Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

October 12, 2020

DEPARTMENT MEMORANDUM
No. 2020 - 0531

FOR : **UNDERSECRETARY AND ASSISTANT SECRETARIES OF FIELD IMPLEMENTATION & COORDINATION TEAM; DIRECTORS OF CENTERS FOR HEALTH DEVELOPMENT; CHIEFS OF DOH MEDICAL CENTERS, HOSPITALS, SANITARIA, AND DOH-DESIGNATED HIV TREATMENT HUBS AND PRIMARY HIV CARE FACILITIES; AND OTHERS CONCERNED**

SUBJECT : **Interim Guidelines on the Management of Patients Diagnosed with Hepatitis C**

I. BACKGROUND

In the Philippines, Hepatitis C is an emerging public health problem which exacts a huge economic and social burden among infected patients. Estimates from modeling studies state that about 0.58% or 614,000 Filipino were infected with the hepatitis C virus (HCV). If conditions remained the same, until the year 2030, the prevalence of HCV in the Philippines is expected to drop to 0.45% by the year 2030, equivalent to roughly 7% reduction of prevalence. Despite this, morbidity and mortality will be expected to increase by about 40% to 45%, respectively. These increases will be seen in HCV-related decompensated cirrhosis, hepatocellular carcinoma (HCC), and liver related deaths. Genotypes 1 and 2 are the most common in the Philippines, accounting for 73.2% and 26.4% of all infections respectively.

Combating hepatitis has been included in the recently ratified Sustainable Development Goals. The World Health Organization (WHO) has released the Global Health Sector Strategy on Viral Hepatitis 2016-2021, and the WHO Western Pacific Regional Office (WPRO) has released the Regional Action Plan on Viral Hepatitis in the Western Pacific 2016-2020.

Effective and safe antiviral therapies for Chronic Hepatitis C (CHC) that have been shown to result in high sustained viral response rates and to prevent the development of cirrhosis and hepatocellular carcinoma are currently available. This guideline was developed to ensure the safe and effective use of antiviral therapy in patients with CHC. These evidence-based guidelines are adapted from the 2014 Hepatology Society of the Philippines Consensus Statements on the Diagnosis and Treatment of Hepatitis C, Hepatology Society of the Philippines 2018 Update to the Consensus Statements on the Treatment of Hepatitis C, and the WHO Guidelines for the care and treatment of persons diagnosed with chronic Hepatitis C Virus Infection, published in July 2018 by the World Health Organization, Geneva. These guidelines shall be updated as new information and treatments become available.

II. OBJECTIVES

To provide all physicians with evidence-based recommendations in the management and treatment of patients with Hepatitis C virus infection.

III. DEFINITION OF TERMS

Anti-HCV antibody	Presence of antibodies to Hepatitis C virus (HCV), which is a biomarker of past or present infection with HCV
Chronic HCV infection	Presence of HCV RNA in the blood
Cirrhosis	Presence of severe scarring (fibrosis) with formation of regenerative nodules in the liver that result from various chronic liver diseases and can lead to various clinical manifestations such as splenomegaly, thrombocytopenia, hypoalbuminemia, hyperbilirubinemia, gastroesophageal varices/variceal bleeding, ascites, and hepatic encephalopathy
Sustained virological response (SVR)	Undetectable HCV RNA in the blood either at 12 weeks (SVR12) or at 24 weeks (SVR24) after the end of HCV treatment
Treatment failure	Detectable HCV RNA in the blood after the end of HCV treatment measured at least 12 weeks after the end of HCV treatment

IV. GENERAL GUIDELINES

1. All Hepatitis C infected persons shall be properly assessed for eligibility for treatment.
2. In resource limited settings, less costly but reliable alternative diagnostic tests/indices may be utilized to guide the clinician in the decision to initiate treatment, and in monitoring response to treatment and disease progression.
3. Treatment-eligible chronic Hepatitis C patients shall be given opportunities to gain access to effective and safe antiviral therapy.
4. Treatment options which obviate the need for expensive diagnostic testing may also be given to CHC patients.
5. Chronic Hepatitis C patients started on treatment shall be judiciously and regularly monitored for response to treatment, adverse effects, resistance, treatment failure and disease progression.
6. Healthcare providers in the first-contact, primary level of care shall be trained to conduct early assessment and timely initiation of treatment, especially in resource-limited settings. Collaboration with specialists with the Healthcare Provider Network involved in the care of CHC patients shall be maximized.

