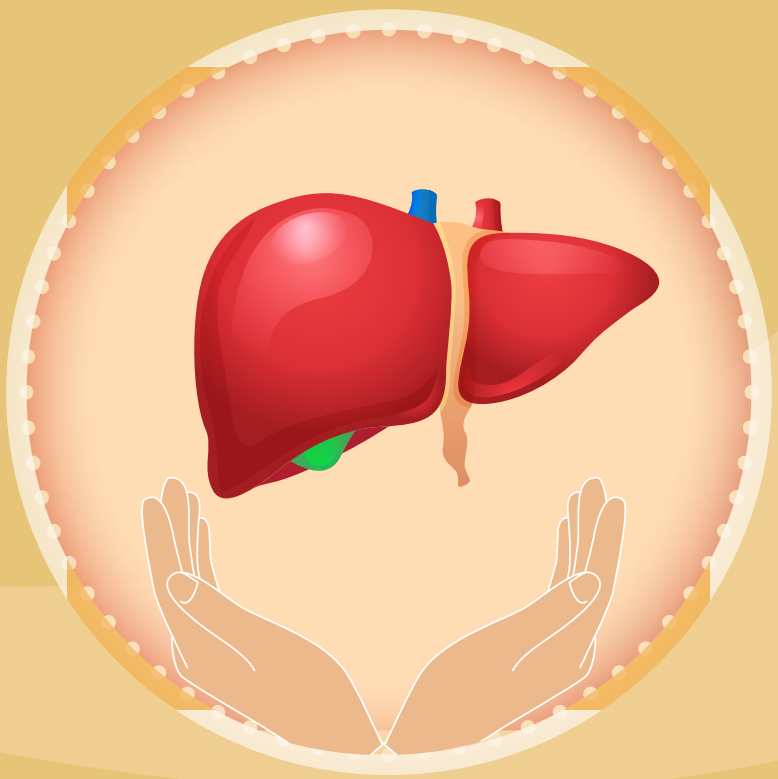
सत्यमेव जयते
Ministry of Health and Family Welfare
Government of India

NATIONAL HEALTH MISSION
राष्ट्रीय स्वास्थ्य मिशन

National Guidelines for

Diagnosis & Management of Viral Hepatitis



2018

National Guidelines for

Diagnosis & Management of Viral Hepatitis

डॉ. एस वेंकटेश
Dr S. VENKATESH
DNB, MD, DPH, MPH (Harv) FAMS, FIPHA
Director General of Health Services

सत्यमेव जयते

भारत सरकार
स्वास्थ्य एवं परिवार कल्याण मंत्रालय
निर्माण भवन, नई दिल्ली -110 108
GOVERNMENT OF INDIA
MINISTRY OF HEALTH & FAMILY WELFARE
NIRMAN BHAWAN, NEW DELHI- 110 108
TEL.: 23061063, 23061438 (O), 23061924 (F)
E-mail : dghs@nic.in

दिनांक/Dated 25.07.2018

Foreword

The National Viral Hepatitis Control Programme is being launched by the Ministry of Health and Family Welfare, Government of India with the aim to reduce morbidity and mortality due to viral hepatitis. It marks the beginning of India's initiative towards eliminating the disease as a public health threat. The key strategies adopted under the programme include preventive and promotive interventions with focus on generating awareness, promoting diagnosis and providing management of viral hepatitis to all in need.

I am confident that this programme, under the ambit of the National Health Mission (NHM), will make all efforts to expand the reach and coverage of testing and management till the most peripheral level. It is reassuring to note that this guideline will complement this determined endeavor of the programme by providing standardized management protocols with focus on treatment of hepatitis B and C.

States have successfully demonstrated their dedication towards reproductive and child health and communicable diseases which has resulted in positive outcomes. We now need to replicate such unwavering attention to addressing viral hepatitis. I hope that this guideline is used by all the stakeholders for implementation of management of viral hepatitis while integrating into the health systems. We need to ensure that patients who are detected with the disease are adequately managed and are not lost to follow up, and that we are able to provide a continuum of care for patients with disease.

Svenkatesh

(Dr S. Venkatesh)

Postgraduate Institute of Medical Education and Research
Department of Hepatology, Chandigarh, 160012, INDIA

Dr R K Dhiman
MD, DM, FAMS, FACG, FRCP Edin., FRCP London, FAASLD
Professor & Head

Preface

Viral hepatitis is increasingly being recognized as a public health problem in India. While hepatitis A and E – that are water and foodborne infections – are often the cause for sporadic or outbreaks of hepatitis in India and recover completely with no clinical sequelae, hepatitis B and C can lead to chronic infection and thereafter sequelae like cirrhosis and hepatocellular carcinoma.

