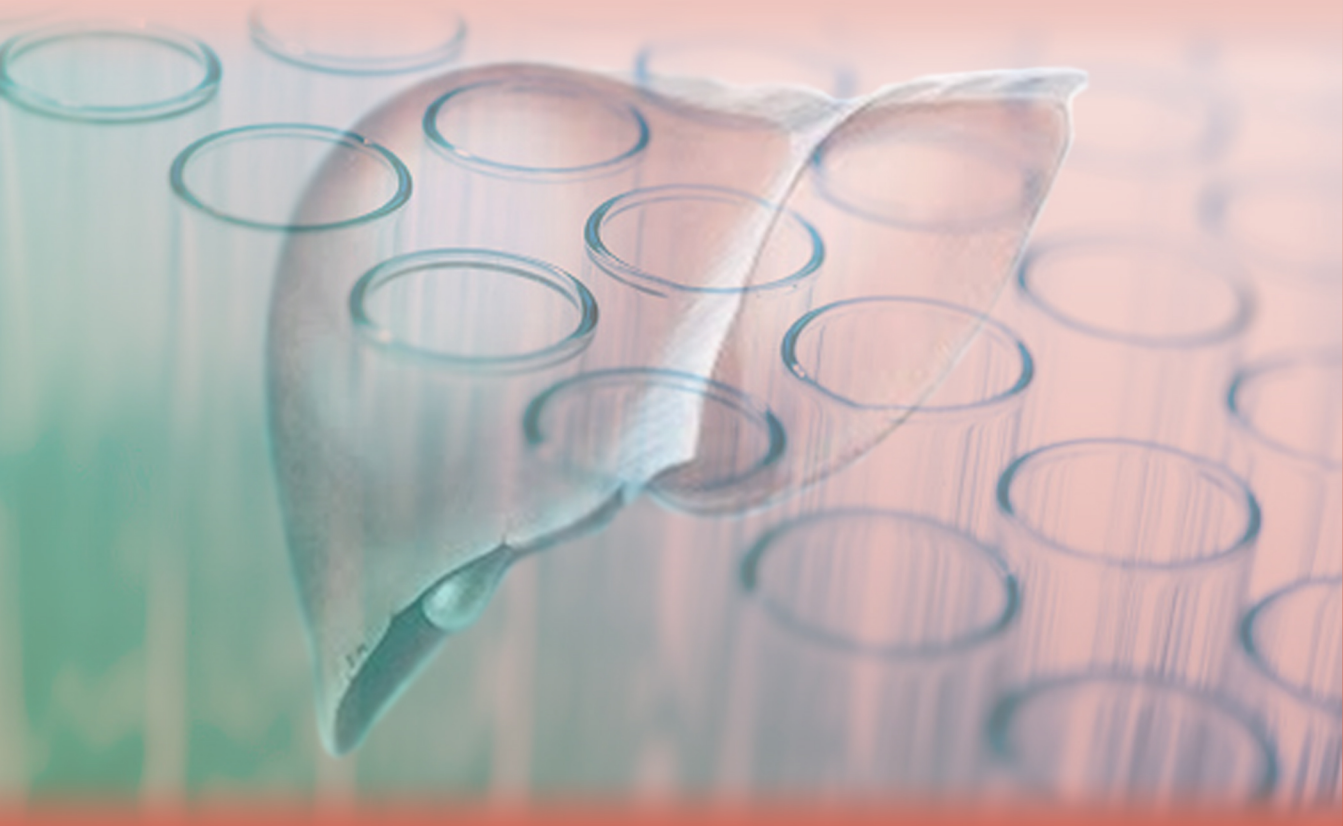
SIMPLIFIED TREATMENT GUIDELINES FOR HEPATITIS C INFECTION



MINISTRY OF HEALTH AND SPORTS MYANMAR

February 2017

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FOREWORD

December 2016

Myanmar GI and Liver Society developed guidelines for the treatment of chronic hepatitis C infection in 2009. With the establishment of National Hepatitis Program, this guideline has been revised as the Simplified Treatment Guidelines for Hepatitis C Infection to include the recently developed direct-acting antiviral drugs (DAAs) and with simple procedure of Viral Load testing and clinical monitoring.

For this purpose, Myanmar's Simplified Treatment Guidelines for Hepatitis C Infection was revised after a series of consultations with Department of Public Health, Department of Medical Services, Departments of Hepatology, National Health Laboratory (NHL), National Blood Center (NBC), and Department of Medical Research (DMR).

This simplified guideline is essential for providing guidance on the use of oral, low cost, DAAs, with the aim to reduce the disease burden of Hepatitis C in the community. This guideline provides a clear guidance to all medical doctors for precise and quick clinical decisions with simplified clinical monitoring methods. We also aim for this guideline to be able to provide updated knowledge about the treatment and laboratory monitoring of HCV infection.

This simplified guideline will be revised periodically in line with a more comprehensive National Hepatitis Guideline inclusive of global clinical updates. This can be used by all medical doctors in different levels of health facilities for the utmost benefit of the community.

For this guideline development, first a sincere thank you will be in order to Honorary Professor Khin Maung Win and Honorary Professor Than Sitt of University of Medicine (1), for their tremendous effort, support and time. We also like to express our gratitude to Dr. Khin Pyone Kyi, Chair Person, Liver Foundation, and all responsible persons from the Ministry of Health, DMS, DPH, NHL, NBC and DMR.

We would also like to express genuine thanks to Professor Andrew Muir, Chief, Duke University, USA and Stephen Ko, Assistant Professor of Global Health at Boston University School of Public Health and Senior Clinical Advisor, Clinton Health Access Initiative, for their technical updates. We would also like to thank Dr. Rakesh Aggarwal, WHO Consultant, Dr. Razia Nasayan Pendse, Regional Advisor, SEARO HIV, Dr. Philippa Easterbrook, Department of HIV/AIDS, WHO HQ for reviewing the draft and for their valuable comments. In addition, we would like to thank Clinton Health Access Initiative and WHO 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	Aminotransferase/platelet ratio index
ART	Antiretroviral Therapy
ATV/r	Atazanavir/Ritonavir
CBP	Complete Blood Picture
CrCl	Creatinine Clearance
CSW	Commercial Sex Worker
DAA	Direct-acting antiviral (drug)
ddI	Didanosine
DMR	Department of Medical Research
DOH	Department of Health
DTG	Dolutegravir
EASL	European Association for the Study of the Liver
eGFR	Estimated Glomerular Filtration Rate
EFV	Efavirenz
ELISA	Enzyme-Linked Immunosorbent Assay
ETV	Etravirine
FBP	Full Blood Picture
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
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NS5A	Non-structural Protein 5A
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
RAL	Raltegravir
RBV	Ribavirin
RDT	Rapid Diagnostic Test
RNA	Ribonucleic acid
SRA	Stringent Regulatory Authority
STI	Sexually Transmitted Infections
TDF	Tenofovir
TPV/r	Tipranavir/Ritonavir
SVR	Sustained Viral Response
USG	Ultrasonography
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 80 million people who are chronically infected and more than 700,000 people who are estimated to die from HCV-related liver disease every year[1,2].

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. From 2000 - 2003, research studies using Particle Agglutination (PA) showed the prevalence of anti-HCV as 2.9% in blood donors, approximately 50% in multiple transfused patients, 2.8% in peri-urban populations[3] and 13.5% in a NE border town of Myanmar[4]. In a 2007 study, the prevalence of anti-HCV among Intravenous Drug Users (IDUs) ranged from 66% to 93%[5]. The 2013 National Blood Center Annual Report showed the prevalence of anti-HCV, (by Immuno-chromatographic test (ICT) method, to be 0.2% in blood donors in Yangon, 0.5% in Mandalay and 2.1% among blood donors in Myitkyinar[6].

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 Mawlamyaing (10.34%), Mandalay (7.17%) and Lashio (5.03%), respectively[7]. The prevalence of

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[1] Gower E, Estes C, Blach S, et al. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol. 2014, 61(1 Suppl):S45-57.

[2]GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015; 385:117-71.

[3]Myo Khin (2001) Research studies that highlight the problems of hepatitis C infections in Myanmar. Proceedings of the Workshop on developing IEC package regarding hepatitis C prevention in Myanmar. pp 16-21

[4]Myo Khin, San San Oo *et al* (2003) Seroprevalence of antibody to HCV in a population in a NE border town of Myanmar. Myanmar Health Research Congress. Programme and abstracts pp 18-19

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

[6] Annual Report of the National Blood Center, 2013

[7] Department of Medical Research. Personal communications 2015. National Project to study the prevalence of hepatitis B & C in Myanmar (ongoing)

Hepatitis B in the general population was 6.5%, 8.95% in males and 5.47% in females. The highest prevalence was seen in Yangon with 12.29%. Myanmar has national policy for hepatitis B (HBV) which includes birth dose and pentavalent hepatitis B vaccination. Pentavalent vaccination as a part of the EPI program was initiated in 2013, but birth dose vaccination is currently limited to hospital deliveries. Due to intermittent supply for birth dose vaccination since 2010, only 20-25% of hospital deliveries have been covered.

The Myanmar GI and Liver Society successfully developed guidelines for the treatment of chronic hepatitis C infection in 2009, which were revised in June 2014 to provide practical management of chronic hepatitis C for practicing physicians in the country[8].

