UNDERSTANDING HEPATITIS C SCREENING, DIAGNOSIS AND TREATMENT

Developed by :
Community Network for Empowerment (CoNE), Manipur, INDIA.

Supported by :
Coalition PLUS

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Abbreviations & Acronyms

AIDS	:	Acquired Immuno Deficiency Syndrome
ALT	:	Alanine aminotransferase
AST	:	Aspartate aminotransferase
APRI	:	**Aminotransferase/platelet ratio**
CD4	:	Cluster of Differentiation 4 (is a glycoprotein found on the surface of immune **cells**)
DDI	:	Drug-Drug Interactions
DAAs	:	Direct Acting Antivirals
CBC	:	Complete Blood Count
HAV	:	Hepatitis A Virus
HBV	:	Hepatitis B Virus
HCV	:	Hepatitis C Virus
HCC	:	Hepatocellular carcinoma
HDV	:	Hepatitis D Virus
HEV	:	Hepatitis E Virus
HGV	:	Hepatitis G Virus
HIV	:	Human Immuno Deficiency Virus
LFTs	:	**Liver Function Tests**
NS5a	:	Non Structural Protein 5a
NS5b	:	Non Structural Protein 5b
PCR	:	Polymerase Chain Reaction
RNA	:	Ribonucleic Acid
SVR	:	Sustainable Virological Response
WHO	:	World Health Organization

Table of Content

Chapter 1: The Liver and Hepatitis

What is the liver?

- The **liver** is the largest and vital internal organ in the body. It is located on the right upper part of the abdomen.

- **Main functions of the Liver are :**

- It secrets bile and helps in digestion of food.
- Stores vitamins, mineral and nutrients.
- Filters and clears the blood of waste products, hormones, drugs and other toxins;
- Helps to balance levels of sugar and hormones;
- Secrets chemicals that help in coagulation/clotting blood

What is hepatitis?

- The word hepatitis means inflammation of the liver. Inflammation is a natural reaction of the body to an injury or an infection.

- Alcohol, some drugs and chemicals, and some viruses and bacteria/ fungi can cause hepatitis. These viruses are named alphabetically (A, B, C, D, E and G) in the order they were discovered. The main viruses that cause hepatitis are hepatitis A virus, hepatitis B virus, hepatitis C virus and Hepatitis E virus.

- Currently, vaccines are available for hepatitis A and B only.

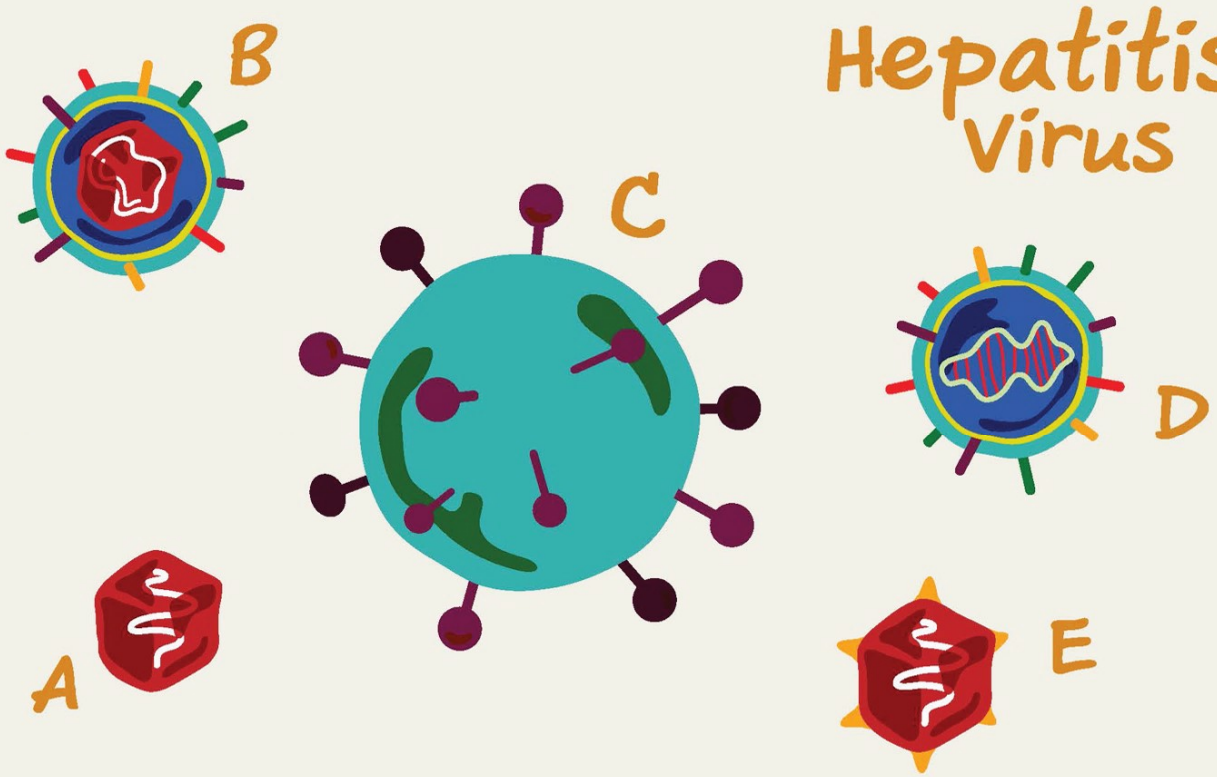
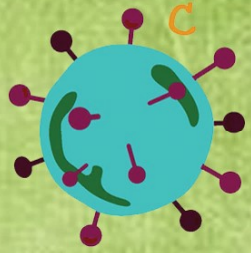


