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World Health Organization
Myanmar

NATIONAL SIMPLIFIED TREATMENT GUIDELINES OF VIRAL HEPATITIS C INFECTION

NATIONAL HEPATITIS CONTROL PROGRAM

MINISTRY OF HEALTH AND SPORTS
MYANMAR

Second Edition

JULY 2019

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FOREWORD

Viral hepatitis is recognized as a global public health concern. Globally estimated that viral hepatitis caused 1.34 million deaths in 2015, a number comparable to deaths caused by tuberculosis and higher than those caused by HIV. However, the number of deaths due to viral hepatitis is increasing over time, while mortality caused by tuberculosis and HIV is declining. Most viral hepatitis deaths in 2015 were due to chronic liver disease (720 000 deaths due to cirrhosis) and primary liver cancer (470 000 deaths due to hepatocellular carcinoma). Globally, in 2015, an estimated 257 million people were living with chronic HBV infection, and 71 million people with chronic HCV infection which was 1% of world's population.

In Myanmar hepatitis prevention and control activities and services has been implementing as a national concern since 2009 with high political commitment. Myanmar Gastrointestine and Liver Society (MGLS) developed guidelines for the treatment of chronic hepatitis C infection in 2009. With the establishment of National Hepatitis Control Program (NHCP) in 2014, this guideline has been revised as the Simplified Treatment Guidelines for Hepatitis C Infection and was published by the NHCP in February 2017, in which the treatment procedure of the direct-acting antiviral drugs (DAAs) and viral load testing and clinical monitoring were included. This work is done by a series of consultations with Department of Public Health (DoPH), Department of Medical Services (DMS), Departments of Hepatology, National Health Laboratory (NHL), National Blood Center (NBC), Department of Medical Research (DMR), World Health Organization (WHO) and Clinton Health Access Initiative (CHAI) and Myanmar Gastrointestine and Liver Society (MGLS).

In the meantime, the availability of the new DAA regimens has changed the hepatitis C treatment landscape. In this light, this second edition of the guidelines augments and provides updates to the 2017 Simplified Treatment Guidelines for Hepatitis C Infection. The guidelines have been updated to include DAA treatment regimens including sofosbuvir/velpatasvir (SOF/VEL) and also provide guidance on the use of oral, low cost, DAAs, with the aim to reduce the disease burden of viral hepatitis C infection in the community. This document provides a clear guidance to all healthcare personnel in the public and private sectors serving hepatitis C patients for precise and quick clinical decisions with simplified clinical monitoring methods.

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We would also like to express genuine thanks to Professor Christian Ramers, Senior Clinical Advisor, Dr Hlaing Thazin Aung, Dr Yee Mon Kyaw, Clinton Health Access Initiative, for their technical updates. We would also like to thank Dr. Aye Myat Soe and Dr Fabio Mesquita, World Health Organization, for initiating this work and Dr Rewari and Dr Amit Goel for reviewing the draft and for their valuable comments. In addition, we would like to thank Clinton Health Access Initiative and staff from World Health Organization for their technical and logistical support for the development of Myanmar's Simplified Guidelines for the Treatment of Hepatitis C Infection.

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Acronyms and Abbreviations

3TC/ FTC	Lamivudine/Emtricitabine
AASLD	American Association for the Study of Liver Diseases (AASLD)
ABC	Abacavir
AD/RUP/SIP	Auto-Disable/Re-Use Prevention/Sharps Injury Prevention
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
APRI	Aspartate Aminotransferase (AST)/platelet ratio index
ART	Antiretroviral Therapy
ATV/r	Atazanavir/Ritonavir
CBP	Complete Blood Picture
CrCl	Creatinine Clearance
CSW	Commercial Sex Worker
CT	Computerized Tomography
DAA	Direct-acting antiviral (drug)
ddI	Didanosine
DMS	Department of Medical Services
DMR	Department of Medical Research
DNA	Deoxyribonucleic acid
DOPH	Department of Public Health
DTG	Dolutegravir
EASL	European Association for the Study of the Liver
eGFR	Estimated Glomerular Filtration Rate
EFV	Efavirenz
ELISA	Enzyme-Linked Immunosorbent Assay
ESRD	End-stage Renal Disease
ETV	Etravirine
Hb	Haemoglobin
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
IA	Immunoassay

ICT	Immuno-Chromatographic Test
IDUs	Intravenous Drug Users
IFN	Interferon
LFT	Liver Function Test
LPV/r	Lopinavir/Ritonavir
MLF	Myanmar Liver Foundation
MSM	Men who have sex with men
NASH	Non-alcoholic Steatohepatitis
NAT	Nucleic Acid Testing
NHCP	National Hepatitis Control Program
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NS5A	Non-structural Protein 5A (of HCV)
NS5B	Non-structural protein 5B (of HCV)
NVP	Nevirapine
PCR	Polymerase Chain Reaction
PEG-IFN	Pegylated interferon
PI	Protease Inhibitor
PWID	People Who Inject Drugs
RBV	Ribavirin
RDT	Rapid Diagnostic Test
RNA	Ribonucleic Acid
SRA	Stringent Regulatory Authority
STI	Sexually Transmitted Infections
TDF	Tenofovir Disoproxil Fumarate
TPV/r	Tipranavir/Ritonavir
SVR	Sustained Viral Response
USG	Ultrasonography
VEL	Velpatasvir
WHO	World Health Organization

1. Introduction

Hepatitis C (HCV), which is mainly a blood borne viral infection, is a global public health problem with approximately 71 million people chronically infected worldwide and that 399 000 died from cirrhosis or hepatocellular carcinoma caused by HCV infection.[1]

HCV is endemic in Myanmar, and studies carried out by the Department of Medical Research showed different prevalence rates in different population groups at different periods and by different test systems. In a 2007 study, the prevalence of anti-HCV among people who inject drugs (PWIDs) ranged from 66% to 93%.[2] As per the National Blood Center annual report 2016, the prevalence of anti-HCV among the blood donors was found to be 0.37%.[3] In 2015, The National Prevalence Survey for Hepatitis B and C was conducted from May to November by the Department of Medical Research across 18 study sites covering all States and Regions. Key preliminary results from the prevalence survey shows that the prevalence of anti-HCV in the general population is 2.65%. The highest occurrence of anti-HCV positivity was found in Mawlamyine 10.34%, Mandalay 7.17% and Lashio (5.03%), respectively.[4]

The Myanmar GI and Liver Society successfully developed guidelines for the treatment of chronic hepatitis C infection in 2009, which were revised and published in 2017 to provide practical management of chronic hepatitis C for practicing physicians in the country.[5]

For many years, the standard treatment for HCV infection was weekly Pegylated Interferon injections combined with Ribavirin, both of which cause significant side effects. The use of interferon requires close monitoring of the patients by physicians for 24 - 48 weeks and has limited efficacy compared with recently developed all-oral drugs. Newly developed Direct Acting Antiviral (DAA) therapies are interferon-free but are combined with Ribavirin in some cases. At present,

1 WHO. (2018, July). WHO Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. https://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2018/en/.

2 Aung Thu, Aung Thaw, Khin May Oo *et al*. (2008). Anti-HCV sero-positivity in injection drug users (IDUs) attending the Registered Drug Treatment Centers. *Myanmar Health Sciences Research Journal*, Vol.20, No.3.

3 National Blood Center. (2016). Annual Report of the National Blood Center.

4 Report on the "National Prevalence of Hepatitis B and C infection in Myanmar", Department of Medical Research, 2016.

5 Myanmar GI and Liver Society, Myanmar Medical association. (2014). Treatment Guideline for the Chronic Hepatitis C Infection.

these all-oral regimens have cure rates of over 90%, shorter treatment periods (of 8 - 24 weeks) and excellent safety profiles. With ground breaking new treatments available, it is anticipated that over the next few years, 9 out of 10 people could be cured of hepatitis C by taking a short course of tablets with little or no side-effects.[6] DAA regimens consist of protease inhibitors, NS5B polymerase inhibitors, NS5A inhibitors and others. Because of their improved safety profile, an important fact is that the oral DAAs are not contraindicated in persons with advanced chronic liver disease. The cure rates for those[7] who are living with cirrhosis or people who did not previously respond well to treatment will also improve markedly.

Among many oral DAAs, the effects vary on the different genotypes of HCV so that the National Treatment Guidelines will have to be tailored according to the prevalence of the HCV genotypes in the country. In Myanmar, the dominant genotypes are genotype 3 (38.6%), genotype 6 (35.5%) and genotype 1 (25%).[8] However, the most recently developed DAA regimens are in fact pan-genotypic, allowing significant simplification of treatment algorithms. As a result, a simple guideline for HCV treatment for practical use throughout the country is preferred so that the treatment can be prescribed by most doctors for all hepatitis C patients in both urban and rural settings. In general, the first line of treatment will preferably be an interferon-free all oral pangenotypic DAAs in combination which will be effective for all the genotypes prevalent in Myanmar so that genotype testing can also be omitted for the therapy.

This guideline and recommendations are mainly based upon;

- Formal review of the recent publications (References)
- National consultation meetings with liver specialists, clinicians of ART centers, NHL, NBC, Liver Foundation, other relevant INGOs and stakeholders
- Myanmar GI and Liver Society, Myanmar Medical Association Treatment Guideline for the Chronic Hepatitis C Infection (2014)
- European Association for the Study of the Liver (EASL) Recommendations on Treatment of Hepatitis C (2018)

6 Hepatitis Australia Inc. (2015, May). Need to know news on hepatitis C treatment.

7 Keith Alcorn. (2019, January). Co-infection with HIV and HCV does not increase the risk of end-stage liver disease or liver cancer. *Infohep.* Retrieved from http://www.infohep.org/Co-infection-with-HIV-and-HCV-does-not-increase-the-risk-of-end-stage-liver-disease-or-liver-cancer/page/3414476/.

8 Hlaing KTN, et al. (2017). Safety and efficacy of sofosbuvir-based direct-acting antiviral regimens for hepatitis C virus genotypes 1-4 and 6 in Myanmar: Real-world experience. *J Viral Hepat.* 24:927–935.