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, these all-oral regimens have cure rates of over 90%, shorter treatment periods (of 12 - 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[9]. DAA regimens consist of protease inhibitors, polymerase inhibitors, NS5A inhibitors and others. An important fact is that the oral Direct-Acting Antivirals (DAAs) are not contraindicated in persons with advanced chronic liver disease. The cure rates for those who are living with cirrhosis or people who did not previously respond well to treatment will also improve markedly.

Among many oral direct acting antivirals (DAAs), the effects vary on the different genotypes of the 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, since the prevalent genotypes are 40% for genotype 3, 27% for

[8]Myanmar GI and Liver Society, Myanmar Medical association (2014) Treatment Guideline for the Chronic Hepatitis C Infection
[9] Hepatitis Australia Inc.(2015) Need to know news on hepatitis C treatment. Updated May 2015

genotype 6, 21% for genotype 1 and 1% for genotype 2[10], relevant drugs will be recommended accordingly including combination therapy as required. For the National Hepatitis Program, 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 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 meeting with liver specialist, clinicians of ART centers, NHL, NBC, Liver Foundation, other relevant INGOs and stakeholders
- Myanmar GI and Liver Society, Myanmar Medical association (2014) Treatment Guideline for the Chronic Hepatitis C Infection
- European Association for the Study of the Liver (EASL) Recommendations on Treatment of Hepatitis C (2015)
- European Association for the Study of the Liver (EASL) Recommendations on Treatment of Hepatitis C (2016)
- American Association for the Study of Liver Diseases (AASLD) Recommendations for Testing, Managing, and Treating Hepatitis C (2016)
- WHO Guidelines for the Screening, Care and Treatment of Persons With Chronic Hepatitis C Infection (2016)
- WHO Guidelines on Hepatitis B and C Testing (2016)
- Hepatitis Australia Inc. (2015) Need to know news on hepatitis C treatment Updated May 2015
- Peer review by liver specialists based on local experiences

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.

[10]Shinji T (2004) Analysis of HCV genotypes from blood donors in Yangon, Myanmar Acta Med Okayama 53 (S) 135-42

2. TRANSMISSION AND PREVENTION

2.1 Transmission:

HCV is mostly transmitted through exposure to infectious blood. This may happen through healthcare-associated practices, such as transfusions of HCV-infected blood and blood products and contaminated injections during medical procedures. Transmission can also occur among injecting drug users through the sharing of needles and syringes. Mother-to-child transmission or sexual transmission is also possible, but is much less common, but occurs at a much 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.

2.2 High-risk groups

- Patients who received blood products or organ transplants prior to the introduction of anti-HCV screening
- People who inject drugs (PWID), including those who injected many years ago and do not consider themselves drug users
- People who have had tattoos, body piercing, scarification or traditional surgical procedures done where infection control practices are substandard
- People who have received medical or dental interventions in healthcare settings where infection control practices were potentially are inadequate
- 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
- Female Sex Workers
- 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)

Source: Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection. Geneva: World Health Organization; 2016 (http://www.who.int/hiv/pub/hepatitis/hepatitis-c-guidelines/en/, accessed 15 April 2016)

2.3 Prevention

In the absence of a vaccine for hepatitis C, 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.

2.3.1 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 (sharing toothbrushes, hand washing, safe blood contact)
Promotion of correct and consistent condom use

2.3.2 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

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

Hand hygiene: including surgical hand-washing and use of gloves
Safe handling and disposal of sharps and waste
Safe cleaning of equipment
Testing of donated blood
Improved access to safe blood
Training of health personnel

[11]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. Geneva: World Health Organization; 2012).

[12]Prevention and treatment of HIV and other sexually transmitted infections among men who have sex with men and transgender people. Geneva: World Health Organization, Department of HIV/AIDS; 2011

[13]WHO guidelines on hand hygiene in health care. Geneva: World Health Organization; 2009

[14]Universal access to safe blood transfusion. Geneva: World Health Organization; 2008 (http://www.who.int/bloodsafety/publications/ UniversalAccesstoSafeBT.pdf, accessed 10 March 2016).

2.3.4 Injection safety

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) The availability of necessary equipment and supplies, namely a transition to the exclusive use of WHO prequalified AD/RUP/SIP syringes for therapeutic injections; (3) The management of sharps waste.[15]

2.3.5 Prevention of HCV Infection among People Who Inject Drugs (PWID)[16,17]

Offer people who inject drugs the rapid hepatitis B vaccination regimen
Offer people who inject drugs incentives to increase uptake and complete the hepatitis B vaccination schedule
Implement program for provision of sterile injection equipment including needles and syringes, and also provide low dead-space for syringes for 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
Targeted information, education and communication for people who inject drugs and their sexual partners

[15] WHO guidelines on drawing blood: best practices in phlebotomy. Geneva: World Health Organization; (2010) (http://www.who.int/ injection safety/sign/drawing_blood_best/en/index.html,

[16] Guidance on prevention of viral hepatitis B and C among people who inject drugs. Geneva: World Health Organization; 2012

[17] WHO guidelines for the psychosocially assisted pharmacological treatment of opioid dependence. Geneva: World Health Organization; 2009

2.3.6 HCV Post Exposure Prophylaxis[18]

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

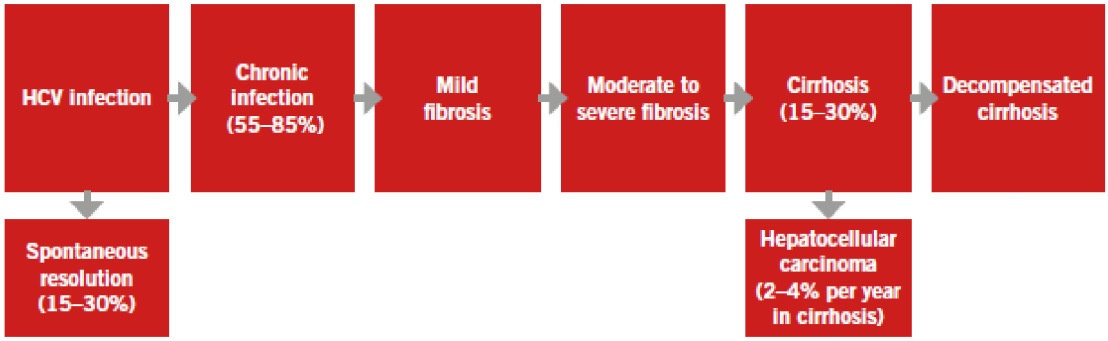
Wash the wound site with soap and water
If eyes are contaminated then rinse them, while they are open, gently but thoroughly with water or normal saline
If blood or other body substances get in the mouth, spit them out and then rinse the mouth with water several times
If clothing is contaminated, remove 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
Baseline evaluation and testing (if source is not infected, no baseline testing; if HCV positive source; test exposed person)
Follow up HIV, HBV and HCV testing and counseling
HBV vaccination

[18] Guideline for the management of occupational exposure to blood and body fluids: (Centre for Healthcare Related Infection Surveillance and Prevention (CHRISP)

3. NATURAL HISTORY OF THE 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.

Figure 1: Natural History of HCV Infection[19]



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. Anti-HCV antibodies 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.

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 cirrhosis and HCC varies depending upon certain patient characteristics or

[19]Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection. Geneva: World Health Organization; 2016 (http://www.who.int/hiv/pub/hepatitis/hepatitis-c-guidelines/en/, accessed 15 April 2016)

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.

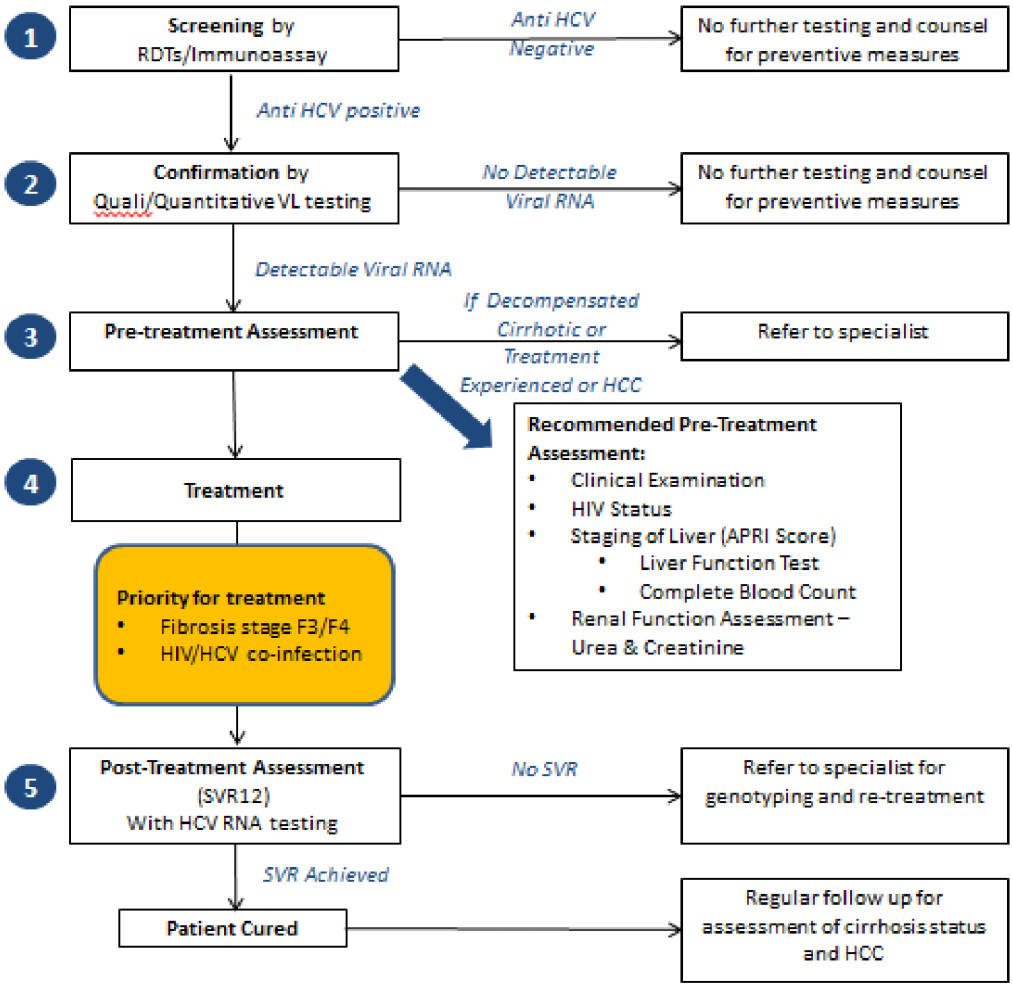
HCV disease association is not confined to the liver and extra-hepatic manifestations can include glomerulonephritis, cryoglobulinaemia, thyroiditis and Sjögren syndrome, insulin resistance type 2 diabetes mellitus, and some skin disorders.[19]