Viral hepatitis is a leading cause of death in the world, which is comparable to that of HIV, tuberculosis and malaria. Cirrhosis and hepatocellular carcinoma, which are the sequelae of chronic hepatitis B and C, accounted for more than 90% of all hepatitis B and C related deaths. Further, mortality from HBV- and HCV-associated cirrhosis and hepatocellular carcinoma is still increasing because of poor access to treatment. While prevention can reduce the rate of new infections, treatment eliminates existing infections; thus combining both prevention and treatment makes hepatitis B and C elimination feasible long term goal.

The Government of India has decided to launch the National Viral Hepatitis Control Program with provision of free diagnosis and treatment for viral hepatitis through the National Health Mission. Consequently, it is of utmost importance to have standard national guidelines that are robust, evidence based, and simple to be followed at the decentralized level. It should also enable the service providers to decide on the assessment of patient, treatment options, managing special situation (like co-infections), parameters for timely referrals and quality service delivery. The current guidelines are a outcome for the collective effort of the members of Technical Resource Group on hepatitis Treatment, constituted by the MoH & FW, and that had representations of clinicians and program managers from across the country, representing different sectors (government, private sector, academic institutes, community members, development partners). The group has taken into considerations the latest available evidence, global guidelines (such as EASL, WHO etc) and adapted them to the Indian context taking relevant considerations from with the extensive experience of delivering services in the state of Punjab.

I hope, these guidelines will offer the needed guidance for delivering quality treatment and services in a public health approach.

Secretary General, *Indian National Association for the Study of the Liver* ***(INASL)***
Editor-in-Chief, *Journal of Clinical & Experimental Hepatology* ***(JCEH)***
Past President, *International Society for Hepatic Encephalopathy & Nitrogen Metabolism* ***(ISHEN)***

Office
Department of Hepatology,
Room Number 6, D Block, Nehru Hospital,
Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India
Email: ripudhiman@hotmail.com
Tel: +911722756335, +917087009337, +919914209337 (PA).

ACRONYMS

AFP	Alfa Feto Protein
AIDS	Acquired Immuno Deficiency Syndrome
ALF	Acute Liver Failure
ALP	Alkaline Phosphatase
ALT	Alanine amino transferase
AntiHBc	Antibody to Hepatitis B core antigen
AntiHBe	Antibody to Hepatitis B envelope antigen
APRI	AST to Platelet Ratio Index
ART	Anti-Retroviral Therapy
ARVs	Anti Retro Virals
AST	Aspartate aminotransferase
CBC	Complete Blood cell Count
CD4	Cluster of Differentiation 4
CEMRI	Contrast Enhanced Magnetic Resonance Imaging
CHB	Chronic Hepatitis B
CT	Computed Tomography
d4T	Stavudine
DAA	Directly acting anti-viral
DCV	Daclatasvir
ddI	Didanosine
DDIs	Drug Drug Interactions
DMLT	Diploma in Medical Laboratory Technology
DNA	Deoxyribo Nucleic Acid
DOEACC	Department of Electronics and Accreditation of Computer Courses
DPT	Diptheria Pertussis Tetanus
EASL	European Association for Study of the Liver
eGFR	estimated Glomerular Filtration Rate
EQA	External Quality Assessment
FEFO	First Expiry First Out
HAV	Hepatitis A Virus
HBIG	Hepatitis B Immuno Globulin
HBV	Hepatitis B Virus
HBsAg	Hepatitis B Surface Antigen
HBeAg	Hepatitis B envelope Antigen
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HCVcAg	Hepatitis C Virus core Antigen
HDV	Hepatitis D Virus
HEV	Hepatitis E Virus
Hib	Haemophilus influenzae type b
HIV	Human Immunodeficiency Virus
HR	Human Resource
ICTC	Integrated Counseling and Testing Centre
ICU	Intensive Care Unit
IDSP	Integrated Disease Surveillance Programme
INR	International normalized ratio