- American Association for the Study of Liver Diseases (AASLD) Recommendations for Testing, Managing, and Treating Hepatitis C (2018)
- WHO Guidelines for the Screening, Care and Treatment of Persons with Chronic Hepatitis C Infection (2018)
- WHO Guidelines on Hepatitis B and C Testing (2017)
- WHO Hepatitis Progress Report (2018)
- Hepatitis Australia Inc. Need to know news on hepatitis C Treatment Updated (May 2015)
- Peer review by liver specialists based on local experiences (2018-2019)

The guideline is developed to provide information to the physicians, general practitioners and healthcare providers in Myanmar for the treatment of chronic Hepatitis C infection and/or for referral to a specialist center when appropriate.

2. Transmission of HCV

2.1 Transmission

HCV is mostly transmitted through exposure to infectious blood. The parenteral transmission occurs mostly with the sharing of contaminated needles and syringes, so that, the people who inject drugs are the most contracted with HCV infections. This may happen through healthcare-associated practices, HCV-infected blood and blood products and contaminated medical procedures. Mother-to-child transmission or sexual transmission is also possible, but is much less common, but occurs at a higher rate among those who are HIV co-infected. Other routes of transmission of HCV include intranasal drug use and other modes of blood borne transmission, such as cosmetic procedures (tattooing and body piercing), scarification and circumcision procedures.

Most HCV infection among children is due to vertical transmission and iatrogenic transmission in hospitals. Some transmission in adolescents is due to injecting drug use. Seroprevalence rates of 10-20% have been reported among children who have received invasive procedures in hospitals, such as hemodialysis or surgical procedures.[9,10]

9 Locasciulli A, Gornati G, Tagger A, Ribero ML, Cavalletto D, Cavalletto L, et al.(1991). Hepatitis C virus infection and chronic liver disease in children with leukemia in long-term remission. *Blood*. *78*(6):1619–22. Retrieved from http://www.bloodjournal.org/content/78/6/1619?sso-checked=true.

10 Rossetti F, Cesaro S, Pizzocchero P, Cadrobbi P, Guido M, Zanesco L. (1992). Chronic hepatitis B surface antigen-negative hepatitis after treatment of malignancy. Journal of Pediatriatrics.121(1):39–43. DOI: https://doi.org/10.1016/S0022-3476(05)82538-7.

2.2 Prioritized populations

In principle, those who come to health facilities should be screened for viral hepatitis C infection due to the high epidemic of Myanmar, emphasis on sub-populations as below.

- Patients who received blood products or organ transplants prior to the introduction of anti-HCV screening since 2000
- People who inject drugs (PWID), including those who injected many years ago and do not consider themselves drug users
- Children born to mothers infected with HCV, especially if HIV co-infected
- People with HIV infection
- People who have used intranasal drugs
- Prisoners and previously incarcerated people
- Men who have sex with men
- Persons who were ever on chronic hemodialysis
- Healthcare or public safety workers after accidental needle sticks, sharps, or other mucosal exposures to HCV-positive blood (or unknown)

3. Prevention

In the absence of a vaccine for hepatitis C infection, the approach for the prevention of HCV transmission is to reduce the risk of exposure to the virus. This is challenging because of the various routes of transmission and the various populations that are affected. A national and integrated prevention strategy should exist to reduce transmission by blood transfusion and other unsafe medical procedures and in addition, population-specific prevention strategies should be followed for high-risk groups such as healthcare workers and PWID. Treatment can prevent development of complications of infection, including cirrhosis and hepatocellular carcinoma, and can also reduce the risk of transmission in high risk groups.

3.1 Prevention of HCV in community settings [11]

- Avoid unsafe practices around non-medical or traditional practice (cosmetic, scarification, tattoos, circumcision procedures, traditional medical practice among others)
- Safe household practice – avoid sharing toothbrushes, razors, nail clippers, avoid sharing contaminated needles and syringes
- Promotion of correct and consistent condom use

It should be emphasized that HCV is not transmitted through household contact such as sharing food, utensils, kissing, hugging, or other casual contact.

3.2 Prevention of sexual transmission of HCV infection [12]

- Avoid multiple partners, seek regular screening and treatment for STIs
- Routine screening of sex workers in high-prevalence settings
- Integrated action to eliminate discrimination and gender violence and increased access to medical and social services for vulnerable persons

3.3 Prevention of HCV Infection in Health-care Settings [13,14]

- Follow universal precautions
- Hand hygiene: including surgical hand-washing and use of gloves
- Safe handling and disposal of sharps and waste
- Single-use needles, syringes and medical devices when possible
- Safe cleaning of equipment
- Testing of donated blood

11 WHO. (2012). Prevention and treatment of HIV and other sexually transmitted infections for sex workers in low- and middle-income countries: recommendations for a public health approach. *Recommendations for a public health approach.* Retrieved from https://apps.who.int/iris/bitstream/handle/10665/77745/9789241504744_eng.pdf?sequence=1.

12 WHO. (2011). Prevention and treatment of HIV and other sexually transmitted infections among men who have sex with men and transgender people. *Recommendations for a public health approach.* Retrieved from https://apps.who.int/iris/bitstream/handle/10665/44619/9789241501750_eng.pdf?sequence=1.

13 WHO. (2009). WHO guidelines on hand hygiene in health care. Retrieved from https://www.who.int/bloodsafety/publications/UniversalAccesstoSafeBT.pdf.

14 WHO. (2008). Universal access to safe blood transfusion. Retrieved from https://www.who.int/bloodsafety/publications/UniversalAccesstoSafeBT.pdf.

- Improved access to safe blood
- Training of health personnel

3.4 Injection safety [15]

A safe injection does not harm the recipient, does not expose the provider to any avoidable risks and does not result in any waste that is dangerous for other people. Among unsafe practices, the re-use of syringes and/or needles without sterilization is of particular concern. Injection-associated transmission of blood borne pathogens can be prevented through the development of a strategy to reduce injection overuse and achieve injection safety.

The three elements of WHO strategy for the safe and appropriate use of injections are:

(1) Behavior change among patients and health-care workers to decrease injection overuse and achieve injection safety

(2) Availability of necessary equipment and supplies, namely a transition to the exclusive use of WHO prequalified AD/RUP/SIP syringes for therapeutic injections

(3) Management of sharps waste [16]

3.5 Prevention of Hepatitis Infections (HCV and HBV Infections) among People Who Inject Drugs (PWID) [17,18]

- Offer hepatitis B screening to people who inject drugs the rapid hepatitis B vaccination regimen if found negative
- Encourage people who inject drugs to increase uptake and complete the hepatitis B vaccination schedule
- Implement program for provision of sterile injection equipment including needles and syringes, and provide low dead-space for syringes for

15 WHO. (2016). WHO guideline on the use of safety-engineered syringes for intramuscular, intradermal and subcutaneous injections in health care settings. Retrieved from https://apps.who.int/iris/bitstream/handle/10665/250144/9789241549820-eng.pdf?sequence=1.

16 WHO. (2010). Guidelines on drawing blood: best practices in phlebotomy. Retrieved from https://apps.who.int/iris/bitstream/handle/10665/44294/9789241599221_eng.pdf?sequence=1.

17 WHO (2012). Guidance on prevention of viral hepatitis B and C among people who inject drugs. Retrieved from https://apps.who.int/iris/bitstream/handle/10665/75357/9789241504041_eng.pdf?sequence=1.

18 WHO. (2009). Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence. Retrieved from https://www.who.int/substance_abuse/publications/opioid_dependence_guidelines.pdf.

distribution for people who inject drugs

- Offer peer interventions to people who inject drugs to reduce the incidence of viral hepatitis
- Offer opioid substitution therapy to treat opioid dependence, reduce HCV risk behavior and transmission through injecting drug use, and increase adherence to HCV treatment
- Integrate opioid substitution therapy and other drug-dependence treatment with medical services for hepatitis
- Provide targeted information, education and communication on HCV prevention for people who inject drugs and their sexual partners

3.6 HCV Post Exposure Prophylaxis [19]

After exposure to blood or other body substances, the following is recommended as soon as possible:

- Wash the wound site with soap and water
- If eyes are contaminated then rinse them, while they are open, gently but thoroughly with water or normal saline
- If blood or other body substances get in the mouth, spit them out and then rinse the mouth with water
- If clothing is contaminated, remove clothing and shower with soap
- Where water is not available use of non-water cleanser or antiseptic should replace the use of soap and water for washing cuts or punctures of the skin or intact skin
- Even after exposure to HCV, every exposed person shall be tested, at the baseline, for HBsAg, anti-HCV an HIV but not alone for HCV; hepatitis B vaccination of the HBsAg negative exposed person shall be initiated immediately
- Follow up testing shall be directed according to the serological status of the source person

19 Queensland health. (2017). Guideline for the management of occupational exposure to blood and body fluids. Retrieved from https://www.health.qld.gov.au/__data/assets/pdf_file/0016/151162/qh-gdl-321-8.pdf.

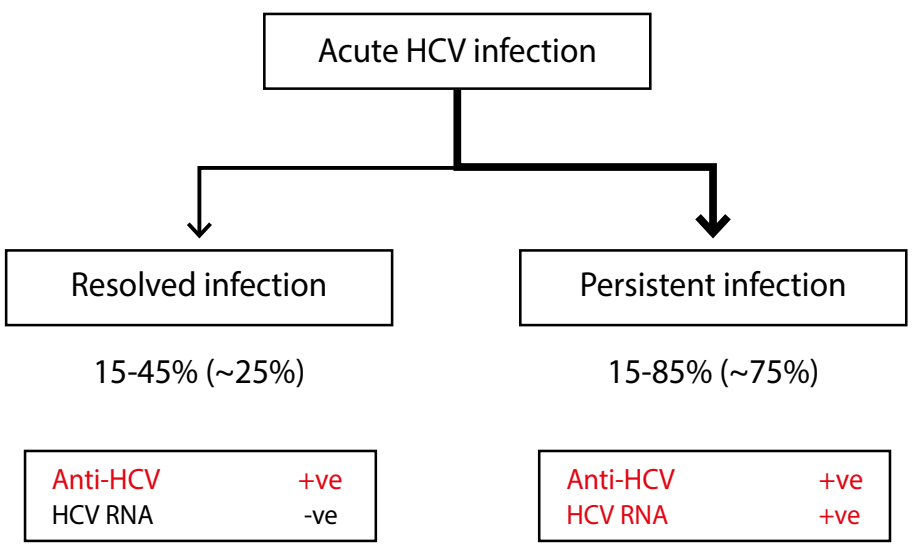
- HBV vaccination

4. Natural History of Disease

The majority of people who are infected with HCV are unaware of their chronic infection. They are at a high risk of developing severe chronic liver disease and associated complications of cirrhosis and hepatocellular carcinoma and can unknowingly transmit the infection to other people.