4. SIMPLIFIED DIAGNOSTIC ALGORITHM

The adoption of DAAs allows for a simplified diagnostic algorithm that was not possible with prior treatment options. With pegylated interferon-based therapy, extensive pre-treatment and on-treatment chemistry, hematology and viral load monitoring is required to ensure patient safety and treatment response. The new 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, eliminate the need for genotyping as well.

Figure 2: HCV Simplified Diagnostic and Treatment Algorithm

Referral to specialist for all those with prior treatment experience and/or decompensated cirrhosis and/or HCC.



For additional information regarding the simplified HCV diagnostic and treatment algorithm, refer to ANNEX D.

4.1 Who should be tested?

- In Myanmar, anti-HCV antibody tests should be administered to hospital admitted patients with signs and symptom of liver pathology (ie jaundice, abdominal pain, fatigue, nausea, vomiting, or abnormal liver function tests or ultrasound), any patient at the discretion of the attending doctor or when requested by a patient.
- Screening of blood, blood products and organ donors is mandatory.
- Screening for the population at higher risk: HIV infected persons, Intravenous Drug Users (IDUs), Men who have sex with men (MSM), Commercial Sex Workers (CSW), repeated transfusion recipients, health care workers, hemodialysis patients
- One time screening (when feasible) is done for
    - Pregnant woman
    - Household contacts
    - Institutionalized populations

4.2 Screening for Anti-HCV antibody

Screening for initial detection of HCV exposure (anti-HCV Ab) should be done with a single serological test. The screening can either be done with a Rapid Diagnostic Test (RDT) or an Immunoassay (IA), ideally with an RDT or 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 NAT prior to initiation of anti-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.

4.3 Confirmatory testing of chronic HCV infection with HCV RNA Assays

It is recommended that nucleic acid testing (NAT) for HCV RNA(either qualitative or quantitative) be performed directly following a positive HCV serological test to confirm current (active) chronic infection since 15-45% of patients will clear the virus naturally and thus will not need anti-HCV treatment. 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.

Patient with negative results on screening or HCV RNA confirmation, no further testing is required and the patient can be counseled for preventive measures.

Interpretation of Test Results

Antibody Test Result	HCV RNA Test Result	Interpretation
Negative	**Negative**	**No HCV exposure / infection**
Positive	**Negative**	**HCV exposed. Resolved infection. *also includes Ab False Positives**
Positive	**Positive**	**HCV exposed & Current Infection**

4.4 HCV Genotyping

Genotyping of HCV can be used to select different combinations of DAA and decide on the duration of therapy. However, genotyping is not required by the National Hepatitis Program, as it is costly and unavailable in most low-resource settings. Pan-genotypic regimens are effective for all genotypes and therefore eliminate the need for this step. There is still a paucity of data on DAA efficacy in those with genotype 5 and 6 which are more common in the region, but a planned trial in Thailand will address this in due course. In Myanmar, the combination of sofosbuvir and daclatasvir is recommended as a pan-genotypic regimen. If genotype testing is available or the genotype is already known, the treatment

regimen should be chosen based on the genotype. Additionally, in instances where patients fail their first line treatment, genotyping can be considered to guide selection of appropriate second-line treatment, if accessible.

4.5 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, AST, Alkaline Phosphate, Bilirubin
    b. Renal Function Assessment - Urea & Creatinine (Cr)
    c. Complete Blood Picture (CBP) to determine platelet count (Plt)
5. Exclusion of HCC by USG if patient demonstrates signs of end stage liver disease
    a. Alphafeto protein (Optional)
6. Other laboratory tests
    a. 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 have been reported in HBsAg-positive patients and those with evidence of resolved infection (HBsAg-negative and anti-HBc positive).[20]

Of these tests, the minimum tests to be performed prior to initiating patients on all oral DAA therapy are:

- AST, Plt and Cr

The AST and Plt will be used to calculate the AST to Platelet Count Ratio Index (APRI) score to stage the patient and Cr will be used to determine renal function.

[20] http://www.fda.gov/downloads/Drugs/DrugSafety/UCM523499.pdf

In addition to the tests above, a physical exam 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: Big liver with hard lower side, 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.

4.6 Staging and scoring

Non-Invasive tests are the preferred method for staging. Liver biopsy is no longer recommended as a routine investigation for staging. Staging is important to identify patients with impaired liver function and advanced stages of the disease that should be prioritized for treatment, may need longer treatment durations or require referral to specialists for clinical management in certain instances. The APRI score correlates with METAVIR scores to indicate the degree of liver fibrosis:

Table 1: ME TAVIR Liver Biopsy Scoring System[21]

METAVIR stage	F0	F1	F2	F3	F4
Definition	No fibrosis	Portal fibrosis without septa	Portal fibrosis with septa	Numerous septa without cirrhosis	Cirrhosis

Table 2: Aminotransferase/Platelets Ratio Index (APRI)

Non-invasive test	Components assessed	Lower cut off	Upper cut off	Fibrosis stage assessed
APRI	AST and platelet count	0.7	2.0	≥ F2 - F4

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

[21] Guidelines for the screening, care and treatment of persons with hepatitis infection, WHO, April, 2014

AST - Aspartate aminotransferase
IU- International Unit
ULN- Upper Limit of Normal of the Lab (often 40 IU/ml)

APRI Calculation Example.

AST Level (IU/L) = 60
AST Upper Limit of Normal (IU/L) = 40
Platelet Count (10^9/L) = 133,000/cumm (Ref: 150,000-400,000/cumm) = 133

APRI = [{60/40} x 100] / 133
APRI = [1.5 x 100] / 133
APRI = 150/133
APRI = 1.128

APRI Score Interpretation

APRI score	Interpretation
> 2	Cirrhosis
0.7 - 2	Fibrosis, risk of cirrhosis
< 0.7	No Fibrosis

An APRI score of greater than 2.0 has 91% specificity to rule in the presence of cirrhosis in the patient. An APRI score greater than 0.7 has 72% specificity and 77% sensitivity to diagnose the presence of significant fibrosis (≥ F2), with the higher the APRI score indicating a greater likelihood of significant fibrosis.

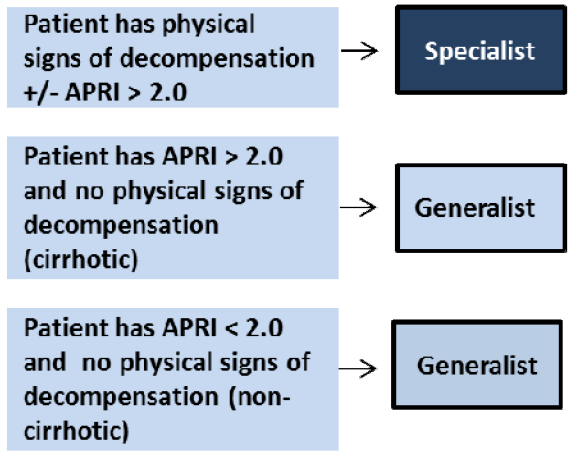
Patients with HCV who are HIV co-infected should be prioritized for treatment, as should cirrhotic patients (APRI >/ = 2.0)
Other laboratory tests such as FBP and blood sugar should also be done.

4.7 Prioritization of patients for HCV treatment

- The following patients should be prioritized for treatment as they are at higher risk for disease progression and developing complications.
  - Patients who are at fibrosis stage F3 and F4
  - Patients with decompensated cirrhosis
  - HIV/HCV and HBV/HCV co-infected patients

4.8 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.



4.9 Counseling and education about HCV infection and treatment[22]

4.9.1 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.
- If the patient has recent or ongoing risk, an explanation of the "window" or "lag" period, along with the recommendation of retesting in 6 months.
- General disease education, with emphasis on prevention and modes of transmission.
- Discussion of benefits of retesting in the future.

[22]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

4.9.2 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 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.