Table 1. Types of Viral Hepatitis

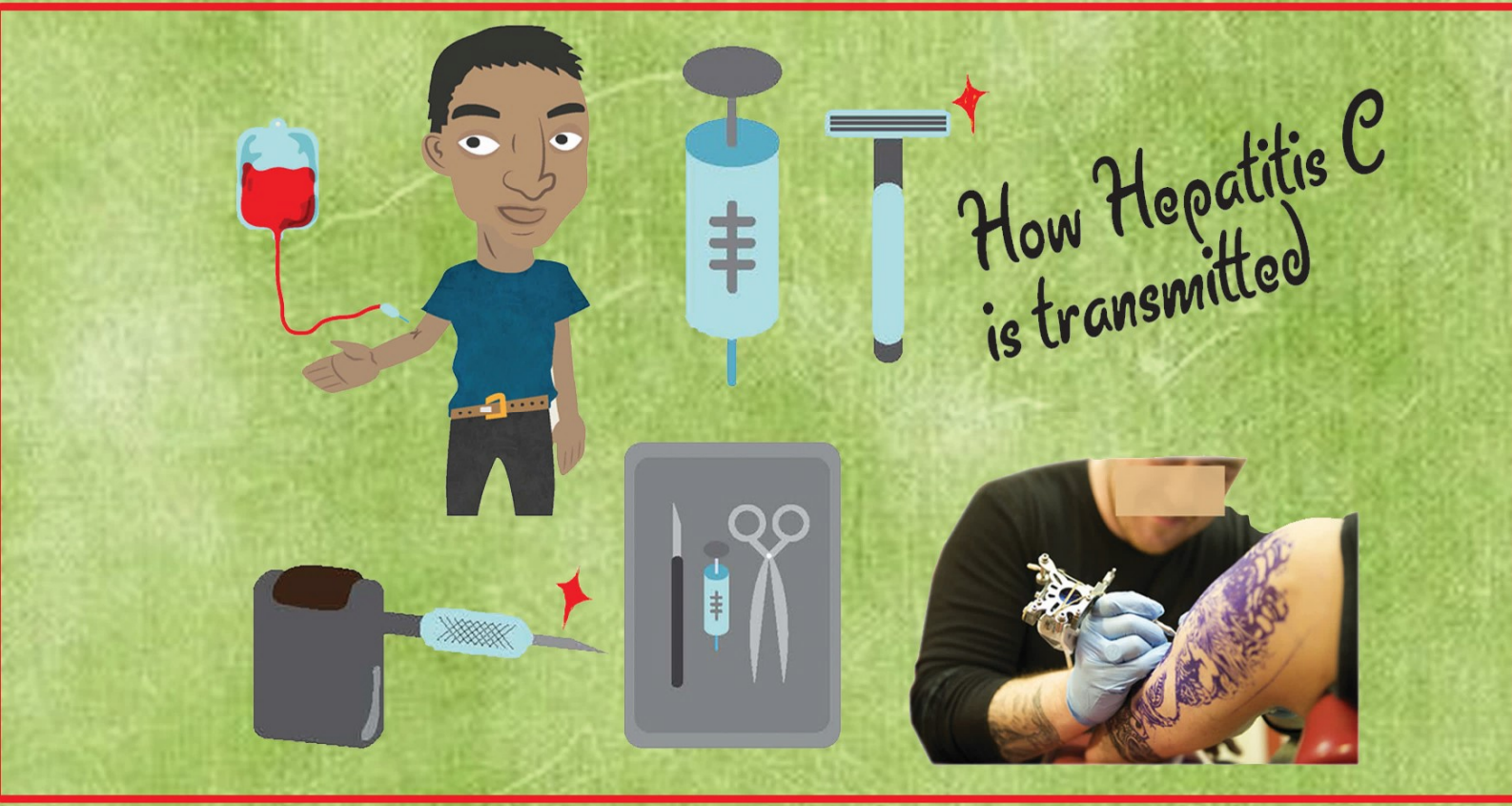
Hepatitis A Virus (HAV) 	• HAV are found in feces (stool) • People become infected when feces from a person who is infected with HAV enters their mouth. This may occur when food (including raw or undercooked)or water is contaminated with sewage; when an infected person handles food without washing his/ her hands after using the bathrooms; through oral-anal sex with an infected person and, rarely, from blood transfusion. • HAV is not a chronic infection; it goes away by itself, usually within 2 months. • A person can be infected with HAV only once. • HAV vaccine is available.
Hepatitis B Virus (HBV) 	• HBV is found in blood, semen, and vaginal fluid of infected persons. Very small amounts of HBV have been found in breast milk and saliva. • A person can get hepatitis B from sharing injection or tattooing equipment, from unprotected anal, vaginal, or oral sex, and from sharing personal care implements (such as toothbrushes and razors). • HBV can be passed from mother to infant during childbirth. • The body can clear itself from HBV. Some people have chronic infection which can be treated. • HBV vaccine is available.