7. The effective and efficient treatment, control and prevention of Chronic Hepatitis C requires a collaborative effort between healthcare providers across all levels of care and other important stakeholders.
8. Patients with CHC shall be counselled about appropriate monitoring and prevention of disease transmission. Avoidance of alcohol shall be encouraged.
9. Vaccination against Hepatitis A and Hepatitis B is recommended for patients with CHC who test negative for anti-HAV IgG, and HBsAg and anti-HBs, respectively.

V. SPECIFIC GUIDELINES

A. Assessment Prior to Treatment

1. All adults and children with CHC, including people who inject drugs, shall be assessed for antiviral treatment. At baseline and before treatment with combination therapy, the following shall be performed:

    a. Medical history, clinical examination - important to evaluate for history of or current jaundice, ascites, gastroesophageal varices/variceal bleeding, hepatic encephalopathy, hepatocellular carcinoma, or liver transplantation. A detailed history of treatment of CHC in the past especially prior treatment with Direct Antiviral Agents (DAAs) should be undertaken. Concomitant medication use should be reviewed and recorded in the chart.
    b. Standard laboratory tests: complete blood count (CBC), creatinine, ALT, AST. *Optional laboratory tests include international normalized ratio (INR), total bilirubin, albumin.* Laboratory test results within the last 6 months for those patients who do not have cirrhosis and within the last 3 months for those with cirrhosis are acceptable.
    c. HCV RNA (quantitative nucleic acid testing) preferably within the past 6 months. Preferred test is one with a limit of detection of 15 IU/mL or lower.
    d. HCV genotype testing (optional).
    e. Pregnancy test – in women of childbearing age. Antiviral therapy should not be given to pregnant women.
    f. Screen for HBV and HIV. For those who are positive for HIV or HBV or both, see Section V.D.2 and V.D.3. HIV testing should follow the DOH guidelines on Provider-initiated Testing and Counseling.
    g. Evaluation for cirrhosis using clinical criteria (splenomegaly, low platelet, low albumin, high bilirubin, ascites, known esophageal varices, hepatic encephalopathy) or by noninvasive tests.
    h. Ultrasound of the liver is recommended for those with cirrhosis for screening and surveillance of hepatocellular carcinoma.

2. In the assessment of the degree of liver fibrosis and cirrhosis, noninvasive tests such as AST to platelet ratio index (APRI) **or** Fibrosis-4 (FIB-4) for the assessment of cirrhosis are recommended. Other non-invasive tests that require more resources such as transient elastography or biomarker panels (LiverFASt®) can be used if these are available.
    a. The formulae for APRI and FIB-4 are
        1. APRI = [((AST (IU/L)/AST upper limit of normal (IU/L))×100]/platelet count (10^9/L)

2. FIB-4 = age (years) x AST (IU/L)/platelet count (10^9)/L x [ALT (IU/L)$^{1/2}$]

b. Online calculators for APRI and FIB-4 are available at http://www.hepatitisc.uw.edu/page/clinical-calculators.

c. An APRI > 2.0 or a FIB-4 > 3.25 is considered cirrhosis.

3. A patient with cirrhosis is considered to have decompensated cirrhosis if they have a history of or current jaundice, ascites, variceal bleeding, or hepatic encephalopathy. A patient with cirrhosis who has a Child-Turcotte-Pugh score of ≥ 7 is also considered to have decompensated cirrhosis. Annex A shows how to calculate the Child-Turcotte-Pugh Score.

B. Treatment

1. All patients with CHC should be offered antiviral treatment with the exception of those who have contraindications to treatment such as known allergy to Sofosbuvir, Velpatasvir, or Daclatasvir, those who do not consent to treatment, or those who are pregnant. All women of childbearing age must be advised to practice safe and effective contraception during the treatment period with DAAs.