4.9.3 People Confirmed with Chronic HCV

All people who receive a positive NAT test and are confirmed positive for chronic hepatitis C 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, and highly efficacious treatment options exist.
- 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 more than 50 grams of alcohol daily is likely to worsen fibrosis. 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 A and 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.

4.9.4 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 infected with hepatitis C, but then cleared the virus naturally. They do not have 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 future immunity.
- 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.

5. TREATMENT

The spectrum of disease in those infected with HCV extends from mild fibrosis to compensated then decompensated cirrhosis and HCC. Cirrhosis of the liver will develop in between 15% and 30% of persons infected with HCV within 20 years and a proportion of these will progress to HCC. The risk is markedly increased in those who consume excess alcohol and in those co-infected with HBV and/or HIV, particularly those who do not have access to ART.As part of the care of persons with HCV related cirrhosis it is essential to assess and follow up for the progression of disease and for evidence of HCC. Compensated cirrhosis may also progress over time to decompensated cirrhosis associated with ascites, oesophageal and gastric varices, and eventually to life threatening liver failure, renal failure and sepsis. The diagnosis of decompensated liver disease is made on both laboratory and clinical assessment, and therefore before starting treatment a careful medical examination of patients must be done. Persons with cirrhosis (including those who have achieved an SVR) should be screened for HCC with six-monthly ultrasound examination and α-fetoprotein estimation, and should have endoscopy every 1-2 years to exclude oesophageal varices.[12]

5.1 Aim

- To reduce mortality related to hepatitis C virus, prevent complications of HCV infected person and reduce transmission of HCV.
  Note: The aim of HCV treatment is viral cure, 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 PWID.

5.2 Anti-viral agents

5.2.1 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.

5.2.2 Indications for antiviral therapy

- All HCV infected patient should be considered for treatment irrespective of prior treatment history, i.e. both treatment-naïve and -experienced patients.

5.3 Recommended Regimens

The WHO recommends that DAA regimens be used for the treatment of persons with hepatitis C infection rather than regimens with pegylated interferon/ ribavirin[23].

5.3.1 Preferred regimen(s) for Public Health Approach (Without Genotyping)

- Sofosbuvir + Daclatasvir
  - 12 weeks (All Genotypes) for non-cirrhotic patients (APRI < 2.0)
  - 24 weeks (All Genotypes) for cirrhotic patients (APRI ≥ 2.0)
  - *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

Alternative regimen

- Sofosbuvir + Ribavirin:
  - 24 weeks for all patients (All genotypes, non-cirrhotic and cirrhotic)
    - Of note, this is a sub-optimal regimen for certain genotypes based on SVR12 rates in clinical trials (AASLD/EASL/WHO

[23] WHO guidelines for the screening, care and treatment of persons with chronic HVC infection, updated version, April 2016.

treatment recommendations). However, with limited availability of DAAs, it remains a secondary option for Myanmar.

- Will require FBC monitoring

5.3.2 Preferred regimen(s) if Genotype available[24,25,26]

A. Patients without cirrhosis (APRI < 2.0)

Table 3: Recommended treatment regimens for patients without cirrhosis (APRI < 2.0)

Genotype	Sofosbuvir/ Daclatasvir	Sofosbuvir/Ledipasvir	Sofosbuvir/ Ribavirin
1	12 [A/E/W]	12[A/W]; 8-12*[E]	
2	12 [A/E/W]		12 [A/E/W]
3	12 [A/E/W]		24 [A/E/W]
4	12[E/W]	12 [A/E/W]	
5	12[E]	12 [A/E/W]	
6	12[E]	12 [A/E/W]	

Notes
A = AASLD 2016 HCV Treatment Guidelines (Treatment naïve patients only)
E = EASL 2016 HCV Treatment Guidelines
W = WHO 2016 HCV Treatment Guidelines
*8 weeks in treatment naïve if baseline HCV RNA below 6 million IU/ml

- Sofosbuvir + Daclatasvir
  - All Genotypes = 12 weeks
  - *Special Considerations for ART patients (See 6.3, Table 10)*

- Sofosbuvir + Ribavirin:
  - Genotype 2 = 12 weeks
  - Genotype 3 = 24 weeks
  - *Special Considerations for ART patients (See 6.3, Table 10)*

[24] AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. .http://www.hcvguidelines.org. April 15, 2016.
[25] EASL Recommendations on Treatment of Hepatitis C 2016. European Association of the Study of the Liver. Journal of Hepatology. http://dx.doi.org/10.1016/j.jhep2016.09.001
[26] WHO guidelines for the screening, care and treatment of persons with chronic HVC infection, updated version, April 2016.

- Sofosbuvir + Ledipasvir
    - Genotypes 1, 4, 5, 6 = 12 weeks
    - Genotype 1 can be treated for 8 weeks if treatment naïve and HCV RNA below 6 million IU/ml (EASL)
    - *Special Considerations for ART patients (See 6.3, Table 10)*

B. Patients with compensated cirrhosis (APR > 2.0)

Table 4: Recommended treatment regimens for patients with cirrhosis (APRI > 2.0)

Genotype	Sofosbuvir /Daclatasvir	Sofosbuvir /Daclatasvir /Ribavirin	Sofosbuvir /Ledipasvir	Sofosbuvir /Ledipasvir /Ribavirin	Sofosbuvir/ Ribavirin
1	12[E]; 24 [A/W]	12[W]; 24 [A]	12[A/E]; 24 [W]	12[W]	
2	12[E/W]; 16-24 [A]				16[W]; 16-20[E]; 16-24[A]
3	24[A]	24 [A/E/W]			24[A]
4	12[E] 24[W]	12[W]	12[A/E]; 24[W]	12[W]	
5	12[E]		12 [A/E]; 24 [W]	12[W]	
6	12[E]		12 [A/E]; 24 [W]	12[W]	

Notes
A = AASLD 2016 HCV Treatment Guidelines (Treatment naïve patients only)
E = EASL 2016 HCV Treatment Guidelines
W = WHO 2016 HCV Treatment Guidelines
* Extension of treatment to 24 weeks if treatment experienced and negative predictors of response

- Sofosbuvir + Daclatasvir
    - All Genotypes = 24 weeks
    - Genotype 2 = treatment can shortened to 12-16 weeks
    - *Special Considerations for ART patients (See 6.3, Table 10)*

- Sofosbuvir + Daclatasvir + Ribavirin
  - Genotype 1 = 12-24 weeks
  - Genotype 3 = 24 weeks
  - Genotypes 4, 5, 6 = 12 weeks
  - *Special Considerations for ART patients (See 6.3, Table 10)*
- Sofosbuvir + Ledipasvir
  - Genotypes 1, 4, 5, 6 = 12-24 weeks
  - *Special Considerations for ART patients (See 6.3, Table 10)*
- Sofosbuvir + Ledipasvir + Ribavirin
  - Genotypes 1, 4, 5, 6 = 12 weeks (EASL recommends extending treatment to 24 weeks if treatment experienced and negative predictors of response such as platelet count < 75 x 10^3/ul)
  - *Special Considerations for ART patients (See 6.3, Table 10)*
- Sofosbuvir + Ribavirin:
  - Genotype 2 = 16-24 weeks
  - Genotype 3 = 24 weeks

5.3.3 Dosing for HCV Treatment Regimens

Table 5: Dosing for Recommended HCV Treatment Regimens

Regimen	Dosage per tablet	Dosing Frequency and Timing
Oral Ribavirin	200 mg capsule or tablet	body weight < 75 kg - 2 in the morning and 3 in the evening body weight ≥ 75 kg - 3 in the morning and 3 in the evening
Sofosbuvir	400 mg tablet	once daily - morning
Daclatasvir*/ Sofosbuvir	30 mg or 60 mg/400 mg tablet (special considerations for ART patients in)	once daily - morning
Ledipasvir/ Sofosbuvir	90 mg /400 mg tablet (special considerations for ART patients in Table 10)	once daily - morning

*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 ketoconazole, itraconazole, posaconazole and voriconazole

5.4 Treatment Monitoring

5.4.1 On Treatment Monitoring

- Monitoring for FBP if on Ribavirin. 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 (CrCl) as both exhibit renal clearance.

        - Dose Adjustments
            - Ribavirin:
                - Moderate (30-50 ml/min) = Alternating doses of 200 mg and 400 mg every other day
                - Severe (< 30 ml/min) = 200 mg/day
                - ESRD = 200 mg/day

                  * Note: Sofosbuvir/Ribavirin only recommended for GT 2, 3 as above if genotype known.

            - Sofosbuvir:
                - Mild-Moderate (30 - 80 ml/min) = No dose adjustment
                - Severe and ESRD = Not recommended
                - Ribavirin based regimens: Severe hemolytic anemia with significant initial drops in hemoglobin may occur, therefore careful monitoring should be initiated. How often?

- Direct Monitoring of viral replication through NAT or core antigen testing is not recommended

- Complex patients in specialist care may require more advanced chemistry and hematology monitoring and prothrombin time

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

5.4.2 Assessment of Response to Therapy (Post-treatment)

- An HCV RNA viral load test (qualitative or quantitative, but qualitative is sufficient) should be conducted 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 for more advanced testing and re-treatment. Core antigen testing is currently not recommended as a test to determine cure.