HCV causes both acute and chronic hepatitis. Acute HCV infection is defined as the presence of HCV within six months of exposure to and infection with HCV. In 15-45% of infected individuals, spontaneous clearance of acute HCV infection will occur within six months of infection in the absence of treatment. Almost all of the remaining 55-85 % will harbor HCV for the rest of their lives (if not treated) and are considered to have chronic HCV infection. HCV antibodies (Anti-HCV) develop as part of acute infection and persist through life. For this reason, a nucleic acid test for HCV RNA is needed to detect the presence of the virus and confirm chronic infection (see figure 1).

Figure 1. Natural history of hepatitis C infection [20]

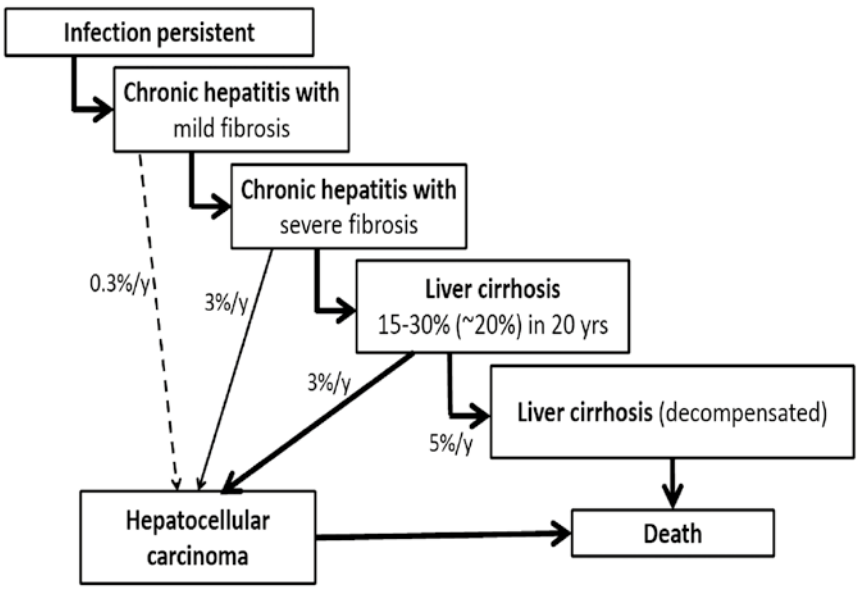


If left untreated, chronic HCV infection can cause liver cirrhosis, liver failure and hepatocellular carcinoma. The risk of liver cirrhosis is 15-30 % within 20 years. The risk of HCC in persons with cirrhosis is approximately 2-4% per year. The risk of

20 Rakesh,A. (2018, November). Natural history of hepatitis C infection. (presentation)TREATASIA training workshop on Hepatitis B and hepatitis C screening, diagnosis and treatment.

cirrhosis and HCC varies depending upon certain patient characteristics or behaviors. For example, persons who consume excess alcohol, persons with HBV or HIV and immunosuppressed individuals are at higher risk of developing cirrhosis and HCC (see figure 2).

Figure 2. Natural History of Chronic Hepatitis C Infection [21]



HCV disease association is not confined to the liver, and extrahepatic manifestations can include glomerulonephritis, cryoglobulinaemia, thyroiditis and Sjögren syndrome, insulin resistance type 2 diabetes mellitus, and some skin disorders.

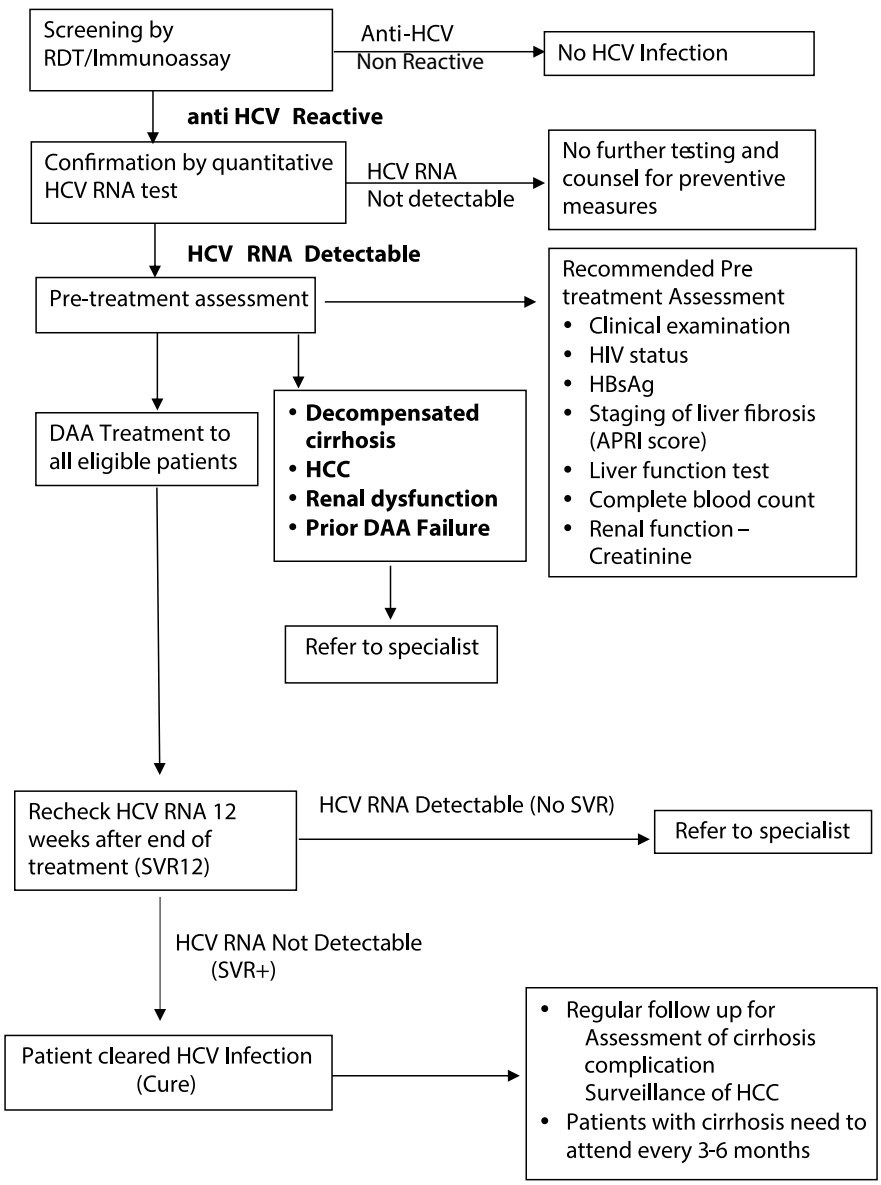
5. Simplified Diagnostic and treatment algorithm

For detailed diagnosis of viral hepatitis infections, kindly refer to the national hepatitis testing guidelines was published by the NHL. The currently available DAAs have far fewer side effects, and therefore eliminate the need for on-treatment monitoring in non-complex patients who do not require specialist care. Pan-genotypic DAA options, such as sofosbuvir/daclatasvir and sofosbuvir/velpatasvir, eliminate the need for genotyping as well in shown in figure 3.

21 Rewari BB. (2018, November). Clinical management of HCV infection. Module 5 (presentation). Training workshop on Hepatitis B and hepatitis C screening, diagnosis and treatment.

Figure 3. HCV Simplified Diagnostic and Treatment Algorithm

Referral to specialist is recommended for all the patients with decompensated liver cirrhosis, hepatocellular carcinoma, prior treatment failure and renal dysfunction.



5.1 Who should be tested

- Anti-HCV antibody tests should be administered to any patient seeking health services

- Screening for the population at higher risk:
    - HIV infected persons, people who inject drugs (PWID),
    - men who have sex with men (MSM),
    - repeated transfusion recipients,
    - health care workers,
    - prisoners
    - hemodialysis patients
- One time screening (when feasible) is done for
    - Pregnant woman
    - Household contacts
    - Institutionalized populations
- Screening of blood, blood products and organ donors is mandatory

5.2 Screening for Anti-HCV antibody

Screening for initial detection of HCV exposure (anti-HCV) should be done with a single serological test. The screening can either be done with a Rapid Diagnostic Test (RDT) or an Immunoassay (IA) that is WHO Prequalified or approved by a stringent regulatory authority (SRA). The single initial screening test is recommended before confirmatory testing regardless of the prevalence level within the population. RDTs should be prioritized over immunoassays in settings where they will increase access to testing. All antibody positive individuals must receive supplementary testing for viraemic active infection with a nucleic acid test (NAT) prior to initiation of HCV treatment. Only patients diagnosed with viraemic current infection will benefit from treatment. Patients who have spontaneously resolved HCV infection (and who are thus anti-HCV positive, but confirmatory test negative) should not be treated. Patients with ongoing risks should be retested.

5.3 Confirmatory testing of chronic HCV infection with HCV RNA Assays

It is recommended that nucleic acid testing* (NAT) for HCV RNA (quantitative) be performed directly following a positive HCV serological test to confirm current (active) chronic infection. An alternative test to confirm viraemic active HCV infection involves direct detection of the HCV core antigen (HCVcAg), which can be performed on automated immune analyzer platforms. Only patients who are

confirmatory test positive (either NAT or core antigen test) should be assessed for treatment eligibility and placed on treatment.