2. The DAAs for the treatment of CHC that are available in the Philippines are listed on the table below:

Drug	Preparation	Dose
Sofosbuvir	400mg/tablet	1 tablet a day
Sofosbuvir/Velpatasvir FDC*	400mg/100mg/tablet	1 tablet a day
Daclatasvir	60mg/tablet	1 tablet a day

*FDC – Fixed Dose Combination

3. The following are the recommended treatment regimens for patients with CHC as well as the recommended treatment duration. These recommendations apply to patients who are treatment naïve as well as those who are treatment-experienced. Treatment-experienced here refers to patients who were previously treated with pegylated IFN-α and ribavirin, pegylated IFN-α, ribavirin and sofosbuvir, and sofosbuvir and ribavirin. See Annex B.

a. Treatment of HCV-Infected Persons Without Cirrhosis

Sofosbuvir 400mg/Daclastavir 60mg	Sofosbuvir 400mg/Velpatasvir 100mg FDC
12 weeks	12 weeks

b. Treatment of HCV-Infected Persons With Compensated Cirrhosis

Sofosbuvir 400mg/ Daclastavir 60mg	Sofosbuvir 400mg/ Velpatasvir 100mg FDC
24 weeks	12 Weeks

4. Drug-drug interactions must be carefully assessed for each patient. This can be checked on the following website - https://www.hep-druginteractions.org/checker. Some common drug-drug interactions are shown on Annex C.

C. Monitoring During Treatment

1. Monitoring for treatment response: HCV RNA 12 weeks after the end of treatment. An HCV RNA quantitative test with a limit of detection of 15 IU/mL or lower is preferred. A patient can have either of the following treatment responses: sustained virological response (SVR) or treatment failure. Please see Definition of Terms in Section III. Treatment failures should be referred to a specialist.
2. During the course of the treatment, the following shall be performed as part of treatment monitoring at the specified time periods:

Time	Tests
	CBC, Creatinine, AST, ALT, *INR, Total Bilirubin, Albumin*
Baseline	X
Week 12 after end of treatment	X

3. Abnormal tests should be addressed accordingly. A referral to a specialist can be made.

D. Special Considerations for Specific Populations

1. Decompensated cirrhosis
   a. Must be co-managed with a specialist in liver disease. Referral for liver transplant evaluation is recommended.
   b. Recommended antiviral regimen

Sofosbuvir 400mg/Daclastavir 60mg/Ribavirin*	Sofosbuvir 400mg/ Velpatasvir 100mg FDC
24 weeks	24 weeks

* *If Ribavirin is available. Ribavirin is weight-based: 1000mg in 2 divided doses for weight <75 kg and 1200mg in 2 divided doses for weight ≥ 75 kg. For Child-Turcotte-Pugh C patients, 600mg in 2 divided doses to be increased as tolerated to weight-based dose. If Ribavirin is not available and Sofosbuvir/Velpatasvir FDC is not available as well, Sofosbuvir 400mg/Daclatasvir 60mg for 24 weeks may be used but SVR is lower.*

2.Patients with hepatocellular carcinoma
   a. Patient with HCV and hepatocellular carcinoma should be co-managed with a specialist in liver disease.
   b. The management of their HCC takes precedence over HCV treatment.
   c. They can be given antiviral therapy for HCV according to Section V-B once their hepatocellular carcinoma has been adequately addressed.

3. Children and adolescents
   a. Most children and adolescents have mild Hepatitis C-related liver disease.
   b. Children with CHC should be co-managed with a pediatrician or pediatric gastroenterologist.
   c. No direct antiviral agent is currently approved for children and adolescents in the Philippines.
4. HIV-HCV Co-infection.
   a. Persons with HIV-HCV co-infection are prioritized for HCV treatment.
   b. Persons with HIV-HCV co-infection generally have more rapid disease progression than HCV monoinfected persons.

c. Even for persons with successful control of HIV infection, the risk of hepatic decompensation among co-infected persons is higher than among persons with HCV monoinfection.
d. Persons with HIV-HCV co-infection should be co-managed with a specialist in HIV infection.
e. DAAs are safe and effective for persons with HIV-HCV co-infection. The same regimens as mono-infected persons are recommended for patients with HIV-HCV co-infection. See Section V.B. Also refer to DOH Department Circular No. 2017-0273.
It is important to remember that there can be important drug-drug interactions (DDIs) between the current pangenotypic HCV regimens and antiretroviral therapy (ART). Therefore, DDIs between HIV and HCV medications should be carefully assessed. This can be checked on the following website - https://www.hep-druginteractions.org/checker. As an important example, velpatasvir should not be given to HIV-infected patients receiving Efavirenz. Moreover, the dose of Daclatasvir should be increased to at least 90 mg a day from 60 mg a day when given with Efavirenz.