- Cirrhotic Patients who achieve SVR still need to be followed-up regularly for the assessment of cirrhosis status

6. ANNEXES

6.1 ANNEX A: TREATMENT CONSIDERATIONS FOR SPECIAL POPULATIONS[27]

6.1.1 HCV/HIV Co-infection

The WHO's 2016 guidelines for the treatment of HCV recommend that all persons with HIV/HCV co-infection 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 CD_4 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 is the same 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. 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 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 CD_4 count.

[27] World Health Organization. (2016). *Guidelines for the screening care and treatment of persons with chronic hepatitis C infection.*

6.1.2 Children and Adolescents

Risk Factors: 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.[28,29]

***Screening*:** Overall likelihood of HCV infection is lower among children and adolescents than adults in most settings. Targeted screening of children at risk is recommended. Infants born to HCV-infected mothers, especially those with HIV co-infection, are a key population to target; as are children who have had had medical interventions, surgical or transfusion.

For infants born to chronically infected mothers (HCV RNA-positive), diagnosis of chronic infection can be difficult due to the presence of maternal antibodies for 13 to 18 months post-birth and spontaneous clearance. An infant is considered chronically infected if they receive two positive HCV RNA tests over six months. Known exposed children should receive an RNA test at 3 months. If the RNA test at 3 months is positive, then the patient should be referred and a confirmatory RNA should be performed at 12 months of age to rule out spontaneous clearance. If the RNA test at 3 months is negative, infection is unlikely, but alanine aminotransferase levels should be monitored every three months. If alanine aminotransferase levels become elevated, the infant should be tested again for viraemia. If alanine aminotransferase levels remain normal, infants should be tested at 18-24 months for antibodies.[30]

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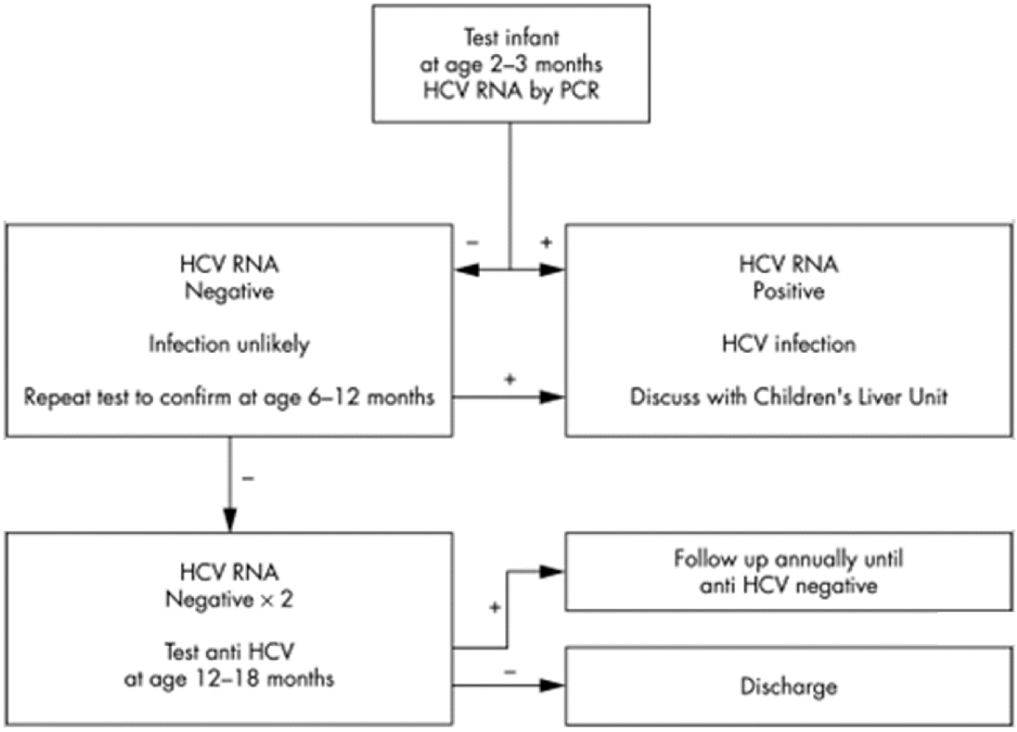
[28] Locasciulli A, Gornati G, Tagger A, Ribero ML, Cavalletto D, Cavalletto L, et al. Hepatitis C virus infection and chronic liver disease in children with leukemia in long-term remission. Blood. 1991;78(6):1619–22.

[29] Rossetti F, Cesaro S, Pizzocchero P, Cadrobbi P, Guido M, Zanesco L. Chronic hepatitis B surface antigen-negative hepatitis after treatment of malignancy. J Pediatr. 1992;121(1):39–43.

[30] Davison, M. et al (2006). Perinatal Hepatitis C Virus Infection: Diagnosis and Management. Arch Dis Child. 2006 Sep; 91(9): 781-785.

Figure 3: Diagnostic Algorithm for Perinatal Transmission



For children who are exposed horizontally after infancy, screening algorithms are the same as for adults.

Care and Treatment: Currently, the only available treatment for children between the ages of 2 and 18 is pegylated interferon and ribavirin. No treatments are recommended for children under the age of 2.

Some patients with rapidly advancing disease may benefit from treatment with pegylated interferon and ribavirin during their childhood. Given the low prevalence of advanced disease among children, clinicians may prefer to wait for new DAA treatments or until adulthood to treat the majority of their pediatric patients. During childhood, HCV infected children should continue to be monitored for liver function and advancing disease.

6.1.3 Pregnant Women

Screening: Screening of pregnant women for HCV can identify women whose infants will need to be tracked postpartum. Due to the lack of treatment available for pregnant women, screening and treating women of child-bearing age prior to pregnancy is recommended.

Care and Treatment: There are currently no treatments available that have been designated as safe during pregnancy. Trials are still required with DAAs. Women who are screened antibody-positive should be linked to care and retained to start treatment following delivery and breastfeeding.

6.1.4 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.[31] 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.

6.1.5 Decompensated Cirrhosis

Decompensated cirrhosis is associated with ascites, oesophageal and gastric varices, and can eventually progress to liver failure, renal failure and sepsis, all of which are life threatening. The diagnosis of decompensated liver disease is based

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

on both laboratory and clinical assessment, and therefore a careful medical examination of patients must be made before starting treatment. While certain treatment regimens have been shown to be safe for use in patients with decompensated liver cirrhosis, close monitoring is required in these patients, and it is thus recommended that treatment for these patients be considered only under close supervision of specialist teams with experience in treating and managing complications.

6.1.6 Treatment Experienced

It is recommended that all treatment experienced patients are referred to specialist teams with experience in treating and managing complicated patients. If treatment experienced, consult AASLD and EASL HCV Treatment Guidelines for further guidance prior to treatment initiation.

6.2. ANNEX B: COMORBIDITIES

6.2.1 HCV/HBV 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.[32,33] 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[34].

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 have been reported in HBsAg - positive patients and those with evidence of resolved infection (HBsAg - negative and anti-HBc positive).[35] 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.

6.2.2 HCV/TB 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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[32] Crespo J, Lozano JL, Carte B, de las Heras B, de la Cruz F, Pons-Romero F. Viral replication in patients with concomitant hepatitis B and C virus infections. *Eur J Clin Microbiol Infect Dis.* 1997 ;16:445-451

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

[34] WHO Guideline on HCV management

[35] http://www.fda.gov/downloads/Drugs/DrugSafety/UCM523499.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 TB infection should complete TB treatment before starting HCV treatment, and should be referred to referred to specialist teams.

6.2.3 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.[36] 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.[37] For patients who continue drinking during treatment, clinicians should provide extra support to ensure adherence. Pharmacists must consider any potential drug-drug interactions.

6.2.4 HCV/NASH

Non-alcoholic steatohepatitis 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

[36] 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.
[37] 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. 2006. 130: 1607-1616.

underlying liver disease. There are currently no treatments for NASH other than lifestyle changes to reduce obesity and promote liver health.

6.2.5 HCV/Mental Health Disorders

HCV is associated with higher rates of mental health disorders compared to the general population. In the case of HCV, the higher rate of disorders can be attributed to multiple causes including a high rate of transmission in populations with psychiatric disorders due to risk behaviors, the effect of HCV on the central nervous system, and the psychosocial effects of stigma and discrimination from the disease.[38]

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.

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[38] 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.

6.2.6 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

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/ledipasvir and sofosbuvir/ daclatasvir.
- 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.[39]
- In patients with low eGFR rates, referral to a specialist is recommended.
- 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 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.

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

6.3 ANNEX C: DRUG-DRUG INTERACTIONS, CONTRAINDICATIONS, WARNINGS AND ADVERSE EVENTS FOR AVAILABLE TREATMENT REGIMENS

6.3.1 Drug-Drug Interactions

Table 6: Potentially significant drug interactions of sofosbuvir[40,41]

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

[40] AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. .http://www.hcvguidelines.org. April 15, 2016.

[41] EASL Recommendations on Treatment of Hepatitis C 2015. European Association of the Study of the Liver. Journal of Hepatology.

Herbal Supplements: St. John's wort (Hypericum perforatum)	↓ sofosbuvir ↓ GS-331007	Co-administration of SOVALDI with St. John's wort, an intestinal P-gp inducer, is not recommended
HIV Protease Inhibitors: tipranavir/ritonavir	↓ sofosbuvir ↓ GS-331007	Co-administration of SOVALDI with tipranavir/ritonavir is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of SOVALDI. Co-administration 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 co-administered with strong inhibitors of CYP3A.