Hepatitis C Virus (HCV) 	• Hepatitis C can be transmitted through contact with blood, for example through transfusion of unsafe blood products, sharing equipment for injecting drugs, use of unclean medical materials or unclean tattooing and body piercing. • HCV vaccine is not yet available, but treatment is available
Hepatitis D Virus (HDV) 	• Hepatitis D virus infects some people with hepatitis B Virus. HDV increases the risk of cirrhosis and the rate of liver disease progression for people with HBV. • HBV vaccine also protect against HDV.
Hepatitis E Virus (HEV) 	• An infectious virus with characteristics similar to hepatitis A. • HEV will clear without treatment over several weeks to months. • It is usually not serious, except during pregnancy. • There is no vaccine for HEV.
Hepatitis G Virus (HGV)	• A virus with structural similarities to hepatitis C. The role and importance of hepatitis G is unclear, especially in people with HIV. • Some research suggests that hepatitis G may slow HIV progression. Other research suggests that clearing hepatitis G can make HIV more serious.

CHAPTER 2: WHY HEPATITIS C IS IMPORTANT FOR PEOPLE LIVING WITH HIV, HOW IT IS TRANSMITTED AND HOW IT CAN BE PREVENTED

- HCV is a prevalent co-infection among people living with HIV/ AIDS. Currently, approximately 2.3 million people globally are co-infected with HIV and HCV. Of these approximately 1.3 million are from a background of people who inject drugs. (According to WHO report 2017)
- Liver disease progression can be five times faster among people living with HIV compared to people who do not have HIV.
- The risk of mother to child transmission can increase five times if the mother has HIV.

How is HCV transmitted?



HCV can also be transmitted through:

- Injecting drugs using shared syringes and/ or spoons, caps and other cookers. Sharing of contaminated water; filters; and ties that may have been used by someone else.

- Tattooing or piercing using unsterilized needles, contaminated ink, or inkwells

- Unsafe medical procedures, such as dental procedures, injection using injecting equipment that may have been used by other people
- Unsafe Blood transfusion
- Unsterile cosmetic procedure (facial, manicure, pedicure, shaving)
- Unprotected sex with someone who has HCV.
- Accidental needle-stick injury (a problem for health care workers)
- Mother to baby, during pregnancy or during labor and delivery. The risk of HCV transmission to an infant is three to four times higher if the mother has both HCV and HIV. This means that up to 20% of pregnant women who are co-infected may pass HCV to their infants
- Sharing items that may contain blood, such as razors and/or toothbrushes

↝ The hepatitis C virus is transmitted when infected blood from an infected person enters the bloodstream of another person.

↝ Hepatitis C does not spread through social contact.

↝ Mosquitoes or other insects, hugging, kissing, sneezing, coughing, sharing food, drinks, plates, eating utensils, laundry and toilet facilities will not transmit hepatitis C.

↝ HCV infection usually stays asymptomatic for a long time. When they do appear, symptoms of liver damage include:

- Fatigue
- Nausea
- Loss of appetite
- Swollen abdomen
- Itchy skin
- Jaundice

Prevention of Hepatitis C

- Sharing of drug-injecting equipment can lead to the transmission of the hepatitis C virus and the hepatitis B virus and HIV.
- Clean up any blood spills carefully using latex gloves, soap, warm water and bleach
- Put any blood stained things such as band-aids, dressings, tampons and sanitary napkins in a plastic bag before putting them in the bin
- Avoid unsafe sex
- Do not share razors, toothbrushes or nail clippers.
- Always take care to dispose of injecting equipment carefully so that no other person can use it again.

