a regimen containing tenofovir DF without an HIV protease inhibitor/ritonavir or cobicistat.
Anticonvulsants: **Carbamazepine** **Phenytoin** **Phenobarbital** **Oxcarbazepine**	↓ Ledipasvir ↓ Sofosbuvir	Coadministration is not recommended.
Tenofovir + ritonavir/ Protease inhibitor, eg: **Darunavir, Atazanavir, Lopinavir**	↑ Tenofovir	The safety not been established. *Consider alternative HCV or antiretroviral therapy to avoid increases in tenofovir level.
Elvitegravir **Cobicistat** **Emtricitabine** **Tenofovir DF**	↑ Tenofovir	The safety not been established. Coadministration is not recommended.
Tipranavir/ritonavir	↓ Ledipasvir ↓ Sofosbuvir	Coadministration is not recommended.
Statin **Pravastatin**		No clinically significant drug interactions have been observed or are expected with HARVONI.

Concomitant Drug	Effect on Concentration	Clinical Comment
HIV Antiretrovirals **Abacavir, Darunavir/ritonavir** **Efavirenz,Emtricitabine Lamivudine, Raltegravir**		No clinically significant drug interactions have been observed or are expected with HARVONI.

iv) Ombitasvir/ Paritaprevir/ Ritonavir (Viekirax®)

Concomitant Drug	Clinical Comment
Alpha1-adrenoceptor Antagonist Alfuzosin HCL	Potential for hypotension
Antibiotic Clarithromycin	Potential for serious and/or life -threatening reactions.
Antiarrhythmics **Amiodarone Quinidine**	Potential for serious and/or life- threatening reactions such as cardiac arrhythmias.
Anticonvulsants **Carbamazepine,** **Phenytoin,** **Phenobarbital**	Viekirax exposures may decrease leading to a potential loss of therapeutic activity of Viekirax.
Anti-gout **Colchicine**	Potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment.
Antifungal Ketoconazole Itraconazole	Potential for serious and/or life-threatening reactions.
Antimycobacterial Rifampicin	Viekirax exposures may decrease leading to a potential loss of therapeutic activity of Viekirax.
Antipsychotic Quetiapine	Potential for serious and/ or life-threatening reactions. (such as cardiac arrhythmias)
Ergot derivatives Ergotamine	Acute ergot toxicity characterized by vasospasm and tissue ischemia has been associated with co-administration of ritonavir and ergotamine.
Ethinylestradiol- containing products	Potential for ALT elevations
GI Motility Agent Cisapride	Potential for serious and/or life threatening reactions such as cardiac arrhythmias.
Herbal Product St. John's Wort	Viekirax exposures may decrease leading to a potential loss of therapeutic activity of Viekirax.

Concomitant Drug	Clinical Comment
HMG-CoA Reductase Inhibitors **Lovastatin & Simvastatin** **Atorvastatin**	Potential for myopathy including rhabdomyolysis.
Non- nucleoside reverse transcriptase inhibitor (NNRTI) **Efavirenz** **Nevirapine**	Co-administration of efavirenz based regimens with paritaprevir, ritonavir plus dasabuvir was poorly tolerated and resulted in liver enzyme elevations.
Phosphodiesterase-5 (PDE5) inhibitors **Sildenafil for the treatment of pulmonary arterial hypertension (PAH)**	There is increased potential for sildenafil- associated adverse events such as visual disturbances, hypotension, priapism, and syncope.
Sedatives/hypnotics **Triazolam** **Midazolam**	Triazolam and orally administered midazolam are extensively metabolized by CYP3A4. Coadministration of triazolam or orally administered midazolam with VIEKIRAX may cause large increases in the concentration of these benzodiazepines. The potential exists for serious and/or life threatening events such as prolonged or increased sedation or respiratory depression.

v) Dasabuvir (Exviera®)

Concomitant Drug	Clinical Comment
Anticonvulsants **Carbamazepine,** **Phenytoin,** **Phenobarbital**	Exviera® exposures may decrease leading to a potential loss of therapeutic activity of Exviera.
Antihyperlipidemia **Gemfibrozil**	Increase in dasabuvir exposure is due to CYP2C8 inhibition by gemfibrozil.
Ethinylestradiol- containing products	Potential for ALT elevations
Herbal Product **St. John's Wort**	Exviera exposures may decrease leading to a potential loss of therapeutic activity of Exviera . ®

DRUG- FOOD INTERACTION

High-fat meal increase AUC and Cmax of ribavirin. Hence, ribavirin should be administered with food.

APPENDIX 14

DOSE ADJUSTMENT FOR SPECIAL POPULATION

a) Patients with Renal Impairment

Renal Impairment eGFR (mL/min)	Mild (50-80)	Moderate (30-50)	Severe (<30)	ESRD with HD
PEG-IFN	PEG-IFN (2a) 180 µg; PEG-IFN (2b) 1.5µg/kg	PEG-IFN (2a) 180 µg; PEG-IFN (2b) 1µg/kg (25% reduction)	PEG-IFN (2a) 135 µg; PEG-IFN (2b) 1 µg/kg (50% reduction)	PEG-IFN (2a) 135µg/wk or PEG-IFN(2b) 1 µg/kg/wk or standard IFN 3 mU3x/wk
Ribavirin	Standard	Alternating doses 200mg and 400mg every other day	200 mg/d	200 mg/d
Sofosbuvir	Standard	Standard	Limited data available	Limited data available
Ledipasvir	Standard	Standard	No Data	Limited data available
Daclatasvir	Standard	Standard	Limited data available	Limited data available
Ombitasvir	Standard	Standard	Limited data available	Limited data available
Dasabuvir	Standard	Standard	Limited data available	Limited data available
Paritaprevir	Standard	Standard	Limited data available	Limited data available

b) Patients with Hepatic Impairment

Hepatic Impairment	Child-Pugh A	Child-Pugh B	Child-Pugh C
PEG-IFN + Ribavirin [3]	Suitable Candidate	Not entirely contraindicated	Not a good candidate
Sofosbuvir [4]	No dose adjustment. Safety and efficacy of sofosbuvir have not been established in patients with decompensated cirrhosis.		
Ledipasvir [6]	No dose adjustment		
Daclatasvir [5]	No dose adjustment		
Ombitasvir/ paritaprevir/ ritonavir + Dasabuvir [7] [8]	No dose adjustment	Not recommended	Contraindicated

c) Pediatric

- Pharmacokinetics of Pegasys® and RBV in paediatric population have not been adequately studied. [9]

- Growth inhibition was observed in treated patients at the end of treatment. [9]

Duration of treatment	Percentage of treated patients with more than 15 percentile below baseline weight curve	Percentage of treated patients with more than 15 percentile below baseline height curve
Post-treatment 2 years	16%	11%

- Ribavirin dose adjustment [9]

Body Weight (kg)	RBV daily dose (approx. 15 mg/kg/day)
23-33	400mg/day
34-46	600mg/day
47-59	800 mg/day
60-74	1000 mg/day
≥ 75	1200 mg/day

- Dose adjustment of Pegasys = 180 mcg/ 1.73 m^2 x BSA

d) Pregnancy & Breast Feeding Women

No adequate human data are available for all direct acting antivirals. However, any regimen is administered with ribavirin or pegylated interferon is contraindicated.

Ministry of Health Malaysia
Putrajaya