5. HBV-HCV Co-infection
a. Persons with HBV-HCV co-infection have increased risk for hepatocellular carcinoma.
b. Screening for HBV is recommended for all patients with CHC. Those who have a positive test for HBsAg are considered to have HBV-HCV co-infection.
c. Persons with HBV-HCV co-infection should be assessed for eligibility for HBV treatment according to the interim guidelines set in DOH Department Memorandum No. 2019-0465 or the updated DOH guidelines (when available) and treated accordingly.
d. If they do not satisfy current criteria for initiating antiviral therapy for HBV, they should be given antiviral therapy for HBV for the duration of the antiviral therapy for CHC and for 6 months after the end of treatment. The antiviral medication of choice is Tenofovir Disoproxil Fumarate 300 mg a day. Co-administration of Tenofovir Disoproxil Fumarate with Velpatasvir requires close monitoring for adverse effects related to Tenofovir Disoproxil Fumarate.

For your information.

By Authority of the Secretary of Health

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Undersecretary of Health
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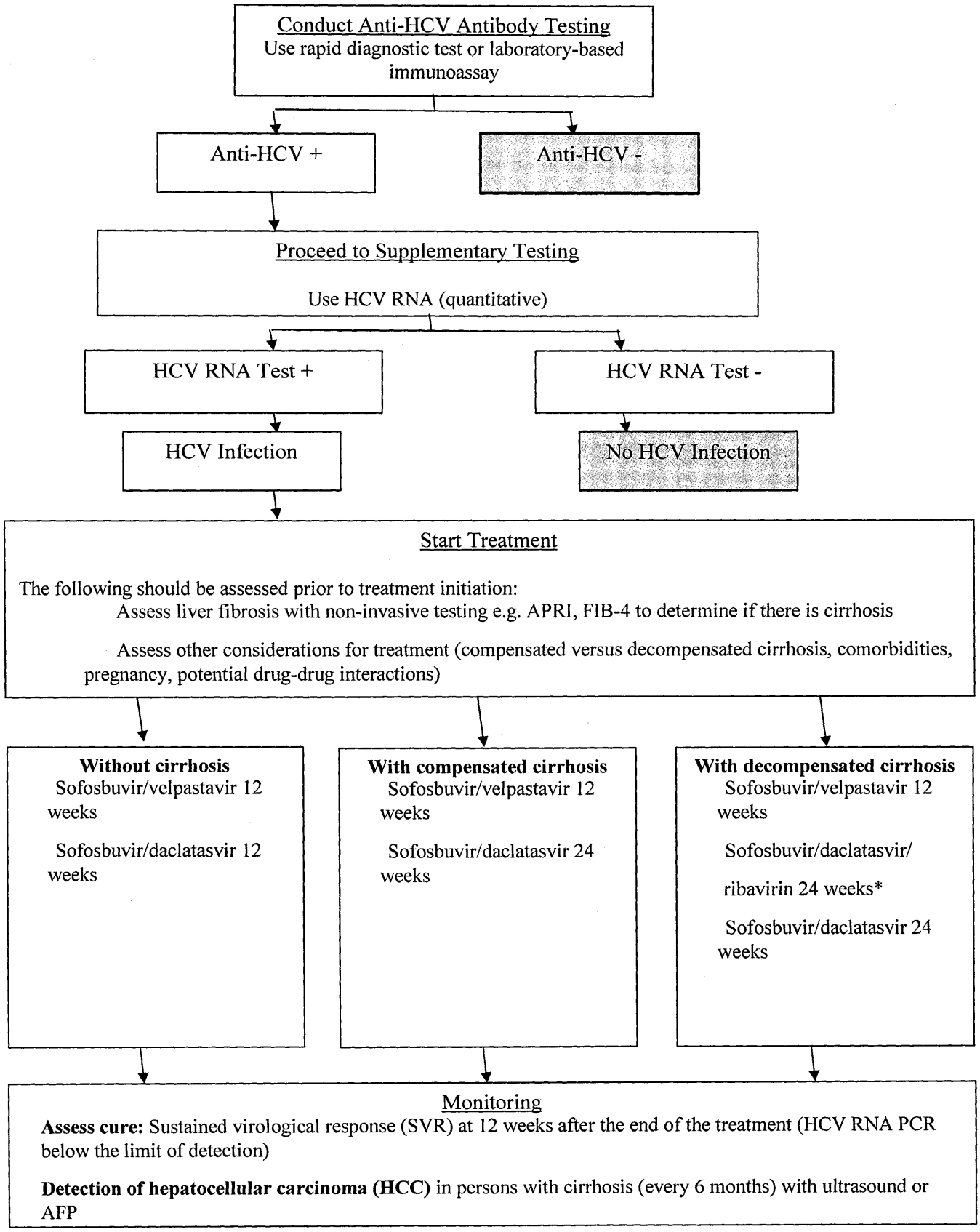
ANNEX A. Child-Turcotte-Pugh Score and Class