CHAPTER 3: DIAGNOSING HEPATITIS C INFECTION

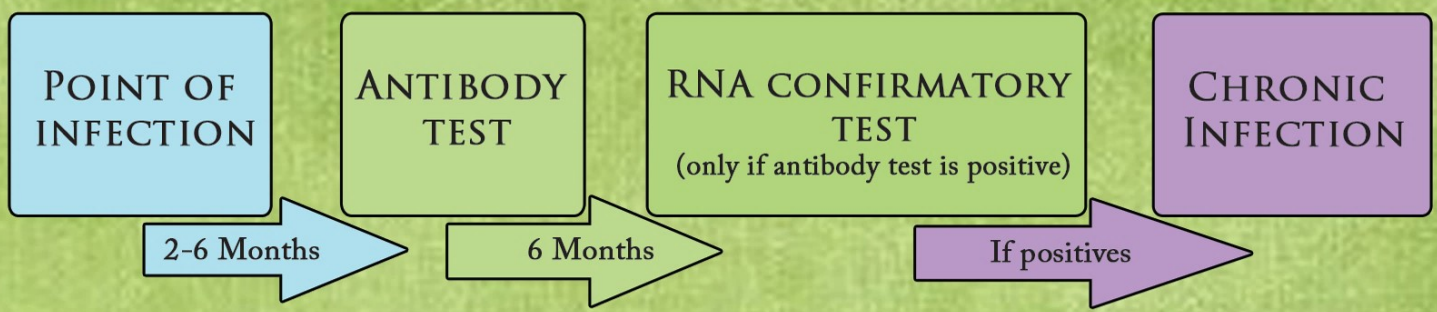
- Hepatitis C testing is a two-stage process. The first test is usually a HCV antibody test. This test is a blood test that is usually done before other tests. The antibody test indicates either past or present contact with the hepatitis C virus. It does not always mean that the hepatitis C virus is active in the body.

- Antibody test results are sometimes negative even when the person has hepatitis C infection. This may occur if:
    - CD4 cell count is low (usually below 200), because the immune system may not be producing antibodies; or

- The Polymerase Chain Reaction Test (PCR): PCR test is used to detect the virus and also to measure the amount of HCV in the blood. It is also known as the viral load test. A viral load test is usually first done after a person has a positive antibody test. A positive result means the hepatitis C virus is active in your body. A negative result means that the virus is no longer present.

- HIV/HCV co-infected people usually have higher hepatitis C viral loads than people with HCV alone. Unlike HIV, the hepatitis C viral load does not indicate or predict the degree of liver damage, nor is it used to decide when to start treatment.

HCV Testing process:



CHAPTER 4: UNDERSTANDING HEPATITIS C AND ITS EFFECTS ON LIVER

- There are 6 types of hepatitis C virus, which is also known as genotype. They are named as genotype 1, 2,3,4,5 and 6. Each genotype also has a subtype which is named as a,b. For eg. Genotype 1(a) or (b).

- The hepatitis C virus can cause chronic infection and liver damage over a long period of time. This results in hardening of the liver and less elastic. Therefore, scarring makes it increasingly difficult for blood and other necessary fluids to flow freely through the liver.

- The first six months of HCV infection are referred to as the acute infection period. 80% of people who do not have symptoms during acute infection, so HCV is rarely diagnosed at this time. When symptoms do occur during acute infection, they include fever, fatigue, abdominal pain, nausea, vomiting, dark urine, and jaundice (yellowed eyes and skin).

- Chronic infection refers to cases in which the hepatitis C virus remains in the body after the acute phase. Most people with HCV are chronically infected. Chronic HCV can have a very wide range of outcomes. Some people will never develop significant liver damage, some will have mild liver scarring, and others (between 20-30%) will eventually develop cirrhosis.

- Over time, more liver cells are damaged and destroyed, causing liver scaring. This is called fibrosis. Severe fibrosis can cause the liver to become hardened, and prevents it from working well. This is called cirrhosis of the liver. In a small number of cases, serious damage to the liver can lead to liver cancer. This damage in the liver usually develops slowly over many years.

- People with cirrhosis from HCV are at risk for liver failure and liver cancer, although not all will develop these complications. Someone experiencing liver failure needs a liver transplant in order to survive. Liver failure resulting from hepatitis C occurs in only a handful of people, usually those who have been infected for many years. Some people with cirrhosis will also develop hepatocellular carcinoma (HCC; liver cancer).

- Compensated cirrhosis may progress to end-stage liver disease, which occurs when a person's liver can no longer function. This is known as de-compensated cirrhosis.

- Some people never seem to experience significant consequences of HCV infection. Others may develop mild to moderate fibrosis (liver scarring) and experience symptoms such as fatigue, depression, and confusion (often called brain fog).

- Some people may accumulate fat in their liver cells, a condition known as steatosis. Steatosis is linked with more serious liver disease.

- Even though a badly damaged liver can keep working, the ongoing effects of HCV and inflammation can slowly interfere with liver functions.