Moderate CYP3A inducers:		
Examples: bosentan, dexamethasone, modafinil, nafcillin, rifapentine	↓ Daclatasvir	Increase daclatasvir dose to 90 mg once daily when co-administered 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	Co-administration 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

Table 8: Potentially significant drug interactions of Ledipasvir[42]

Concomitant Drug Class: Drug Name	**Effect on Concentration**	**Clinical Comment**
Acid Reducing Agents:	↑ ledipasvir	Ledipasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease concentration of ledipasvir.
Antacids (e.g., aluminum and magnesium hydroxide)		It is recommended to separate antacid and HARVONI administration by 4 hours.
H_2-receptor antagonists c (e.g., famotidine)		H_2-receptor antagonists may be administered simultaneously with or 12 hours apart from HARVONI at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.

[42] EASL Recommendations on Treatment of Hepatitis C 2015. European Association of the Study of the Liver. Journal of Hepatology.

Proton-pump inhibitors c (e.g., omeprazole)		Proton-pump inhibitor doses comparable to omeprazole 20 mg or lower can be administered simultaneously with HARVONI under fasted conditions.
Antiarrhythmics: amiodarone	Effect on amiodarone, ledipasvir, and sofosbuvir concentrations unknown	Co-administration of amiodarone with HARVONI may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. Co-administration of amiodarone with HARVONI is not recommended; if co-administration is required, cardiac monitoring is recommended
digoxin	↑ digoxin	Co-administration of HARVONI with digoxin may increase the concentration of digoxin. Therapeutic concentration monitoring of digoxin is recommended when co-administered with HARVONI.
Anticonvulsants: carbamazepine phenytoin phenobarbital oxcarbazepine	↓ ledipasvir ↓ sofosbuvir	Co-administration of HARVONI with rifabutin or rifapentine is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of HARVONI. Co-administration is not recommended. Co-administration of HARVONI with rifampin, a P-gp inducer, is not 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 HARVONI 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 HARVONI 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 co-administration 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 HARVONI and the combination of elvitegravir, cobicistat, emtricitabine and tenofovir DF has not been established. Co-administration is not recommended.
tipranavir/ritonavir	↓ ledipasvir ↓ sofosbuvir	Co-administration of HARVONI with tipranavir/ritonavir is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of HARVONI. Co-administration is not recommended.
HCV Products: simeprevir	↑ ledipasvir ↑ simeprevir	Concentrations of ledipasvir and simeprevir are increased when simeprevir is co-administered with ledipasvir. Co-administration of HARVONI with simeprevir is not recommended.

Herbal Supplements: St. John's wort (Hypericum perforatum)	↓ ledipasvir ↓ sofosbuvir	Co-administration of HARVONI with St. John's wort, a P-gp inducer is not recommended
HMG-CoA Reductase Inhibitors: rosuvastatin	↑ rosuvastatin	Co-administration of HARVONI with rosuvastatin may significantly increase the concentration of rosuvastatin which is associated with increased risk of myopathy, including rhabdomyolysis. Co-administration of HARVONI with rosuvastatin is not recommended.

Co administration of Harvoni with Elvitegravir, Cobicistat, Emtricitabine, Tenofovir is not recommended.

Table 9: Potentially significant drug interactions of ribavirin[43]

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 anaemia
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

[43] EASL Recommendations on Treatment of Hepatitis C 2016. European Association of the Study of the Liver. Journal of Hepatology.

Table 10: Drug-drug interactions between co-administered HCV and HIV treatment[44]

		Sofosbuvir	Ledipasvir***	Daclatasvir
NRTIs	ABC			
	3TC/FTC			
	TDF		LDV ↔; TFV↑	
NNRTIs	EFV		*	DCV ↓**
	ETV			DCV ↓**
	NVP			DCV ↓**
Protease Inhibitors	ATV/r		LDV ↑; ATV ↑*	DCV ↑**
	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 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".[45]

**** 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.

[44]University of Liverpool Hepatitis drug interactions webpage (http://www.hep-druginteractions.org/ and HIV drug interactions webpage *www.**hiv-druginteractions**.org/*.

6.3.2 Side effects[45]

New DAA regimens appear to be well tolerated by patients in both clinical studies and "real-world" observational studies.

	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
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.**
Sofosbuvir/ Ledipasvir	**Fatigue and Headache**	Ledipasvir is an inhibitor of P-gp and breast cancer resistance protein (BCRP). Co-administration with ledipasvir/Sofosbuvir and amiodarone may result in serious symptomatic bradycardia. Gastric acid-reducing agents should also be used with caution as they reduce concentrations of ledipasvir. Ledipasvir is safe for use with many HIV medications but should be avoided in those taking tipranavir/ritonavir. Adequate fluid intake: Limit coffee, tea, and soda with caffeine

[45] AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. .http://www.hcvguidelines.org. April 15, 2015.

		Suggest behavioural strategies to conserve energy e.g. rest periods, napping, planning ahead SOF/LDV is not recommended in patients with severe renal impairment (estimated GFR < 30 mL/ min/1.73 $m^{2)}$ or end stage renal disease.
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.	Administration 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 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/ 1.73 m^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. **<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 600 mg 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.

6.4 ANNEX D: JUSTIFICATION OF SIMPLIFIED DIAGNOSTIC ALGORITHM FOR PAN-GENOTYPIC REGIMEN

The following table provides an overview of the diagnostic algorithm that was necessary during the pegylated-interferon era and the justification for the inclusion/exclusion of each stage in the simplified diagnostic algorithm made possible by DAAs.

Item	Protocol Section	High Income Standard of Care Lab Description	Included (Yes/No)	Justification for inclusion/exclusion
1.	Pre-treatment Screen	**Hepatitis C antibody** (Serum HCV Ab)	**Yes**	The HCV Ab can be performed using an ELISA assay or one of the rapid tests. These are a number of rapid tests available and they have been reported to have varying test characteristics. When possible, these test characteristics should be considered in the selection of choice of screening test. Regardless of the possibility of false positives, a confirmatory qualitative RNA will be performed in the pre-treatment assessment which confirms whether the patient has an active HCV infection.
2.	Pre-treatment Assessment	**Qualitative HCV RNA**	**Yes**	This is a sensitive test for detecting the presence of HCV and confirming the diagnosis of HCV, even when the amount of circulating HCV virus is low. Since some people with a positive HCV Ab may have a false positive or may have cleared the virus on their own (cured themselves), this test essentially confirms the diagnosis of HCV prior to treatment.
3	Pre-treatment Assessment	**Physical Exam**: Blood pressure, heart rate, pulse, cardiac, respiratory, abdominal, and neurological exam	**Yes**	This vital step in the protocol will allow for an evaluation for advanced liver disease (decompensated cirrhosis). This will be manifested by evidence of bleeding from varices in the stomach or esophagus, jaundice, ascites (fluid in abdomen), edema of the lower extremities, and confusion. Individuals with evidence of decompensated cirrhosis will be referred to a liver disease specialist, as decision

				making on the benefit of therapy and additional liver disease management will be required.
4	Pre-treatment Assessment	**HCV Genotype and subtype**	**No**	The treatment regimen used in this protocol is a pan-genotypic regimen that should have excellent cure rates given the HCV genotypes seen in the countries of interest.
5	Pre-treatment Assessment	**Complete Blood Count (CBC) Hemoglobin/ Hematocrit White blood cell Platelet count**	**Yes - Plt** **No - Hgb, Hct, Wbc**	1. The medications we are using should not cause a significant anemia (low Hgb/Hct) 2. The medications we are using should not cause a significant thrombocytopenia (low PLT) 3. The Hgb, PLT or WBC will not change management with this regimen as has been the case with the older treatment regimens 4. Platelet (PLT) will allow us to calculate the AST to Platelet ratio index (APRI score). This can be used as a non-invasive measure of the degree of liver damage with respect to advanced scarring (fibrosis) or cirrhosis. The APRI score will be used to determine length of therapy and will determine which patients require ongoing liver disease care after cure, when/where available
6	Pre-treatment Assessment	**Hepatic Function Panel: Albumin Bilirubin Alkaline phosphatase Alanine aminotransfe -rase and aspartate aminotransfe -rase**	**Yes - AST** **No - Alb, Bili, Alk Phos, ALT**	While the hepatic function panel provides insight into the overall liver function and degree of inflammation from the HCV infection, these parameters will not impact the treatment decision in this protocol. We would treat regardless of these lab values. Furthermore, those individuals with evidence of advanced liver disease (ascites, encephalopathy, GI bleeding) will be referred to a tertiary treatment center to be evaluated by a specialist. The AST and Plt will allow us to calculate the AST to Platelet ratio index (APRI score). This can be used as a non-invasive measure of the degree of liver damage (advanced scarring (fibrosis) or cirrhosis) and as discussed above guides length of treatment decision making and need for ongoing liver disease management after cure. Referral to