IP	In Patient
LDV	Ledipasvir
M&E	Monitoring and Evaluation
MLT	Medical Laboratory Technology
MO	Medical Officer
MRI	Magnetic Resonance Imaging
MTC	Model Treatment Centres
NACO	National AIDS Control Organization
NACP	National AIDS Control Program
NAs	Nucleos(t)ide analogues
NAT	Nucleic Acid Testing
NITs	Non Invasive Tests
NCDC	National Centre for Disease Control
NHM	National Health Mission
NSAID	Non Steroidal Anti Inflammatory Drug
NVHMU	National Viral Hepatitis Management Unit
NVP	Nevirapine
OP	Out Patient
OST	Opioid Substitution Therapy
PIP	Program Implementation Plan
PCR	Polymerase Chain Reaction
PEG-IFN	Pegylated Interferon
PLHIV	People Living with HIV
PMU	Program Management Unit
PWID	People Who Inject Drugs
QC	Quality Control
RAS	Resistance-Associated Substitution
RBV	Ribavarin
RNA	Ribo-nucleic acid
SoE	Statement of Expenditure
SOF	Sofosbuvir
SOP	Standard Operating Procedure
SSO	State Surveillance Officer
SVHMU	State Viral Hepatitis Management Unit
SVR	Sustained Virological Response
TAF	Tenofovir Alafenamide Fumarate
TB	Tuberculosis
TC	Treatment Centre
TDF	Tenofovir Disoproxil Fumarate
TG	Transgender
TPCT	Tri Phasic Computerised Tomography
UID	Unique Identification
ULN	Upper limit of normal
USG	Ultra Sono Graphy
VEL	Velpatasvir
WHO	World Health Organization

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SECTION 1

GUIDELINES FOR DIAGNOSIS AND MANAGEMENT OF VIRAL HEPATITIS

Introduction

Viral hepatitis is recognized as a public health problem globally. Various etiological agents (Hepatitis A, B, C, D and E viruses) have been implicated that can lead to acute, chronic or sequel of chronic infection. While hepatitis A and E are often the cause for sporadic or outbreaks of hepatitis, hepatitis B and C can either clear spontaneously or can lead to chronic infection and there after sequelae like cirrhosis and hepatocellular carcinoma (HCC).

Viral hepatitis is increasingly being recognized as a public health problem in India.

Hepatitis A Virus (HAV) and Hepatitis E Virus (HEV) are important causes of acute viral hepatitis and acute liver failure (ALF). Due to paucity of data, the exact burden of disease for the country is not established. However, available literature indicates a wide range and suggests that HAV is responsible for 10-30% of acute hepatitis and 5-15% of acute liver failure cases in India. It is further reported that HEV 10-40% of acute hepatitis and 15-45% of acute liver failure.

Hepatitis B surface antigen (HBsAg) positivity in the general population ranges from 1.1% to 12.2%, with an average prevalence of 3-4%. Anti-Hepatitis C virus (HCV) antibody prevalence in the general population is estimated to be between 0.09-15%. It is estimated that there are 40 million people chronically infected with Hepatitis B Virus (HBV) and based on some regional level studies, it is estimated that there are 6-12 million people with Hepatitis C in India. Chronic HBV infection accounts for 40-50% of HCC and 20-30% cases of cirrhosis in India. Chronic HCV infection accounts for 12-32% of hepatocellular carcinoma (HCC) and 12-20% of cirrhosis.

Population based syndromic and health facility based surveillance of viral hepatitis is mandated under the Integrated Disease Surveillance Program (IDSP).

Recently, a meta-analysis of studies on hepatitis C prevalence was undertaken by SGPGI, Lucknow. The study documented the pooled prevalence of Hepatitis C amongst various sub populations.

This meta-analysis concluded that based on the above studies, it can be estimated that India (current population = ~1.3 billion) has 5.2 to 13 million anti-HCV positive persons. The data on HCV viremia rates among anti-HCV antibody positive persons were not available. Hence it is difficult to arrive at a conclusion on this. However, using data from elsewhere that 60%-70% of anti-HCV persons have HCV viremia, it can be estimated that India as ~3 million to ~9 million persons with active HCV infection.

Estimating the problem statement

There are a few estimates that are available from global publications. However, it is assumed that these estimates are likely to change, as data sets and evidence increase across India.

Table 1: WHO Global Disease estimates 2016 viral hepatitis could be contributing to nearly 2.85% of all deaths in India:

Hepatitis		Numbers in thousands	Total (in thousands)
a.	Acute hepatitis A	5.0	78.7
b.	Acute hepatitis B	43.3	
c.	Acute hepatitis C	1.1	
d.	Acute hepatitis E	29.2	
Liver cancer		Numbers in thousands	Total (in thousands)
a.	Liver cancer secondary to hepatitis B	15.3	20.1
b.	Liver cancer secondary to hepatitis C	4.9	
Cirrhosis of the liver		Numbers in thousands	Total (in thousands)
a.	Cirrhosis due to hepatitis B	141.8	173.6
b.	Cirrhosis due to hepatitis C	31.9	

Estimated Total Deaths (All causes)		9559.1
% of deaths attributed to viral hepatitis		2.85%

Similarly, the Global Burden of diseases in 2016, suggests that the mortality attributable to viral hepatitis in India could be 1.18% of all deaths. The National Health Profile 2016 identified viral hepatitis to contribute to 3% of all deaths related to communicable diseases in India in 2015.