- A person with chronic HCV experiences health complications when his or her liver is no longer able to carry out important tasks.

- **Symptoms of advance liver fibrosis or cirrhosis may include:**
  - Jaundice, Bleeding, Swollen abdomen, Mental disorientation or confusion (known as hepatic encephalopathy), Extreme fatigue

Factors that can accelerate HCV disease progression:

- HIV co-infection
- Alcohol intake, especially more than 50 grams/ day, or the equivalent of four to five glasses of wine
- Aging
- Duration of infection
- Older at time of infection (over 40 years of age)
- Hepatitis B co-infection

CHAPTER 5: TESTS TO ASSESS LIVER CONDITION

- Liver Function Tests (LFTs):
  - A blood test that measures if there is an inflammation or damage to the liver, by measuring the liver enzymes.
  - The liver enzyme levels can increase to abnormal levels, usually caused by liver toxicity from prescription and over-the-counter medications, herbs, exposure to toxic fumes; heavy alcohol consumption; acute or chronic viral hepatitis.
  - Liver enzyme tests usually include ALT/ AST, albumin, and GGT.

- Liver enzyme tests (ALT* and AST**):
  - Increases in ALT are usually a signal of liver inflammation or damage; however, ALT is not a reliable marker for predicting whether HCV will progress, or for indicating the severity of liver disease, since liver enzyme levels often fluctuate in people with chronic HCV.
  - Up to a third of all people with chronic HCV have persistently normal ALT, even though some of these people have serious liver damage.
  - ALT should be monitored routinely, since persistently increasing levels may suggest HCV progression.

- APRI
  - APRI stands for aminotransferase/platelet ratio. This is validated for the diagnosis of both significant fibrosis and cirrhosis.
  - The score to understand the condition is calculated using the formula

    APRI = [(AST (IU/L)/AST_ULN (IU/L))×100]/ platelet count (109/L)

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

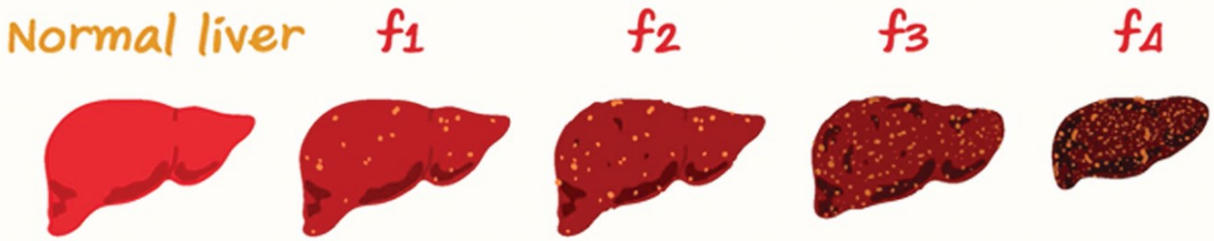
- FIB- 4
  - FIB 4 is also an indirect marker of fibrosis. It is evaluated for mainly significant fibrosis and above.
  - The score to understand the condition is calculated using the formula

    FIB-4= age (yr) x AST (IU/L)/platelet count (109/L) x [ALT (IU/L)1/2]

*Alanine aminotransferase (ALT)

**Aspartate aminotransferase (AST)

• stages of liver fibrosis •



- The Fibroscan®
  - The Fibroscan ® is a non-invasive approach to measure the stiffness or elasticity of the liver using an ultrasound probe on a vibrating apparatus to create waves and measure their speed.
  - Although this scan is much less sensitive in detecting mild or moderate liver damage, it is very sensitive to severe damage and can identify people who may urgently need HCV treatment.

Fibrosis Score by using Fibroscan	
Fibrosis Stage 0 (F0)	No Fibrosis
Fibrosis Stage 1 (F1)	Minimal Fibrosis
Fibrosis Stage 2 (F2)	Moderate Fibrosis
Fibrosis Stage 3 (F3)	Severe Fibrosis
Fibrosis Stage 4 (F4)	Cirrhosis

CHAPTER 6: UNDERSTANDING HIV/HEPATITIS C CO-INFECTION

- Co-infection means infection with more than one virus. Generally co-infection with HIV and hepatitis C complicates both diseases. Hepatitis C progresses more quickly in people who are also HIV-positive.

- So long as hepatitis C infection is stable, many people, especially if they have been infected with hepatitis C for a long time, will treat their HIV first. Treating HIV may delay hepatitis C disease progression by maintaining immune health.

- Women living with HIV and hepatitis C co-infection has approximately five times higher chances of transmitting the hepatitis C to the child than a women who do not have HIV.

Can hepatitis C be cured?