Patients who are Anti-HCV negative or viral load undetectable do not require further testing, and the patient can be counseled for preventive measures.

*National Hepatitis Control Program uses GeneXpert platform for HCV VL testing. Other NAT platforms such as Roche, Abbott are also available in the country.

Interpretation of Test Results

Antibody Test Result	HCV RNA Test Result	Interpretation
Negative	Negative	No HCV exposure / infection
Positive	Negative	HCV exposed or resolved or treated infection *also includes antibody false positives
Positive	Positive	HCV exposed & current infection

5.4 HCV Genotyping

Genotyping is not required due to availability of highly efficacious pan-genotypic regimens. If patients fail their first line treatment, genotyping will be useful for selection of appropriate second-line treatment.

6. Pre-treatment assessments

HCV-infected patients should be properly and thoroughly assessed before initiation of treatment

1. Alcohol consumption (ANNEX E: Alcohol Consumption Assessment: Audit interview questions)
2. HIV status, current ART treatment regimen
3. Pregnancy status - contraception during treatment and 6 months after the treatment
4. Baseline biochemical tests
    a. Liver Function Test (LFT) -ALT, Aspartate transferase (AST), Alkaline Phosphate, Bilirubin
    b. Renal Function Assessment - Creatinine

5. Complete Blood Count (CBC) to determine platelet count
6. Exclusion of HCC by ultrasonography (USG) if patient demonstrates signs of end stage liver disease

a. Alphafetoprotein (Optional)

7. Other laboratory tests
    a. All HCV patients should be screened for evidence of current HBV infection before initiating HCV therapy [22]
    b. The minimum tests to be performed prior to initiating patients on all-oral DAA therapy are: AST, Platelets and Creatinine

The AST and Platelets will be used to calculate the AST to Platelet Ratio Index (APRI) score to assess the presence of cirrhosis stage and creatinine will be used to determine renal function. An APRI calculator can be found here: https://www.hepatitisc.uw.edu/page/clinical-calculators/apri. [23]

In addition to the tests above, a physical examination by a trained medical professional is necessary to determine whether the patient is suspected of having advanced liver disease (decompensated cirrhosis or HCC), in which case, they should be referred to a specialist.

Clinical signs of cirrhosis: firm liver on abdomen palpation, spider nevi, palmar erythema, white nail, gynecomastia, and wasting syndrome.

Clinical signs of decompensation: jaundice, ascites, distended abdominal veins and caput medusa, hepatic encephalopathy, haematemesis and malena, and coagulopathy.

7. Staging and scoring

It is important to assess whether the patients have cirrhosis or not before starting DAAs therapy because cirrhosis will influence the possible addition of ribavirin or duration of therapy.

22 American association for the study of liver disease and Infectious diseases society of America. (2018, May). HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C:Monitoring Patients Who Are Starting HCV Treatment, Are on Treatment, or Have Completed Therapy. Retrieved from https://www.hcvguidelines.org/evaluate/monitoring.

23 Online score calculators are available at http://gihep.com/calculators/hepatology/fibrosis-4-score/ and http://www.hepatitisc.uw.edu/page/clinical-calculators/apri.

Therefore, for the practical purposes the following methods are recommended to assess the cirrhosis

1. Clinical examination
2. APRI
3. Metavir (fibroscan/elastography)
4. Ultrasound or CT

The APRI score correlates with METAVIR scores to indicate the degree of liver fibrosis:

Table 1. METAVIR Scoring System [24]

METAVIR stage	Definition
F0	No fibrosis
F1	Portal fibrosis without septa
F2	Portal fibrosis with septa
F3	Numerous septa without cirrhosis

Table 2. Aspartate Aminotransferase (AST)/Platelets Ratio Index (APRI)

Non-invasive test	Components assessed	Lower cut off	Upper cut off
APRI	AST and platelet count	0.5	1.5

Formula: APRI = [{AST (IU/L)/ AST_ULN (IU/L)} ×100]/platelet count (10^9/L)

AST - Aspartate aminotransferase

IU- International Unit

ULN- Upper Limit of Normal of the Lab (often 40 IU/ml)

24 WHO. (2018, July). Guidelines for the care and treatment of persons diagnosed with chronic hepatitis c virus infection Guidelines for the screening, care and treatment of persons with hepatitis infection.

APRI Calculation Example.

AST Level (IU/L) = 60

AST Upper Limit of Normal (IU/L) = 40

Platelet Count (10^9/L) = 133,000/mm^3 (Ref : 150,000 - 400,000/mm^3) = 133

APRI = [{60/40} x 100] / 133

APRI = [1.5 x 100] / 133

APRI = 150/133

APRI = 1.128

Table 3. APRI Score Interpretation

APRI score	Interpretation
> 1.5	Cirrhosis
0.5 - 1.5	Fibrosis, risk of cirrhosis
< 0.5	No Fibrosis

APRI – at the WHO recommended threshold of 2.0 – failed to identify most patients in need of treatment, with a sensitivity of 8.5% and a specificity of 99.3% compared to the EASL guidelines. Lowering the APRI threshold, however, improved the sensitivity without a substantial decrease in specificity [25]:

_ APRI >1.5: sensitivity 12.0% and specificity 98.5%

_ APRI >1.0: sensitivity 21.2% and specificity 98.0%

_ APRI >0.5: sensitivity 46.6% and specificity 94.8%

8. Treatment of patients with chronic HCV infection

All patients with chronic HCV infection should be considered for treatment, regardless of fibrosis stage or presence of co-infection (except pregnant women).

Prioritized populations

The National Hepatitis Control Program prioritizes the following patients for treatment:

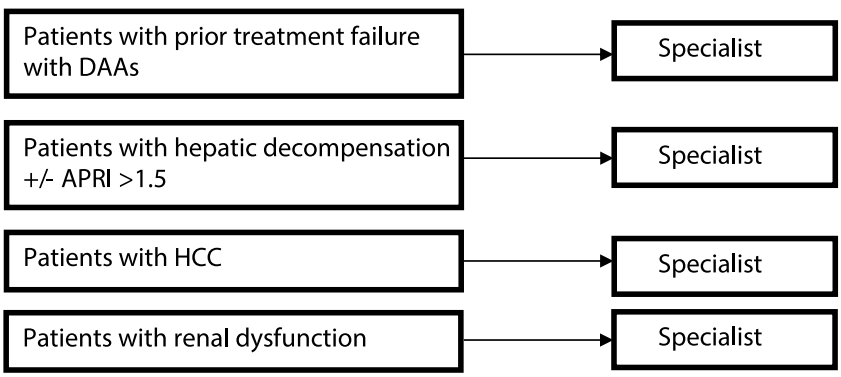
- Patients who are at fibrosis stage F3 and F4

25 Thet HM & Tun KS. (2018, January 21). Effectiveness of APRI score as a non-invasive marker of liver fibrosis in Chronic hepatitis C infected patients.

- Patients with decompensated cirrhosis
- HIV/HCV co-infected patients

9. Referral to Specialist

Patients with decompensated cirrhosis, irrespective of APRI score, should be referred to specialists for clinical management. The referral pathways for Myanmar are listed below.



10. Counseling and education about HCV infection and treatment [26]

10.1 People Testing Anti-HCV Negative

All patients who are confirmed anti-HCV negative should receive post-test counseling with the aim of reducing or eliminating risky behaviors which could lead to future transmission. The counseling session should include the following:

Explanation of the results and implications: if the antibody test is nonreactive, no antibodies were found in the blood, and this usually means the patient doesn't have HCV, but should not be confused for future immunity.

10.2 People Testing Anti-HCV Positive

All people who receive a positive anti-HCV test result should receive education and counseling about their HCV infection, care and treatment. The aim of the counseling should be to encourage confirmatory testing and to prevent

26 Center for Disease Control. (n.d.). A Guide to Comprehensive Hepatitis C Counseling and Testing. Retrieved from www.cdc.gov/hepatitis/resources/professionals/pdfs/counselingandtesting.pdf.

transmission before confirmatory testing. The counseling session should include the following:

- Explanation of the results and implications: Patient has been infected with the hepatitis C virus, but may or may not currently have hepatitis C as some people are able to clear the virus, although most do not. Patient will need to have another blood test to find out if they currently have hepatitis C
- Emphasis on the need for confirmatory testing and assistance with determining next steps
- Acknowledgement of concerns about HCV transmission, barriers to returning for additional testing, and addressing questions regarding potential illness
- General disease education, with emphasis on prevention and modes of transmission.
- Until the confirmatory tests, adherence counseling on standard prevention practices to avoid transmission in case chronic infection exists

10.3 People Confirmed with Chronic HCV

All people with a positive NAT test (detectable HCV RNA) are confirmed for chronic hepatitis C infection and should receive education and counseling about their HCV infection, care and treatment. The aim of the counseling should be to help the person reduce progression of liver disease and prevent him/her from transmitting HCV to others. The counseling session should include the following:

- Explanation of the results and implications: Patient has been infected with hepatitis C virus, and the confirmatory test is positive, which means the patient has hepatitis C, emphasizing that many people with hepatitis C remain healthy throughout their lives, but highly efficacious treatment options exist and they can be cured in more than 95% of cases with newer drugs
- Acknowledgement of concerns about stigma, transmission, and disease progression.
- Education on how to prevent transmission to others, especially in the case of injecting drug users. The counseling should also include an explanation of how HCV is not transmitted (sneezing, coughing, sharing drinking glasses, utensils).