				specialist is not required for patients with APRI > 2 and no signs of decompensation for treatment, but when/where available should result in at minimum liver cancer screening.
7	Pre-treatment Assessment	**Creatinine/ Calculated glomerular filtration rate (GFR): Measure of kidney function.**	**Yes**	One of the medications used in this protocol (sofosbuvir) is really cleared and there is currently limited safety data in patients with poor kidney function. A GFR < 30 ml/min would be an indication to consider delay in therapy until more safety data is available or other regimens are available.
8	Pre-treatment Assessment	**International normalized ratio (INR)**	**No**	This test may be elevated (prolonged INR) in the setting of advanced liver disease. The treatment regimen for this protocol will not adversely affect the INR.
9	Assessment during therapy at 4 weeks	**Interim tests done after 4 weeks on treatment**: CBC, INR, Cr, GFR, hepatic function panel, Quantitative HCV Viral Load (tests for amount of virus in blood stream)	**No**	While testing of labs remains standard of care in high income countries, the DAA therapies are extremely safe with < 1% of patients in registration trials discontinuing therapy due to laboratory adverse events. The recommended regimen here (daclatasvir + sofosbuvir) does not include ribavirin, thus close monitoring of blood counts and renal function are not necessary. The low incidence of severe laboratory AE is so uncommon that the additional cost is not felt to balance the benefit of that testing.
10	Post-treatment Assessment at week 12 (End of Treatment)	**At Week 12** (end of treatment): CBC, INR, Cr, GFR, hepatic function panel, Qualitative HCV RNA	**No**	The labs would provide information on the changes in the blood counts (CBC), platelet count (CBC), kidney function (Cr and GFR), liver function (hepatic function panel and INR), liver inflammation (hepatic function panel), and amount of HCV virus in the blood stream (quantitative HCV). Theoretically, if these labs were normal prior to starting therapy, the medications should not adversely affect them. The HCV test of cure is not required until 12-weeks after the end of treatment.

11	Post-treatment Assessment at week 24 (End of Treatment + 12 Weeks)	**At Week 24** (12 weeks after ending treatment): Qualitative HCV RNA	**Yes**	This is where we measure sustained virological response (SVR). If there is no HCV detected in the blood stream 12 weeks after finishing treatment, the patient has achieved "SVR 12" and is considered to have been cured
12	Post-treatment Assessment at week 24	**At Week 24** (12 weeks after ending treatment): HCV Genotype and subtype	**May be**	If the patient is not cured based on the SVR 12, the patient will have a HCV genotype with sub-type performed. This will occur in the minority of patients, thus assuming the cost of genotyping at this point in the treatment protocol will significantly decrease the cost of the treatment while providing the necessary information to plan retreatment when additional therapies are available.

6.5 ANNEX E: THE ALCOHOL USE DISORDERS IDENTIFICATION TESTS: INTERVIEW VERSION

* Skip to Questions 9 and 10 if reply to Question 1 is never, or if both answers to Question 2 and Question 3 are 0

Questions	Frequency and Timing	Scores
1. How often do you have a drink containing alcohol?	Never*	0
	Monthly or less	1
	2 to 4 times a MONTH	2
	2 to 3 times a WEEK	3
	4 or more times a week	4
2. How many units of alcohol do you drink on a typical day when you are drinking?	1 or 2 drinks	0
	3 or 4 drinks	1
	5 or 6 drinks	2
	7 or 8 or 9 drinks	3
	10 or more drinks	4
3. How often have you had 6 or more units if female, or 8 or more if male, on a single occasion in the last year?	Never	0
	Less than monthly	1
	Monthly	2
	Weekly	3
	Daily or almost daily	4
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never	0
	Less than monthly	1
	Monthly	2
	Weekly	3
	Daily or almost daily	4
5. How often during the last year have you failed to do what was normally expected from you because of drinking?	Never	0
	Less than monthly	1
	Monthly	2
	Weekly	3
	Daily or almost daily	4
6. How often during the last year have you needed an alcoholic drink in the morning to get yourself going after a heavy drinking session?	Never	0
	Less than monthly	1
	Monthly	2
	Weekly	3
	Daily or almost daily	4

7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	0
	Less than monthly	1
	Monthly	2
	Weekly	3
	Daily or almost daily	4
8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?	Never	0
	Less than monthly	1
	Monthly	2
	Weekly	3
	Daily or almost daily	4
9. Have you or someone else been injured as a result of your drinking?	No, never	0
	Yes, but not in the last year	2
	Yes, during the last year	4
10. Has a relative or friend or a doctor or another health worker been concerned about your drinking or suggested you cut down?	No, never	0
	Yes, but not in the last year	2
	Yes, during the last year	4

6.6 ANNEX F: MEDICINE PRODUCTS INSERTS

1. Sofosbuvir

Full prescription information contents are here:

http://www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/sovaldi/sovaldi_pi.pdf

SOVALDI® (sofosbuvir) tablets, for oral use Initial U.S. Approval: 2013

Indication and usage

SOVALDI is a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor indicated for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen.

SOVALDI efficacy has been established in subjects with HCV genotype 1, 2, 3 or 4 infections, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 co-infection.

Dosage and Administration

- One 400 mg tablet taken once daily with or without food
- Should be used in combination with Daclastavir with or without Ribavirin for the treatment of Chronic hepatitis C
- SOVALDI in combination with ribavirin for 24 weeks can be considered for CHC patients with genotype 1 infection who are interferon ineligible.
- Should be used in combination with ribavirin for treatment of CHC in patients with hepatocellular carcinoma awaiting liver transplantation for up to 48 weeks or until liver transplantation, whichever occurs first
- A dose recommendation cannot be made for patients with severe renal impairment or end stage renal disease

Dosage Forms and Strengths
Tablets: 400 mg

Contraindications

- When used in combination with peg interferon alfa/ribavirin or ribavirin alone, all contraindications to peg interferon alfa and/or ribavirin also apply to SOVALDI combination therapy
- Because ribavirin may cause birth defects and fetal death, SOVALDI in combination with peg interferon alfa/ribavirin or ribavirin is contraindicated in pregnant women and in men whose female partners are pregnant.

Warnings and Precautions

- Bradycardia with amiodarone co-administration: Serious symptomatic bradycardia may occur in patients taking amiodarone and SOVALDI in combination with another direct acting antiviral (DAA), particularly in patients also receiving beta blockers, or those with underlying cardiac co-morbidities and/or advanced liver disease. Co-administration of amiodarone with SOVALDI in combination with another DAA is not recommended. In patients without alternative, viable treatment options, cardiac monitoring is recommended. (5.1, 6.2, 7.2)
- Pregnancy: Ribavirin may cause birth defects and fetal death and animal studies have shown interferons have abortifacient effects; avoid pregnancy in female patients and female partners of male patients. Patients must have a negative pregnancy test prior to initiating therapy, use at least 2 effective methods of contraception and have monthly pregnancy tests. (5.2)

Adverse Reactions

The most common adverse events (incidence greater than or equal to 20%, all grades) observed with SOVALDI in combination with ribavirin were fatigue and headache. The most common adverse events observed with SOVALDI in combination with peg interferon alfa and ribavirin were fatigue, headache, nausea, insomnia and anemia

Drug Interactions

- Co-administration of amiodarone with SOVALDI in combination with another DAA may result in serious symptomatic bradycardia
- Drugs that are potent intestinal P-gp inducers (e.g., rifampin, St. John's wort) may alter the concentrations of sofosbuvir
- Consult the full prescribing information prior to use for potential drug-drug interactions

Use in Specific Populations

- Patients with HCV/HIV-1 co-infection: Safety and efficacy have been studied
- Patients with hepatocellular carcinoma awaiting liver transplantation: Safety and efficacy have been studied

2. Daclatasvir

Full prescription information contents are here:
http://packageinserts.bms.com/pi/pi_daklinza.pdf

DAKLINZA™ (daclatasvir) tablets, for oral use Initial U.S. Approval: 2015

Indication and usage

DAKLINZA is a hepatitis C virus (HCV) NS5A inhibitor indicated for use with sofosbuvir, with or without ribavirin, for the treatment of chronic HCV genotype 1 or 3 infection

Limitations of Use

- Sustained Viral Response (SVR12) rates are reduced in genotype 3 patients with cirrhosis receiving DAKLINZA in combination with sofosbuvir for 12 weeks

Dosage and Administration

- Testing prior to initiation: HCV genotype 1a with cirrhosis, consider testing for the presence of virus with NS5A resistance-associated polymorphisms
- 60 mg taken orally once daily with or without food in combination with sofosbuvir with or without ribavirin
- Recommended treatment duration: 12 weeks
- Dose modification: Reduce dosage to 30 mg once daily with strong CYP3A inhibitors and increase dosage to 90 mg once daily with moderate CYP3A inducers

Dosage Forms and Strengths
Tablets: 60 mg, 30 mg, and 90 mg

Contraindications

Strong inducers of CYP3A, including phenytoin, carbamazepine, rifampin, and St. John's wort

Warnings and Precautions

Bradycardia When Co-administered with Sofosbuvir and Amiodarone: Serious symptomatic bradycardia may occur in patients taking amiodarone with sofosbuvir in combination with another HCV direct-acting agent, including DAKLINZA (daclatasvir), particularly in patients also receiving beta blockers or those with underlying cardiac co-morbidities and/or advanced liver disease. Co-administration of amiodarone with DAKLINZA in combination with sofosbuvir is not recommended. In patients with no alternative treatment options, cardiac monitoring is recommended.

Adverse Reactions

Most common adverse reactions (≥ 10%) observed with DAKLINZA in combination with sofosbuvir were headache and fatigue. Most common adverse reactions (≥ 10%) observed with DAKLINZA in combination with sofosbuvir and ribavirin were headache, anemia, fatigue, and nausea.