By either of the two ways below;

- The person's immune system responds effectively to the virus during the first few months of infection and eliminates it from the body; or
- A full treatment course using direct-acting antivirals either for 3 months or 6 months, depending on the condition of the liver.

- If hepatitis C is cured, either by immune system or through treatment, the person may not experience any long-term health consequences.

- About 25% of people infected with hepatitis C will get rid of the virus within 12 months on their own. They are therefore no longer affected and cannot pass the virus on. This is also known as natural clearance or spontaneous clearance.

CHAPTER 7: GOAL AND PREPARING FOR HEPATITIS C TREATMENT

- The primary goal is to get rid of hepatitis C and get a cure.
- The secondary goal is to improve liver health by reducing inflammation, and sometimes, reversing fibrosis. This happens even in patients who do not have an SVR, although only in about half the number of cases.
- Treatment also reduces the risk of complications (cirrhosis, liver cancer, and liver-related death), especially for those who have an SVR. For co-infected people, the additional benefit is less risk of liver-related side effects from HIV drugs
- Hepatitis C can be treated, regardless of a person's HIV status.
- Anyone who has a confirmed RNA viral load test should choose to get treated irrespective of the liver condition.
- It has been shown that earlier the treatment, better the treatment response is.
- Cure is the best prevention.

Before initiating treatment it is good to know the results of the following;

- ☑ HCV RNA test
- ☑ Genotype (It's not mandatory if you use Velpatasvir/sofosbuvir or sofosbuvir/daclatasvir as your medicines regimen)
- ☑ Fibrosis stage (either by FibroScan, APRI or FIB-4)
- ☑ Liver Function test
- ☑ Complete Blood count
- ☑ Kidney Function test.

CHAPTER 8: TREATMENT OF HEPATITIS C

The World Health Organization (WHO) has recommended the use of all oral direct-acting antivirals, also known as DAAs, for the treatment of hepatitis C.

There are 3 major class of DAAs; they are:

*NS5a inhibitors,
*NS5b inhibitors and
*protease inhibitors.

The guidance on the treatment are discussed below;

Recommended regimens

The WHO recommends pan-genotypic DAA regimens be used for the treatment of persons with hepatitis C infection. , The recommended regimen for Manipur has been considered based on recommendations from WHO and the India National Guidelines for Diagnosis and Management of Viral hepatitis.

Regimen(s) for public health approach: Non-Cirrhotic patients

Sofosbuvir + daclatasvir

- 12weeks(All genotypes) for non-cirrhotic patients(APRI < 2.0)

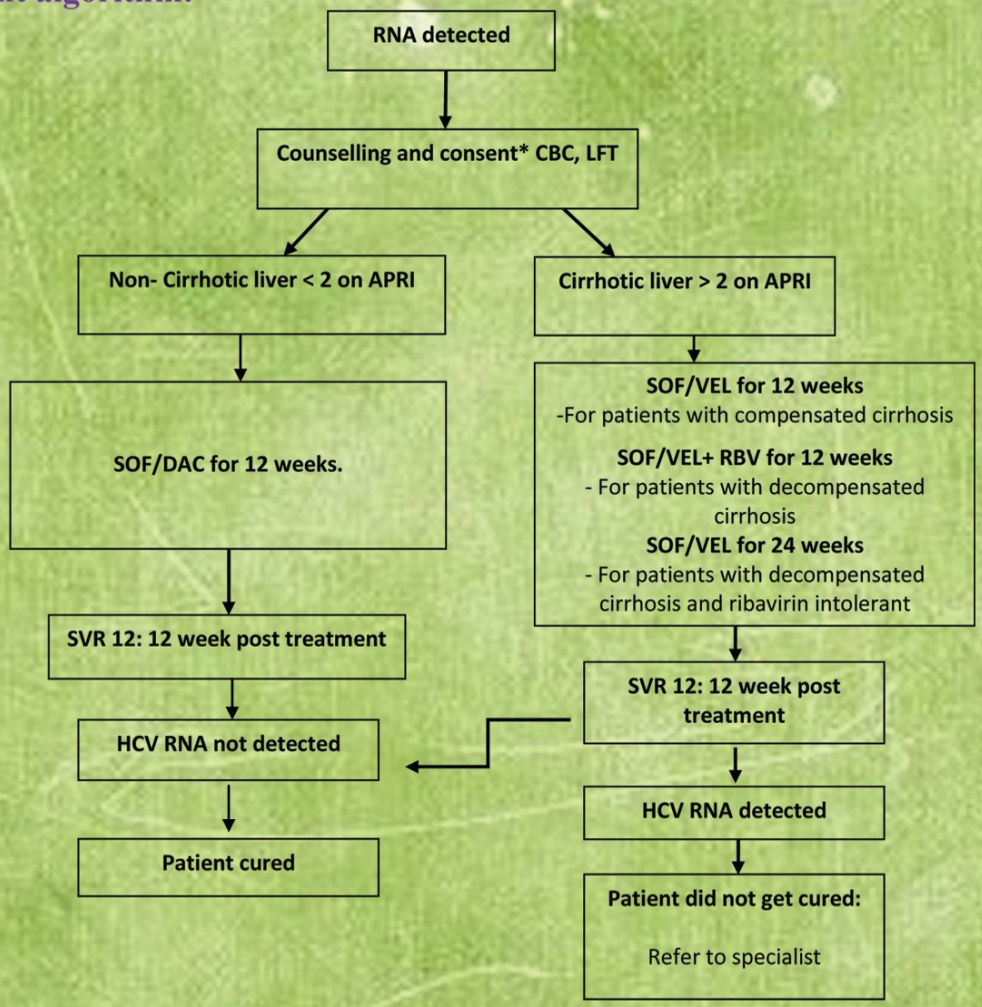
Regimen(s) for public health approach: Compensated cirrhosis
Sofosbuvir/Velpatasvir