- Discussion on other measures that can be taken to stay healthy: Alcohol and Liver Wellness: Consumption of alcohol can worsen the condition and they should be counseled to give up alcohol. All patients should be counseled on the importance of abstaining from alcohol and if necessary support in identifying resources to support the cessation of alcohol consumption.
- Weight Management: HCV-infected people with a body mass index (BMI) of greater or equal to 25 kg/m^2 should be counseled on how to reduce weight via nutrition, exercise or medical intervention.
- Vaccinations/Testing: Consider hepatitis B vaccination if susceptible and if liver disease is present. Consider testing for HIV.
- Caution/Medications: Avoid new medicines, including over-the-counter and herbal agents without first checking with a healthcare provider. Help patient understand the need to seek additional care and potential treatment, and connect him or her with the necessary services if not available on-site.

10.4 People Testing RNA Negative

All patients who are confirmed RNA negative should receive post-test counseling with the aim of assessing and then reducing or eliminating risky behaviours which could lead to future transmission. The counseling session should include the following:

- Explanation/interpretation of results: The patient was anti-HCV positive, but RNA negative, so the patient was exposed to the hepatitis C virus, but then cleared the virus naturally or has been treated and cured. They do not have chronic hepatitis C.
- Education on disease if patient has not received this education prior, highlighting that not having a current infection should not be confused with immunity to infection upon subsequent exposure.
- If there is an ongoing risk to the patient, emphasis on disease transmission and prevention awareness.
- Emphasis on the benefits of retesting in the future if engaging in risky behaviors.

11. Treatment

11.1 Goals of Therapy

- To reduce mortality related to HCV infection, prevent complications of HCV infected person and reduce transmission of HCV.

  Note: The aim of HCV treatment is viral cure having undetectable HCV RNA, but it should be noted that anti-HCV will be detectable for life. Additionally, cure does not prevent re-infection so it is important to ensure robust infection prevention and control procedures, especially among those at high ongoing risk such as PWIDs.

11.2 Anti-viral agents

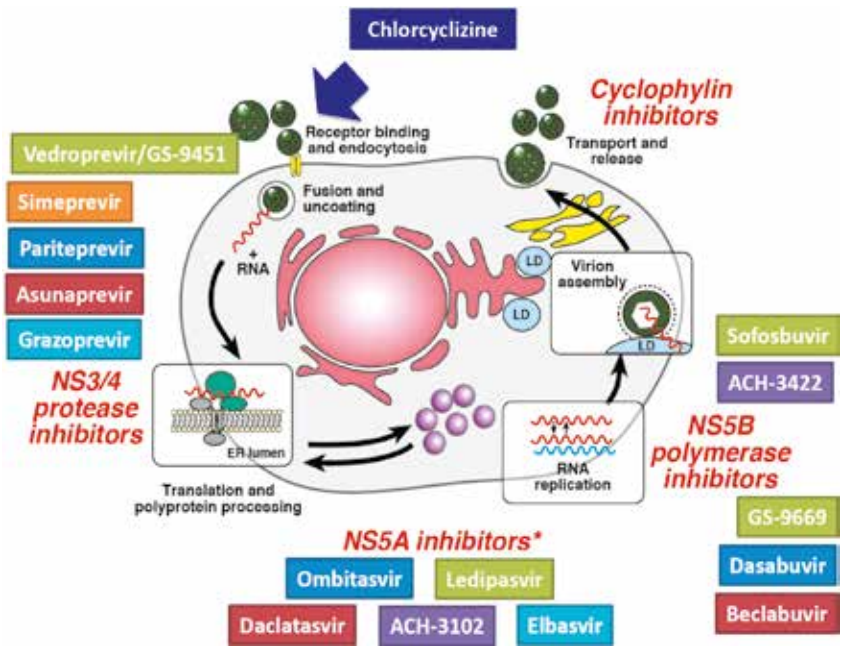
11.2.1 Direct-acting Antivirals (DAAs)

The treatment of chronic HCV infection has been transformed by the development of oral Direct-Acting Antivirals (DAAs). These medicines have a shorter duration, are associated with fewer side effects, and result insignificantly higher SVR rates than pegylated interferon-based treatment regimens. Given these benefits, it is recommended that DAAs be used for the treatment of HCV rather than pegylated interferon regimens.

There are various classes of DAAs including:

- Protease Inhibitors (PI)
- Nucleotide and Non-nucleotide NS5B Inhibitors
- NS5A inhibitors

Figure 4. Site of action of DAA [27]



11.2.2 Indications for antiviral therapy

All patients with chronic HCV infection must be considered for treatment irrespective of prior treatment history, i.e. treatment-naïve patients as well as treatment- experienced patients who failed to achieve SVR with interferon-based regimen or DAAs.

11.2.3 Recommended Regimens

DAA regimens can be used for the treatment of persons with hepatitis C infection rather than regimens with ribavirin.

Table 4. Recommended regimens in Myanmar

Recommendations for treatment	Regimen type	Treatment duration (weeks)	
		Cirrhosis	Non-cirrhosis
Preferred regimen	SOF/VEL	12	12
Alternative regimen 1	SOF/DCV	24	12
Alternative regimen 2	SOF/DCV+ Ribavirin	12	12

27 Bhawna Poonia & Shyam Kottilil (2015). Newer therapeutics for hepatitis C. *Annual Translational Medicine*. 4(2), 31. doi: 10.3978/j.issn.2305-5839.2015.10.06.

If any other DAAs combinations become available, according to the WHO guidelines it is also be considered to use.

Preferred regimen

- **Sofosbuvir + Velpatasvir**
  - 12 weeks for both non-cirrhotic and cirrhotic patients
  - *Special Considerations for ART patients (See 6.3, Table 10):*
    - Velpatasvir is safe for use with most HIV medications but should be avoided in those taking Ritonavir boosted tipranavir, Efavirenz, Atravirine, and Nevirapine.
    - SOF/VEL is not recommended in patients with severe renal impairment (estimated GFR <30mL/min/1.73m$^{2)}$ or end stage renal disease.

Alternative regimen 1

- **Sofosbuvir + Daclatasvir**
  - 12 weeks for non-cirrhotic patients (APRI < 1.5)
  - 24 weeks for cirrhotic patients (APRI ≥ 1.5)
  - *Special Considerations for ART patients (See 6.3, Table 10):*
    - Increase daclatasvir dosage to 90 mg per day when co-administered with Efavirenz
    - Decrease daclatasvir dosage to 30 mg per day when co-administered with Atazanavir/Ritonavir
    - Decrease dosage to 30 mg per day with the antibacterials clarithromycin, telithromycin, erythromycin and the antifungals ketoconazole, itraconazole, posaconazole and voriconazole.
    - Sofosbuvir is not recommended in patients with severe renal impairment (estimated GFR <30mL/min/1.73m$^{2)}$ or end stage renal disease.

Alternative regimen 2

- **Sofosbuvir + Daclatasvir + Ribavirin**
  - 12 weeks for non-cirrhotic patients (APRI < 1.5)
  - 12 weeks for cirrhotic patients (APRI ≥ 1.5)
  - Special Considerations for ART patients
  - Ribavirin dose adjustments and close monitoring should be made based on the severity of the renal dysfunction.

11.2.4 Dosing for HCV Treatment Regimens

Table 5. Dosing for Recommended HCV Treatment Regimens

Regimen	Dosage per tablet	Dosing Frequency and Timing
Velpatasvir/ Sofosbuvir	100mg/400mg FDC (special considerations for ART patients in table 10)	Once daily
Daclatasvir*/ Sofosbuvir	30 mg and/or 60 mg/400 mg tablet (special considerations for ART patients in table 10)	once daily - morning
Oral Ribavirin	200 mg capsule or 400 mg tablet or 500 mg tablet	Twice daily with a weight-based dose of 15 mg/kg/day

*Increase daclatasvir dosage to 90 mg per day when co-administered with Efavirenz. Decrease daclatasvir dosage to 30 mg per day when co-administered with Atazanavir/Ritonavir. Decrease daclatasvir dosage to 30 mg per day with the antibacterials clarithromycin, telithromycin, erythromycin and the antifungals keto-conazole, itraconazole, posaconazole and voriconazole

12. Treatment Monitoring

12.1 On Treatment Monitoring

On-treatment monitoring is not generally required when using all-oral DAA regimen, except in the following situations:

- **Renal impairment**: If Sofosbuvir or Ribavirin based regimens are utilized in patients with chronic kidney disease, renal function should be monitored (Creatinine clearance) as both exhibit renal clearance.
- **Treatment with Ribavirin based regimens:** Severe hemolytic anemia with significant initial drops in hemoglobin may occur, therefore careful monitoring should be initiated. Complete blood count and renal function should be monitored at baseline before the initiation of treatment, at week 4 during the treatment and at week 12 after the completion of treatment.[28]
- Monitoring for complete blood count if on Ribavirin.
- Direct Monitoring of viral replication through NAT or core antigen testing during treatment is not recommended.

**** Attending physician should stop the treatment on own discretion at any time for reasons such as clinical deterioration and life threatening conditions**

12.2 Assessment of Response to Therapy (Post-treatment)

- HCV RNA viral load test should be conducted at 12 weeks after the completion of treatment to confirm Sustained Viral Response (SVR12). Patients that do not achieve SVR should be referred to a specialist. Core antigen testing is currently not recommended as a test to determine cure
- Cirrhotic Patients who achieve SVR12 still need to be followed-up regularly for the assessment of complications of cirrhosis and hepatocellular carcinoma (HCC) with ultrasound with/without AFP.
- Patients with cirrhosis - Follow up with ultrasound within 3-6 months
- Patients without cirrhosis – should be discharged provided that they have no other comorbidity

28 WHO. (2018, July). Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection.

- Patients who do not achieve SVR should be referred to a specialist.

13. Treatment considerations for special populations [29]

13.1 HCV/HIV Coinfection

The WHO's 2018 guidelines for the treatment of HCV recommend that all persons with HIV/HCV coinfection be considered for HCV treatment as there is generally a more rapid progression of liver fibrosis in HIV/HCV co-infected persons, especially in patients with a CD4 count of < 200 cells/mm^3 In addition, the risk of hepatic decompensation remains higher in co-infected patients even if successful control of HIV infection has been achieved.