Drug Interactions

Drug Interactions: Co-administration of DAKLINZA can alter the concentration of other drugs and other drugs may alter the concentration of daclatasvir. Consult the full prescribing information before use for contraindicated drugs and other potential drug-drug interactions

3. Harvoni (Sofosbuvir/Ledipasvir)

Full prescription information contents are here:

www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/ harvoni/ harvoni_pi.pdf

HARVONI® (ledipasvir and sofosbuvir) tablets, for oral use Initial U.S. Approval: 2014

Indications and usage

HARVONI is a fixed-dose combination of ledipasvir, a hepatitis C virus (HCV) NS5A inhibitor, and sofosbuvir, an HCV nucleotide analog NS5B polymerase inhibitor, and is indicated with or without ribavirin for the treatment of chronic hepatitis C virus (HCV) genotype 1, 4, 5 or 6 infection

Dosage and Administration

- Recommended dosage: One tablet (90 mg of ledipasvir and 400 mg of sofosbuvir) taken orally once daily with or without food
- HCV/HIV-1 co-infection: For patients with HCV/HIV-1 co-infection, follow the dosage recommendations in the table above
- If used in combination with ribavirin, follow the recommendations for ribavirin dosing and dosage modifications
- A dosage recommendation cannot be made for patients with severe renal impairment or end stage renal disease

Dosage Forms and Strengths
Tablets: 90 mg Ledipasvir and 400 mg sofosbuvir

Contraindications

If used in combination with ribavirin, all contraindications to ribavirin also apply to HARVONI combination therapy

Warnings and Precautions

- Bradycardia with amiodarone co-administration: Serious symptomatic bradycardia may occur in patients taking amiodarone, particularly in patients receiving beta blockers, or those with underlying cardiac co-morbidities and/or advanced liver disease. Co-administration of amiodarone with HARVONI is not recommended. In patients without alternative, viable treatment options, cardiac monitoring is recommended
- Use with other drugs containing sofosbuvir is not recommended

Adverse Reactions

The most common adverse reactions (incidence greater than or equal to 10%, all grades) observed with treatment with HARVONI were fatigue, headache and asthenia

Drug Interactions

- Co-administration with amiodarone may result in serious symptomatic bradycardia. Use of HARVONI with amiodarone is not recommended
- P-gp inducers (e.g., rifampin, St. John's wort): May alter concentrations of Ledipasvir and sofosbuvir. Use of HARVONI with P-gp inducers is not recommended
- Consult the full prescribing information prior to use for potential drug interactions

4. COPEGUS (Ribavirin)

Full prescription information contents are here:

http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021511s023lbl.pdf

Indications

COPEGUS is a nucleoside analogue indicated for the treatment of chronic hepatitis C (CHC) virus infection in combination with PEGASYS in patients 5 years of age and older with compensated liver disease not previously treated with interferon alpha, and in adult CHC patients co-infected with HIV.

Dosage and Administration

- CHC: COPEGUS is administered according to body weight and genotype
- CHC with HIV co-infection: 800 mg by mouth daily for a total of 48 weeks, regardless of genotype
- Dose reduction or discontinuation is recommended in patients experiencing certain adverse reactions or renal impairment

Dosage Forms and Strengths
COPEGUS: tablets 200 mg

Contraindications

- Pregnant women and men whose female partners are preganent
- Hemoglobinopathies
- Co-administration with didanosine

COPEGUS in combination with PEGASYS is contraindicated in patients with:

- Autoimmune hepatitis
- Hepatic decompensation in cirrhotic patients

Warnings and Precautions

Birth defects and fetal death with ribavirin: Do not use in pregnancy and for 6 months after treatment. Patients must have a negative pregnancy test prior to therapy, use at least 2 forms of contraception and undergo monthly pregnancy tests

PEGASYS/COPEGUS: Patients exhibiting the following conditions should be closely monitored and may require dose reduction or discontinuation of therapy:

- Hemolytic anemia may occur with a significant initial drop in hemoglobin. This may result in worsening cardiac disease leading to fatal or nonfatal myocardial infarctions
- Risk of hepatic failure and death: Monitor hepatic function during treatment and discontinue treatment for hepatic decompensation
- Severe hypersensitivity reactions including urticaria, angioedema, bronchoconstriction, and anaphylaxis, and serious skin reactions such as Stevens-Johnson Syndrome
- Pulmonary disorders, including pulmonary function impairment and pneumonitis, including fatal cases of pneumonia
- Severe depression and suicidal ideation, autoimmune and infectious disorders, suppression of bone marrow function, pancreatitis, and diabetes
- Bone marrow suppression with azathioprine co-administration
- Growth impairment with combination therapy in pediatric patients

Adverse Reactions

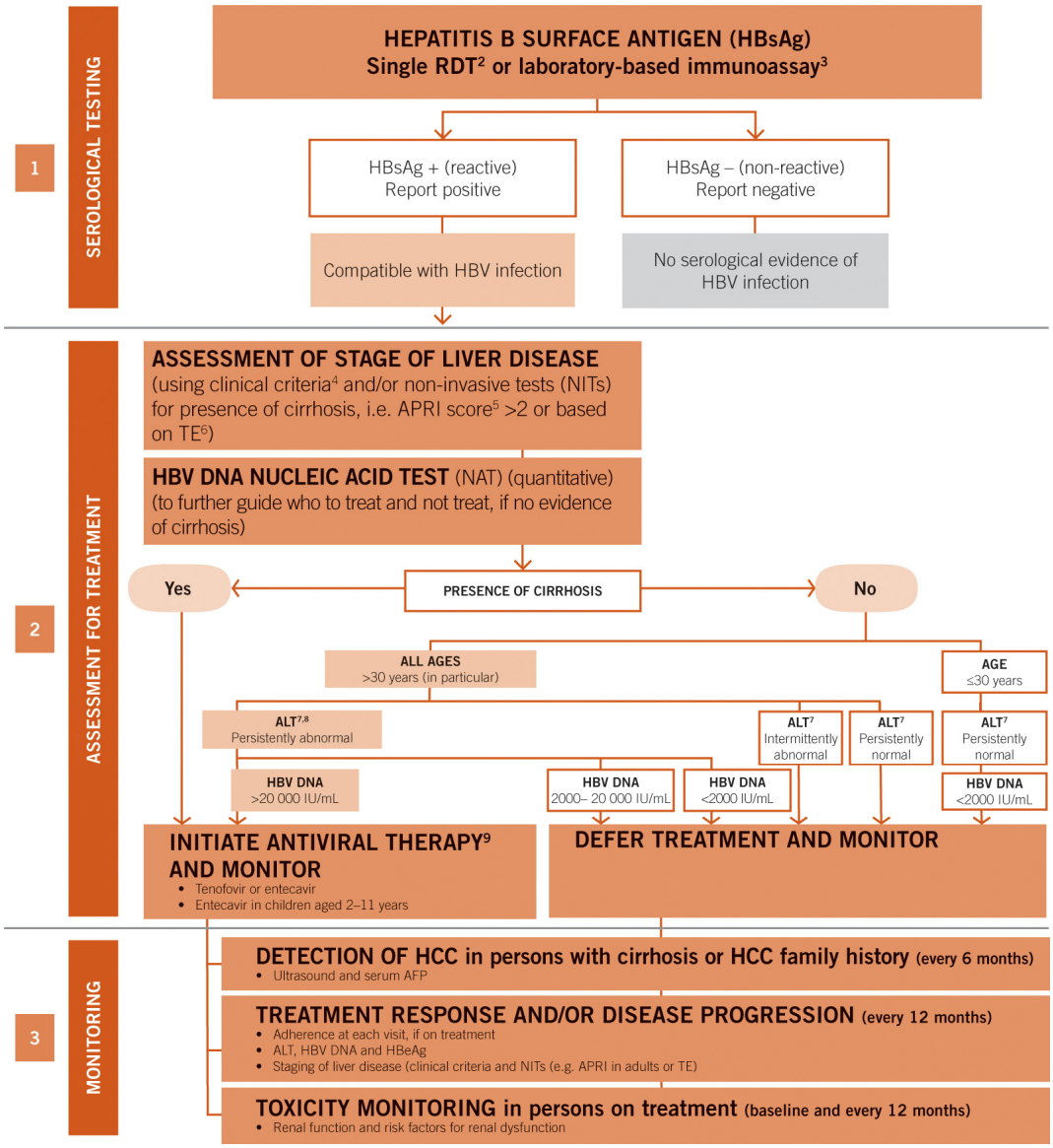
The most common adverse reactions (frequency greater than 40%) in adults receiving combination therapy are fatigue/asthenia, pyrexia, myalgia, and headache.

The most common adverse reactions in pediatric subjects were similar to those seen in adults.

Drug Interactions

- Nucleoside analogues: Closely monitor for toxicities. Discontinue nucleoside reverse transcriptase inhibitors or reduce dose or discontinue interferon, ribavirin or both with worsening toxicities
- Azathioprine: Concomitant use of azathioprine with ribavirin has been reported to induce severe pancytopenia and may increase the risk of azathioprine-related myelotoxicity

6.7 ANNEX G: SUMMARY ALGORITHM FOR DIAGNOSIS, TREATMENT AND MONITORING OF CHRONIC HBV INFECTION[46]



[46]Guidelines on hepatitis B and C testing, WHO, February 2017