- 12weeks(All genotypes)for cirrhotic patients(APRI > 2.0)

Regimen(s) for public health approach: Decompensated cirrhosis
Sofosbuvir/Velpatasvir + Ribavirin

- 12 weeks(All genotypes)for decompensated cirrhotic patients
- 24 weeks (All genotypes) for decompensated patients with ribavirin intolerance

Treatment algorithm:



Dosing for HCV treatment regimen

Dosing for Recommended HCV Treatment Regimens

Regimen	Dosage per tablet	Dosing Frequency and Timing
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
Daclatasvir	30 mg or 60 mg tablet (special considerations for ART patients)	(Refer-Page-17 for doze adjustment on ARV for HCV)
Velpatasvir/ sofosbuvir	100 mg /400 mg tablet (consider contra-indications with ART)	Once daily

CHAPTER 9: TREATMENT MONITORING

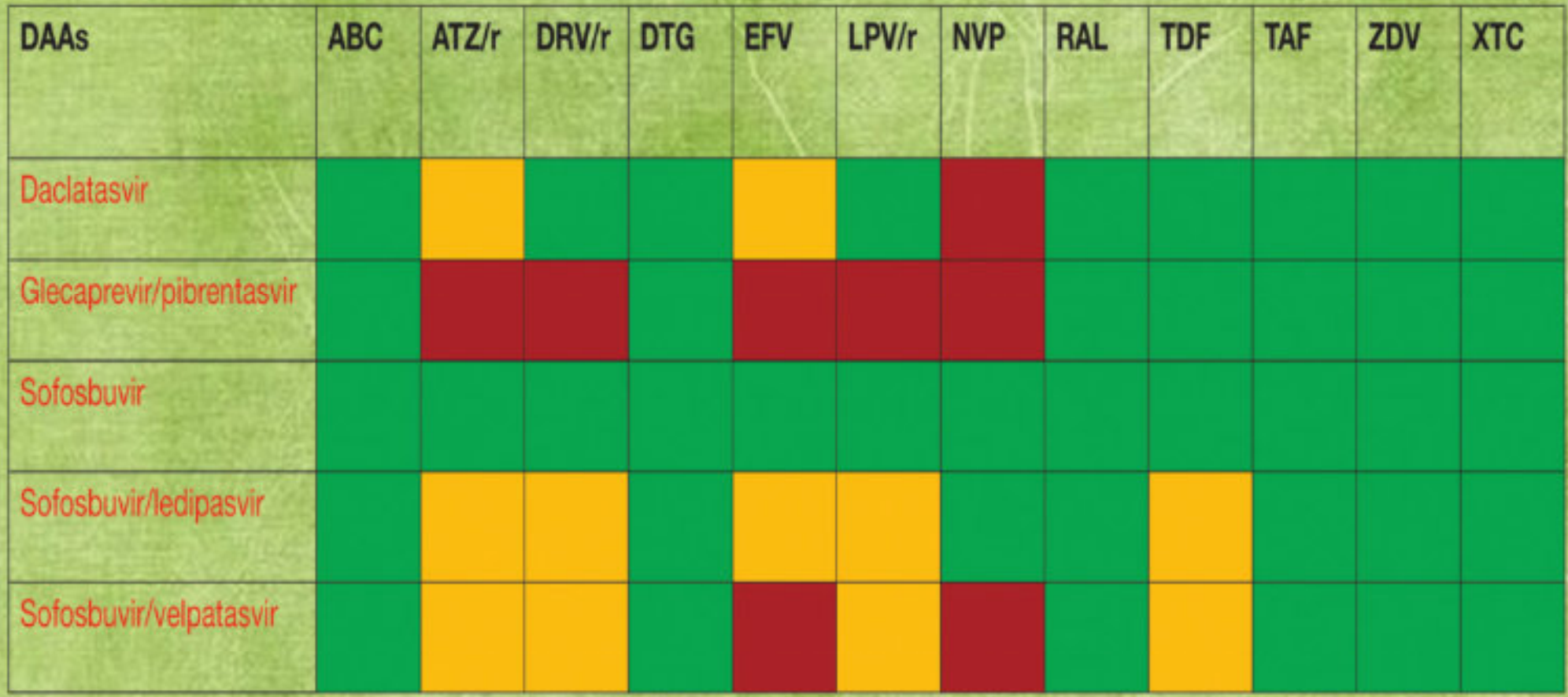
Treatment week	DAA Alone			DAA+RBV		
	CBC, renal, liver function	Adherence, side effects	HCV RNA	CBC, renal, liver function	Adherence, side effects	HCV RNA
Baseline	✓		✓	✓		✓
Week 1				✓	✓	
Week 2				✓	✓	
Week 4	✓	✓		✓	✓	
Week 8				✓	✓	
Week 12				✓	✓	