The choice of ART for persons with HIV/HCV co-infection should follow the same guidelines as for those with HIV alone, although the choice of HCV treatment must take into account drug-drug interactions between ARVs and DAAs and dose adjustments of DAA therapy, depending on the DDI in question. If there is a need to alter the HIV regimen in order to avoid a drug-drug interaction between ART and DAA regimen, this should only be done in consultation with the patient's HIV provider. While treatment of this population was traditionally difficult with interferon and ribavirin regimens, DAA therapy has simplified treatment, and the treatment of mono-infected and co-infected patients with DAAs is now largely the same.

Treatment initiation:

- In the majority of cases, it is advisable to first initiate treatment for HIV and achieve HIV suppression before staring HCV treatment, although in specific circumstances, it may be advisable to treat the HCV infection first.
- This could include persons at risk of rapid liver disease progression, not experiencing significant immunosuppression
- It is recommended that DAA treatment is initiated once HIV viral load is suppressed, regardless of CD4 count.

13.2 Children and Adolescents

Children and adolescents with HCV infection should be referred to specialist.

29 WHO. (2016). *Guidelines for the screening care and treatment of persons with chronic hepatitis C infection.*

13.3 Pregnant Women

Screening: Screening is recommended for all pregnant women to enhance detection of cases.

Care and Treatment: Pregnant women who are HCV RNA positive should be linked to care and retained to start treatment after delivery. DAA should be deferred during lactation.

13.4 People who Inject Drugs

Screening: PWIDs should be prioritized for screening due to their high rates of prevalence, morbidity and ongoing transmission. Screening should be performed as part of the harm reduction package annually among PWID, which also includes opioid substitution therapy, sterile injection equipment and addiction counselling. For PWID who have successfully achieved SVR12 and are continuing to inject drugs, re-infection is possible. Therefore, screening should be continued annually using nucleic acid testing.

Care and Treatment: HCV treatment has been proven effective in PWID, and may have a treatment as prevention effect if networks of drug users are treated. Multiple studies have demonstrated no difference between SVR12 rates for PWID and non-PWID, even when PWID are active users. A recent study of treatment response on sofosbuvir/velpatasvir among people receiving opioid substitution therapy (OST) demonstrated no impact of OST on adherence, treatment completion, Sustained Viral Response or safety.[30] PWID who complete treatment must receive counseling on the possibilities of re-infection due to continuing risk behaviors such as sharing of needles and paraphernalia.

13.5 Decompensated Cirrhosis

They should be referred to specialist.

13.6 Antiviral Treatment Experienced

All patients who failed to respond to DAA should be referred to specialist.

30 Grebeley et al. *Efficacy and safety of sofosbuvir/velpatasvir in patients with chronic hepatitis C virus infection receiving opioid substitution therapy: Analysis of Phase 3 Astral Trials.* Clin Inf Dis. 2016. http://cid.oxfordjournals.org.

14. Comorbidities

14.1 HCV/HBV co-infection

Hepatitis C virus may suppress HBV replication in acutely or chronically infected patients with reduction of HBsAg serum titer observed in HCV/HBV co-infected patients.[31],[32] Although some studies demonstrate mutual suppression of HCV and HBV, dual infection of both viruses may lead to increased hepatitis related morbidity. Additionally, during treatment with DAA medications and after HCV clearance, there is a risk of HBV reactivation and potentially fatal acute flares.[33]

Given the risk of reactivation, **all HCV patients should be screened for evidence of current or prior HBV infection before initiating HCV therapy**. The US Federal Drug Administration (FDA) recommends screening all patients for evidence of current or prior HBV infection by measuring HBsAg and anti-HBc as cases of liver flares during HCV treatment have been reported in HBsAg-positive patients and those with evidence of resolved infection (HBsAg-negative and anti-HBc positive).[34] Chronic HCV patients with evidence of active or resolved HBV infection should be treated by physicians with expertise in managing and monitoring hepatitis B and with consideration for HBV antiviral treatment in HBV/HCV co-infected patients. It has been recommended to start patients who meet criteria for treatment of active HBV infection on therapy at the same time (or before) HCV DAA therapy is started. Monitoring of patients with active or resolved HBV infection should include clinical and laboratory monitoring (i.e. HBsAg, HBV DNA, serum aminotransferase levels, bilirubin) of hepatitis flare or HBV reactivation during DAA treatment and post-treatment follow-up.

14.2 HCV/TB co-infection

TB screening should be completed before consideration of HCV treatment, especially among those with advanced immunosuppression. The absence of cough, fever, weight loss or night sweat is reasonable to exclude active TB infection.

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31 Crespo J, Lozano JL, Carte B, de las Heras B, de la Cruz F, Pons-Romero F. (1997). Viral replication in patients with concomitant hepatitis B and C virus infections. *Eur J Clin Microbiol Infect Dis. 16*:445-451.

32 Liaw YF, Tsai SL, Chang JJ, Sheen IS, Chien RN, Lin DY, Chu CM. (1994). Displacement of hepatitis B virus by hepatitis C virus as the cause of continuing chronic hepatitis. *Gastroenterology. 106*:1048-1053.

33 Aggeletopoulou I, Konstantakis C, Manolakopoulos S, and Triantos C. (2017, June). Risk of hepatitis B reactivation in patients treated with direct-acting antivirals for hepatitis C. *World J Gastroenterol. 23(24)*: 4317–4323.

34 Calvaruso V and Craxì A. (2017). HBV recurrence after HCV clearance on DAAs: Sometimes they come back. Journal of Hepatology. *67* j 898–901. Retrieved from https://www.journal-of-hepatology.eu/article/S0168-8278(17)32256-0/pdf.

Concurrent treatment of TB and HCV should be avoided secondary to interactions between HCV DAAs and TB medications. Specifically, anti-tuberculosis medicines such as rifampicine, rifapentin or rifabutin modulate the concentration of several HCV DAAs when given concurrently. HCV infected patients diagnosed with active TB infection should complete TB treatment before starting HCV treatment, and should be referred to specialist teams.

14.3 HCV and Alcohol Use

The consumption of alcohol, even in moderate amounts, in people with chronic HCV infection results in more rapid progression of advanced liver disease and HCC.[35] People diagnosed with chronic HCV should be counseled to limit or abstain from alcohol consumption and offered access to alcohol cessation services, where possible. The WHO ASSIST framework can provide a framework and tools for evaluating alcohol dependence and implementing counseling.

For patients with alcohol disorders who are eligible for treatment, it is recommended that patients stop drinking prior to treatment due to its deleterious effects on adherence.[36] For patients who continue drinking during treatment, clinicians should provide extra support to ensure treatment adherence.

14.4 HCV/Non-alcoholic steatohepatitis (NASH)

Non-alcoholic steatohepatitis (NASH) is a liver disease characterized by a build-up of fat in the liver along with inflammation and damage. Like hepatitis C, NASH develops slowly over time and progresses to advanced liver disease.

Chronic HCV patients with NASH are a recommended target population for treatment in order to halt progression of liver disease. Patients should be monitored carefully during treatment for any complications arising from more severe underlying liver disease. There are currently no treatments for NASH other than lifestyle changes to reduce obesity and promote liver health.

14.5 HCV/Mental Health Disorders

HCV is associated with higher rates of mental health disorders compared to the general population. Increased prevalence of psychiatric co-morbidity in patients with HCV infection can be attributed to multiple causes including risk behaviours

35 Vandenbulcke, H. et al. (2016). Alcohol Intake Increases the Risk of HCC in hepatitis C virus-related compensated cirrhosis: A prospective study. *J Hep Vol. 65.* 543-551.

36 Anand BS, Currie S, Dieperink E, Bini EJ, Shen H, Ho SB, et al. (2006). Alcohol Use and Treatment of Hepatitis C Virus: Results of a National Multicenter Study. *Gastroenterology*. *130:* 1607-1616.

in patients with psychiatric disorders, the effect of HCV on the central nervous system, and the psychosocial effects of disease stigma and discriminination.[37]

Pegylated interferon treatment is also associated with various neurological and psychiatric effects including debilitating fatigue, depression, anxiety and cognitive disturbances, with rare cases of suicidal thoughts. DAAs have not been associated with significant impact on mental health and are not believed to have neuropsychiatric effects.

Mental health disorders have a high likelihood of affecting treatment access adherence rates and a robust assessment of a patient's psychiatric history prior to treatment history is essential for mitigating any negative effects on treatment success. Involvement of appropriate mental health personnel in the care and treatment plan of the patient is important. Depending on the degree of mental health disorder, pretreatment of the mental health disorder may be warranted prior to initiating HCV treatment.

During treatment, patients with mental health disorders on treatment should be assessed for mood changes every four weeks. There is a high risk of drug-drug interactions between psychiatric medications and DAAs. Pharmacists must pay attention to potential drug-drug interactions between mental health medications and HCV medications. St John's Wort, commonly prescribed for depression, and carbamazepine, are contra-indicated with sofosbuvir.

14.6 HCV/Chronic Kidney Disease

Co-morbidity between HCV and renal impairment is common. Renal impairment includes patients with:

- Stage 4 disease where eGFR is between 15 and 29 ml/min/1.73m^2
- Stage 5 disease where eGFR is less than 15ml/min/1.73m^2 and patients are on dialysis
- Post-renal transplant patients
- Mixed essential cryoglobulinemia and related liver damage

37 Schaefer M et al. (2012). Hepatitis C infection, antiviral treatment and mental health: A European expert consensus statement. *J Hepatol*. http://dx.doi.org/10.1016/j.hep.2012.07.037.

Renal impairment patients have a high risk of morbidity, disease progression and mortality and are a priority group for treatment, where clinically safe to do so. However, limited treatment options for patients with advanced renal disease currently exist.