Clinical and Laboratory Criteria	Points		
	1	2	3
Encephalopathy	None	Mild to moderate (Grade 1 or 2)	Severe (Grade 3 or 4)
Ascites	None	Mild to moderate (diuretic-responsive)	Severe (diuretic-refractory)
Bilirubin (mg/dL)	< 2	2-3	> 3
Albumin (g/dL)	> 3.5	2.8-3.5	< 2.8
Prothrombin time			
Seconds prolonged	< 4	4-6	> 6
International normalized ratio	< 1.7	1.7-2.3	>2.3
Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points) Class A = 5 to 6 points (least severe liver disease) Class B = 7 to 9 points (moderately severe liver disease) Class C = 10 to 15 points (most severe liver disease)			

Annex B. Algorithm for the diagnosis, treatment, and monitoring of chronic HCV infection in adults.



ANNEX C: Common Drug-Drug Interactions and their Management

Drug	Direct Acting Antiviral	Management
Amiodarone	Sofosbuvir Sofobuvir/Velpatasvir Daclatasvir	Do not co-administer amiodarone with any of the three DAAs.
Antacid (Aluminum/Magnesium Hydroxide)	Sofosbuvir/Velpatasvir	Administration of an antacid and sofosbuvir/velpatasvir should be separated by 4 hours.
Atorvastatin	Sofobuvir/Velpatasvir Daclatasvir	Monitor for myopathy.
Digoxin	Sofosbuvir/Velpatasvir Daclatasvir	Monitoring of serum digoxin levels is recommended as velpatasvir or daclatasvir can increase serum digoxin levels.
Efavirenz	Daclatasvir	Increase dose of Daclatasvir to 90mg a day.
Efavirenz	Sofosbuvir/Velpatasvir	Do not co-administer.
Omeprazole	Sofosbuvir/Velpatasvir	Administer omeprazole not to exceed a dose 20 mg a day 4 hours after sofosbuvir/velpatasvir.
Other Proton Pump Inhibitors (PPIs)	Sofosbuvir/Velpatasvir	Administer PPI 4 hours after sofosbuvir/velpatasvir at a dose not to exceed the equivalent of omeprazole 20 mg a day.
Ranitidine	Sofosbuvir/Velpatasvir	Administer Ranitidine 12 hours apart from sofosbuvir/velpatasvir at a dose not to exceed the equivalent of famotidine 40 mg twice daily.
Rifampicin	Sofosbuvir Sofosbuvir/Velpatasvir Daclatasvir	Do not co-administer rifampicin with any of the three DAAs.
Rosuvastatin	Sofobuvir/Velpatasvir Daclatasvir	Monitor for myopathy. Do not exceed rosuvastatin 10mg a day.
Tenofovir Disoproxil Fumarate	Sofosbuvir/Velpatasvir	Monitor closely for adverse effects of Tenofovir Disoproxil Fumarate.