[20]World Health Organization, Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection, http://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2018/en/, 2018

[21]National Guidelines for Diagnosis and Management of viral hepatitis, Ministry of Health and Family Welfare, Government of India, July 2018

Drug–drug interactions between hepatitis C and HIV medicines

Some HIV medicines can interact with the DAAs used to treat hepatitis C. When these drug-drug interactions are anticipated, substitutions for HIV medications should be made before starting hepatitis C treatment.



DAAs	ABC	ATZ/r	DRV/r	DTG	EFV	LPV/r	NVP	RAL	TDF	TAF	ZDV	XTC
Daclatasvir												
Glecaprevir/pibrentasvir												
Sofosbuvir												
Sofosbuvir/ledipasvir												
Sofosbuvir/velpatasvir												

Do not co-administer.

May need dose adjustment for DAAs.

No known interaction; can be co-administered.

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

- A person who use efavirenz for his/her HIV treatment should be given 90mg daily of daclatasvir instead of the normal 60mg daily, if it is both these medicines are used together at the same time.

- A person who uses atazanavir/lopinavir for his/her HIV treatment should be given 30mg daily of daclatasvir instead of the normal 60mg daily, if it is both these medicines are used together at the same time.

- No dose adjustment of daclatasvir is required when given together with Opiate Substitution Therapy i.e. either methadone or buprenorphine.

PUBLISHER'S NOTE

This booklet for Hepatitis C (HCV) screening, diagnosis and treatment was developed by Community Network for Empowerment (CoNE), Imphal from a public health perspective to enhance the awareness and knowledge on HCV among health care workers. The booklet was developed in consultation with various experts from Public health section of Directorate of Health Services, Government of Manipur, Regional Health and Family Welfare Training Institute, Manipur State AIDS Control Society (MACS), State Tuberculosis (TB) Hospital, Experts from Jawaharlal Nehru Institute of Medical Sciences (JNIMS), Regional Institute of Medical Sciences (RIMS) and Shija Hospital and Research Institute.

This booklet aims to increase awareness on HCV screening, diagnosis and treatment among registered medical practitioners, physicians of various specialities, nursing students during their training course, health care workers and paramedic staff working in government health settings and private hospitals.

A state level consultation was organized on 30th August 2017 for seeking technical inputs on the first draft of the booklet inviting various experts from the institution mentioned above. After minor modifications, all the members present at the consultation strongly recommended that the booklet be used to enhance the capacity on HCV among different level of the public health response in the state of Manipur.

We, at CoNE, would like to thank all the members involved in the process of developing and finalizing the booklet for their inputs, suggestions and critically examining the contents of the booklet prior to its finalization. We would like to extend our special appreciation to Dr. Kh. Sasheekumar Mangang, Additional Director (Public Health); Dr. O. Sanahanbi Devi, Principal, Regional Health & Family Welfare Training Institute; Dr. Kh. Lokeshwar Singh, Associate Professor, Department of Medicine, JNIMS; Dr. K. Romeo Singh, Associate Professor, Gastroenterology, RIMS; Dr. Goldie Longjam, Consultant Gastroenterologist, Shija Hospital & Research Institution; Dr. Gopal Krishna, State TB Officer; Mr. Abhiram Mongjam, Joint Director (Targeted Intervention), MACS for their profound contribution and providing us with the technical inputs.

Our appreciation also goes to TREAT Asia/amf AR, Bangkok, Thailand for their Technical inputs and guidance not only on this booklet but also in our overall response to HCV.

We hope that the booklet contributes in its intended aim which will allow people living with HCV in the state, and beyond, getting appropriate diagnosis and treatment of their infection. We also hope that this booklet contributes significantly in reducing the stigma and discrimination towards people living with the infection and clarify myths and misconceptions that surround HCV.

For more related information, please contact

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