- Patients with eGFR rates above 30 ml/min/1.73 m^2 can be treated with normal doses of DAAs, including sofosbuvir/ daclatasvir and sofosbuvir/ Velpatasvir.
- Studies are ongoing to further investigate the safety of Sofosbuvir in patients with eGFR rates below 30 ml/min/1.73 m^2
- However, eGFR rates below 30 ml/min/1.73 m^2, are currently contra-indicated for treatment with sofosbuvir as it is eliminated through the renal system. Limited clinical studies have been conducted in this population, and studies like the TARGET 2.0 real-world cohort study showed progressive deterioration of renal function among patients with advanced renal disease taking sofosbuvir-containing regimens.[38]
- Another newer pan-genotypic DAA combination: Glecaprevir / Pibrentasvir can be used in patients with severe renal failure (eGFR < 30 ml/min/1.73 m^2), however access to this combination is limited currently in Myanmar.
- Ribavirin is also associated with treatment difficulties for patients with end stage renal disease. Patients with an eGFR <50 ml/min/1.73 m^2 require ribavirin dose adjustment and those on dialysis must have the dose lowered to 200 mg per day or take it three times per week. Increased monitoring is required in this group.
- Referral to specialist is recommended in patients with renal dysfunction, especially with low eGFR.

38 Saxena V, Koraishy FM, Sise ME, Lim JK, Schmidt M, Chung RT, et al. (2016). Safety and efficacy of sofosbuvir-containing regimens in hepatitis C-infected patients with impaired renal function. *Liver Int*. *36*:807–816.

15. Annexes

15.1 ANNEX A: Drug-drug interactions, contraindications, warnings and adverse events for available treatment regimens

15.1.1 Drug - Drug Interactions

Table 6. Potentially significant drug interactions of Sofosbuvir [39,40]

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
Antiarrhythmics: amiodarone	Effect on amiodarone and sofosbuvir concentrations unknown	Coadministration of amiodarone with sofosbuvir in combination with another DAA may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. Coadministration of amiodarone with sofosbuvir in combination with another DAA is not recommended; if coadministration is required, cardiac monitoring is recommended.
Anticonvulsants: carbamazepine, phenytoin, phenobarbital, oxcarbazepine	↓ sofosbuvir ↓ GS-331007	Coadministration of sofosbuvir with carbamazepine, phenytoin, phenobarbital or oxcarbazepine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of sofosbuvir. Coadministration is not recommended.
Antimycobacterials: rifabutin rifampin rifapentine	↓ sofosbuvir ↓ GS-331007	Coadministration of HARVONI with rifabutin or rifapentine is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of HARVONI. Coadministration is not recommended. Coadministration of HARVONI with rifampin, a P-gp inducer, is not recommended.

39 AASLD-IDSA. (2018, May). Recommendations for testing, managing, and treating hepatitis C. Retrieved from https://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/HCVGuidance_May_24_2018b.pdf.

40 European Association of the Study of the Liver. (2018). Clinical practice guidelines. EASL Recommendations on Treatment of Hepatitis C 2018. Journal of Hepatology. 1-5. Retrieved from https://easl.eu/wp-content/uploads/2018/10/HepC-English-report.pdf.

Herbal Supplements: St. John's wort (Hypericum perforatum)	↓ sofosbuvir ↓ GS-331007	Coadministration of sofosbuvir with St. John's wort, an intestinal P-gp inducer, is not recommended.
HIV Protease Inhibitors: tipranavir/ritonavir	↓ sofosbuvir ↓ GS-331007	Coadministration of sofosbuvir with tipranavir/ritonavir is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of sofosbuvir. Coadministration is not recommended.

Table 7. Potentially significant drug interactions of Daclatasvir [41]

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
HIV antiviral agents:		
Protease inhibitors: Atazanavir with ritonavir Indinavir Nelfinavir Saquinavir	↑ Daclatasvir	Decrease daclatasvir dose to 30 mg once daily.
Other antiretrovirals: Cobicistat-containing antiretroviral regimens Examples: atazanavir/cobicistat, elvitegravir/cobicistat/ emtricitabine/ tenofovir disoproxil fumarate	↑ Daclatasvir	Decrease daclatasvir dose to 30 mg once daily except with darunavir combined with cobicistat.
Non-nucleoside reverse transcriptase inhibitors (NNRTI): Efavirenzb Etravirine Nevirapine	↓ Daclatasvir	Increase daclatasvir dose to 90 mg once daily.
Strong CYP3A inhibitors:		

Examples: clarithromycin, itraconazole, ketoconazole,b nefazodone, posaconazole, telithromycin, voriconazole	↑ Daclatasvir	Decrease daclatasvir dose to 30 mg once daily when coadministered with strong inhibitors of CYP3A.
Moderate CYP3A inducers:		
Examples: bosentan, dexamethasone, modafinil, nafcillin, rifapentine	↓ Daclatasvir	Increase daclatasvir dose to 90 mg once daily when coadministered with moderate inducers of CYP3A.
Anticoagulants:		
Dabigatran etexilate mesylate	↑ Dabigatran	Use of daclatasvir with dabigatran etexilate is not recommended in specific renal impairment groups, depending on the indication. Please see the dabigatran prescribing information for specific recommendations.
Cardiovascular agents:		
Antiarrhythmic: Amiodarone	Amiodarone: effects unknown	Coadministration of amiodarone with DAKLINZA in combination with sofosbuvir is not recommended because it may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. If co-administration is required, cardiac monitoring is recommended.

Antiarrhythmic: Digoxinb	↑ Digoxin	**Patients already receiving daclatasvir initiating digoxin**: Initiate treatment using the lowest appropriate digoxin dosage. Monitor digoxin concentrations; adjust digoxin doses if necessary and continue monitoring. **Patients already receiving digoxin prior to initiating daclatasvir**: Measure serum digoxin concentrations before initiating daclatasvir. Reduce digoxin concentrations by decreasing digoxin dosage by approximately 15% to 30% or by modifying the dosing frequency and continue monitoring.
Lipid-lowering agents:		
HMG-CoA reductase inhibitors: Atorvastatin Fluvastatin Pitavastatin Pravastatin Rosuvastatinb Simvastatin	↑ Atorvastatin ↑ Fluvastatin ↑ Pitavastatin ↑ Pravastatin ↑ Rosuvastatin ↑ Simvastatin	Monitor for HMG-CoA reductase inhibitor associated adverse events such as myopathy.
Narcotic Analgesic/Treatment of Opioid Dependence:		
buprenorphine buprenorphine/naloxone	↑ buprenorphine ↑ norbuprenorphine	For buprenorphine or buprenorphine/naloxone, no adjustment is needed, but clinical monitoring for buprenorphine associated adverse events is recommended.
HIV Antiretrovirals:		
Regimens containing tenofovir DF without a HIV protease inhibitor/ritonavir or cobicistat	↑ tenofovir	Monitor for tenofovir-associated adverse reactions in patients receiving sofosbuvir/ledipasvir concomitantly with a regimen containing tenofovir DF without a HIV protease inhibitor/ritonavir or cobicistat. Refer to VIREAD or TRUVADA prescribing information for recommendations on renal monitoring.

Regimens containing tenofovir DF and a HIV protease inhibitor/ritonavir or cobicistat •atazanavir/ritonavir or cobicistat + emtricitabine/tenofovir DF •darunavir/ritonavir or cobicistat + emtricitabine/tenofovir DF •lopinavir/ritonavir + emtricitabine/tenofovir DF	↑ tenofovir	The safety of increased tenofovir concentrations in the setting of sofosbuvir/ledipasvir and a HIV protease inhibitor/ritonavir or cobicistat has not been established. Consider alternative HCV or antiretroviral therapy to avoid increases in tenofovir exposures. If coadministration is necessary, monitor for tenofovir-associated adverse reactions. Refer to VIREAD or TRUVADA prescribing information for recommendations on renal monitoring.
elvitegravir, cobicistat, emtricitabine, tenofovir DF	↑ tenofovir	The safety of increased tenofovir concentrations in the setting of sofosbuvir/ledipasvir and the combination of elvitegravir, cobicistat, emtricitabine and tenofovir DF has not been established. Coadministration is not recommended.
tipranavir/ritonavir	↓ ledipasvir ↓sofosbuvir	Coadministration of sofosbuvir/ledipasvir with tipranavir/ritonavir is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of HARVONI. Coadministration is not recommended.
HCV Products: simeprevir	↑ ledipasvir ↑ simeprevir	Concentrations of ledipasvir and simeprevir are increased. when simeprevir is coadministered with ledipasvir. Coadministration of HARVONI with simeprevir is not recommended.
Herbal Supplements: St. John's wort (Hypericum perforatum)	↓ledipasvir ↓ sofosbuvir	Coadministration of sofosbuvir/ledipasvir with St. John's wort, a P-gp inducer is not recommended

HMG-CoA Reductase Inhibitors: rosuvastatin	↑ rosuvastatin	Coadministration of sofosbuvir/ledipasvir with rosuvastatin may significantly increase the concentration of rosuvastatin which is associated with increased risk of myopathy, including rhabdomyolysis. Co-ad-ministration of sofosbuvir/ledipasvir with rosuvastatin is not recommended.

Table 8. Potentially significant drug interactions of ribavirin [40]

Drug Name	Effect on Concentration	Clinical comment
Atazanavir (ATV)	Increased risk of jaundice when used with ribavirin, although this is unlikely to be clinically significant	Patient should be warned of possible increased jaundice and reassured that this is unlikely to be dangerous
Abacavir (ABC)	Possible antagonism with ribavirin	Use weight based ribavirin dosing to ensure adequate levels
Zidovudine (AZT)		Risk of anemia
Didanosine (ddI)	Ribavirin may increase toxicity of Didanosine and may also increase the serum concentration	Should not be used together. *ddI is no longer recommended for the treatment of HIV infection due to mitochondrial toxicity.
Azathioprine	Ribavirin may increase concentrations	Consider using alternative agents OR monitor very closely for signs of bone marrow suppression
Influenza virus vaccine	Ribavirin may decrease the therapeutic effect of the vaccine	Repeat vaccine if received ribavirin within 2 weeks of the vaccination

Table 9. Potentially significant drug interactions of Sofosbuvir/Velpatasvir [41]

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Effect/Recommendation
Acid Reducing Agents:	↓ velpatasvir	Velpatasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease concentration of velpatasvir.
Antacids (e.g., aluminum and magnesium hydroxide)		Separate antacid and EPCLUSA administration by 4 hours.
H2 -receptor antagonistsc (e.g., famotidine)		H2 -receptor antagonists may be administered simultaneously with or 12 hours apart from EPCLUSA at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
Proton-pump inhibitorsc (e.g., omeprazole)		Coadministration of omeprazole or other proton-pump inhibitors is not recommended. If it is considered medically necessary to coadminister, EPCLUSA should be administered with food and taken 4 hours before omeprazole 20 mg. Use with other proton pump-inhibitors has not been studied.
Antiarrhythmics: amiodarone	Effect on amiodarone, sofosbuvir, and velpatasvir concentrations unknown	Coadministration of amiodarone with EPCLUSA may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. Coadministration of amiodarone with EPCLUSA is not recommended; if coadministration is required, cardiac monitoring is recommended *[see Warnings and Precautions (5.1) and Adverse Reactions (6.2)]*.

41 HIV insite. (2019). All interactions with Sofosbuvir/velpatasvir (Epclusa). Retrieved from http://hivinsite.ucsf.edu/insite?page=ar-00-02&post=4&param=327.

digoxinc	↑ digoxin	Therapeutic concentration monitoring of digoxin is recommended when coadministered with EPCLUSA. Refer to digoxin prescribing information for monitoring and dose modification recommendations for concentration increases of less than 50%.
Anticancers: topotecan	↑ topotecan	Coadministration is not recommended.
Anticonvulsants: carbamazepine phenytoin phenobarbital oxcarbazepine	↓ sofosbuvi ↓ velpatasvir	Coadministration is not recommended.
Antimycobacterials: rifabutin rifampinc rifapentine	↓ sofosbuvir ↓ velpatasvir	Coadministration is not recommended.
HIV Antiretrovirals:		
efavirenzc	↓ velpatasvir	Coadministration of EPCLUSA with efavirenz-containing regimens is not recommended.
Regimens containing tenofovir DF	↑ tenofovir	Monitor for tenofovir-associated adverse reactions in patients receiving EPCLUSA concomitantly with a regimen containing tenofovir DF. Refer to the prescribing information of the tenofovir DF-containing product for recommendations on renal monitoring.
tipranavir/ritonavir	↓ sofosbuvir ↓ velpatasvir	Coadministration is not recommended.
Herbal Supplements: St. John's wort *(Hypericum perforatum)*	↓ sofosbuvir ↓ velpatasvir	Coadministration is not recommended.
HMG-CoA Reductase Inhibitors: rosuvastatinc	↑ rosuvastatin	Coadministration of EPCLUSA with rosuvastatin may significantly increase the concentration of rosuvastatin, which is associated with increased risk of myopathy, including rhabdomyolysis. Rosuvastatin may be administered with EPCLUSA at a dose that does not exceed 10 mg.

atorvastatin	↑ atorvastatin	Coadministration of EPCLUSA with atorvastatin is expected to increase the concentrations of atorvastatin, which is associated with increased risk of myopathy, including rhabdomyolysis. Monitor closely for HMG-CoA reductase inhibitor-associated adverse

Table 10. Drug-drug interactions between co-administered HCV and HIV treatment [42]

		Sofosbuvir	Daclatasvir	Velpatasvir
NRTIs	ABC			
	3TC/FTC			
	TDF			
NNRTIs	EFV		**	
	ETV		**	
	NVP		**	
Protease inhibitors	ATV/r		**	*
	LPV/r			*
	TPV/r			
Entry/ Integrase inhibitors	RAL			
	DTG			

These drugs should not be co-administered

Potential interaction

No clinically significant interaction expected

*Only problematic when administered with tenofovir disoproxil fumarate; tenofovir levels are increased.

** Decrease daclatasvir dose to 30 mg once daily with atazanavir; increase daclatasvir dose to 90

42 University of Liverpool Hepatitis drug interactions. (2019). Retrieved from http://www.hep-druginteractions.org/ and HIV drug interactions webpage www.hiv-druginteractions.org/.

mg once daily with efavirenz, etravirine or nevirapine

*** The AASLD 2015 guidelines advise caution with ledipasvir in patients with HIV/HCV co-infection: "Because ledipasvir increases tenofovir levels, when given as Tenofovir Disoproxil Fumarate, concomitant use mandates consideration of creatinine clearance (CrCl) rate and should be avoided in those with CrCl below 60 mL/min. Because potentiation of this effect occurs when Tenofovir is used with Ritonavir-boosted HIV protease inhibitors, Ledipasvir should be avoided with this combination, unless antiretroviral regimen cannot be changed and the urgency of treatment is high".[44]

**** 3D + EFV led to premature study discontinuation due to toxicities;

Please refer to www.hep-druginteractions.org, Liverpool drug interaction database. Lexicomp, or similar program for comprehensive drug interactions.

15.1.2 Side effects [43]

New DAA regimens appear to be well tolerated by patients in both clinical studies and "real-world" observational studies. Discontinuation rates due to side effects are very low, in most cases less than 1%. Nevertheless, adverse events did occur at rather low frequency in DAA clinical trials.

Table 11: Side effects of drugs and its management

Drugs	Side Effect	Suggested Management Strategies
Sofosbuvir	**Fatigue, headache, insomnia and nausea**	Check haemoglobin Screen for depression Review for contributing factors including anaemia, Sleep disturbance Suggest behavioural strategies to conserve energy e.g. rest periods, napping, planning ahead Adequate fluid intake

43 Canadian Hemophilia Society and CATIE. (2017). Common hepatitis C symptoms and treatment side effects with tips for coping with them. Retrieved from https://www.catie.ca/sites/default/files/hep%20c%20symptoms%20EN%202017%2007%2004_0.pdf.

Drugs	Side Effect	Suggested Management Strategies
Sofosbuvir/ **Daclatasvir**	**Fatigue, headache and nausea**	Check haemoglobin Screen for depression Review for contributing factors including anaemia, Sleep disturbance Suggest behavioural strategies to conserve energy e.g. rest periods, napping, planning ahead Adequate fluid intake **Note: Paracetamol should not be used in patients with liver impairment.**
Regimen containing Ribavirin	**Anaemia** Ribavirin can cause haemolytic anaemia and bone marrow suppression. Usually occurs within 1-2 weeks of starting treatment in about 10% patients.	dministration of ribavirin is complicated because it should be taken with food and causes a predictable, dose-dependent haemolytic anaemia. Therefore, it should not be administered to patients with anaemia or those with blood disorder such as thalassaemia. Moreover, patients with cirrhosis, cardiovascular disease, pulmonary disease, renal impairment and all those older than 60 years of age need close monitoring when treated with ribavirin-containing regimens. Dose reductions maybe required (*see* text bow below). Careful clinical evaluation of patients before and during treatment is important to identify those in need of closer monitoring. **<u>Dose adjustment of ribavirin</u>** Anaemia is a common, predictable side-effect of ribavirin therapy and dose adjustment is often required. Patients whose haemoglobin (Hb) level falls below 10 g/dL should have their ribavirin dose reduced from 800-1200 mg/day (depending on the patient's weight and HCV genotype) to 600 mg/day. A patient whose Hb level falls below 8.5 g/dL should discontinue ribavirin therapy. For patients with a history of stable cardiovascular disease, dose reduction of ribavirin is required if the Hb decreases by ≥ 2 g/dL during any 4-week period. In addition, for these patients, if the Hb remains < 12 g/dL after

Drugs	Side Effect	Suggested Management Strategies
Regimen containing Ribavirin	**Anaemia** Ribavirin can cause haemolytic anaemia and bone marrow suppression. Usually occurs within 1-2 weeks of starting treatment in about 10% patients.	4 weeks on a reduced dose, the patient should discontinue combination therapy. The dose of ribavirin in patients with renal failure must also be adjusted; ◆ Patients with an eGFR < 50 mL/min/1.73m^2 should not be treated with ribavirin and those on dialysis must have the dose lowered to 200 mg per day or take it three times per week. Increased monitoring is required in this group.
Regimen containing Ribavirin	**Anaemia** Ribavirin can cause haemolytic anaemia and bone marrow suppression. Usually occurs within 1-2 weeks of starting treatment in about 10% patients.	**<u>Ribavirin with Decompensated Cirrhosis</u>** Among patients with decompensated cirrhosis, ribavirin dosing should either be weight-based or started at an initial dose of 600mg and increased as tolerated. **<u>Ribavirin cannot be used during pregnancy</u>** Ribavirin is teratogenic and thus cannot be used during pregnancy and breast feeding. Women of childbearing age must avoid pregnancy by using at least two reliable forms of contraception. Ribavirin also has a long half-life; thus, pregnancy must be prevented for at least 6 months after the end of ribavirin therapy. It is recommended to ensure that the patients and male partners can access and use reliable contraception.

Drugs	Side Effect	Suggested Management Strategies
Sofosbuvir/ Velpatasvir	**Bradycardia** SOF/VEL treatment may result in bradycardia along with other symptoms when taken with amiodarone **Headache and Fatigue**	Velpatasvir is a substrate of P-gp and BCRP with slow metabolism noted with CYP2B6, CYP2C8, and CYP3A4. Therefore, P-gp inducers and moderate/strong inducers of cytochrome P-450 system may decrease plasma concentrations of VEL and should not be used. Acid reducing agents should be used with caution secondary to VEL solubility decreasing with decreasing acidity. Co-administration with SOF/VEL and amiodarone may result in serious symptomatic bradycardia. Velpatasvir is safe for use with most HIV medications but should be avoided in those taking Ritonavir boosted Tipranavir, Efavirenz, Atravirine, and Nevirapine. Adequate fluid intake: Limit coffee, tea, and soda with caffeine Suggest behavioural strategies to conserve energy e.g. rest periods, napping, planning ahead SOF/VEL is not recommended in patients with severe renal impairment (estimated GFR less than 30mL/min/1.73m$^{2)}$ or end stage renal disease. Insufficient data exists for the use of SOF/VEL in pregnant women or post-partum breast-feeding mothers.