Acute viral hepatitis is a systemic infection affecting the liver predominantly. Almost all cases of acute viral hepatitis are caused by one of five viral agents: HAV, HBV, HCV, the HBV-associated delta agent or hepatitis D virus (HDV) and HEV. All these human hepatitis viruses are RNA viruses, except for hepatitis B, which is a DNA virus but replicates like a retrovirus. Although these agents can be distinguished by their molecular and antigenic properties, all types of viral hepatitis produce clinically similar illnesses. These range from asymptomatic and inapparent to fulminant and fatal acute infections common to all types, on the one hand, and from subclinical persistent infections to rapidly progressive chronic liver disease with cirrhosis and even hepatocellular carcinoma, common to the blood borne types (HBV, HCV, and HDV), on the other.

Hepatitis A Infection

HAV is a non-enveloped RNA virus belonging to the picornavirus family, with 4 genotypes belonging to one serotype.

This agent is transmitted almost exclusively by the fecal-oral route. It is an outbreak prone disease with an incubation period of around 4 weeks. Person to person spread of HAV is enhanced by poor personal hygiene and overcrowding. Excretion in the stool occurs for only 7-14 days after the onset of the clinical illness and is diagnostic of an acute HAV infection. No carrier state has been identified. Inactivated attenuated vaccine, which is safe, immunogenic and effective, is available.

Clinical presentation

The incubation period for HAV ranges from 15-45 days. The prodromal symptoms of acute viral hepatitis are systemic and quite variable. Constitutional symptoms of low grade fever, anorexia, nausea and vomiting,

fatigue, malaise, arthralgias, myalgias, headache, photophobia, pharyngitis, cough and coryza may precede onset of jaundice by 1-2 weeks.

Dark urine and clay colored stools may be noticed by the patient from 1-5 days before the onset of clinical jaundice. With the onset of clinical jaundice, the constitutional prodromal symptoms usually diminish. The liver becomes enlarged and tender and may be associated with right upper quadrant pain and discomfort.

During recovery phase the constitutional symptoms disappear, but usually some liver enlargement and abnormalities in liver biochemical tests are still evident.

Laboratory Diagnosis

HAV has an incubation period of ~4 weeks. Its replication is limited to the liver, but the virus is present in liver, bile, stools and blood during late incubation period and acute pre-icteric / pre-symptomatic phase of illness.

In acute hepatitis with clinical jaundice, the serum bilirubin levels are above 2.5mg/dL and serum alanine aminotransferase (ALT) is more than 10 times the upper limit of normal.

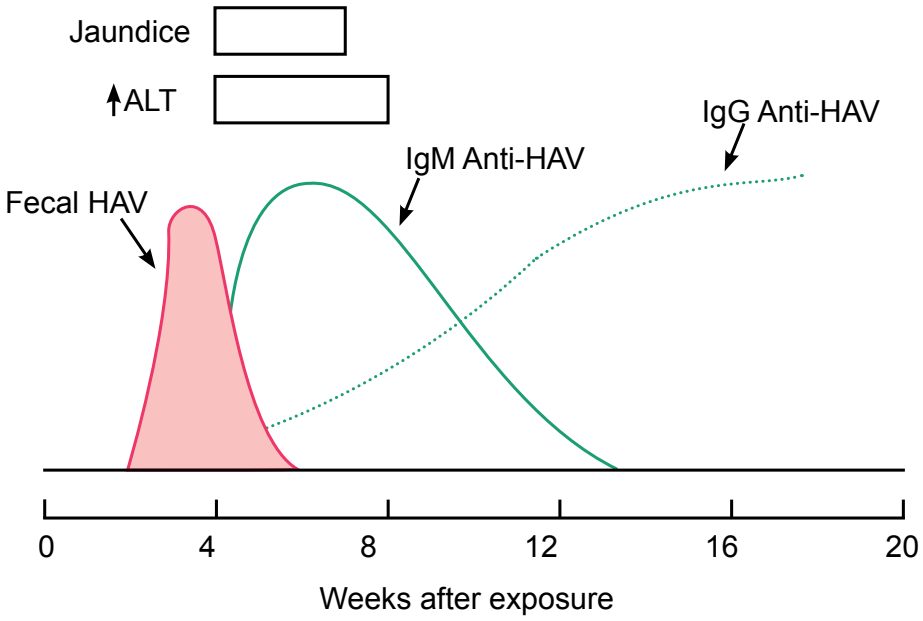


Fig.1: Laboratory Markers of HAV Infection

Source: Faud AS, Kasper DL, Braunveld E, Hauser SL, Longo DL, Jameson JL, Loscalzo J, Harrison's Principles of Internal medicine, 19th Edition: http://www.accessmedicine.com

Detection of anti- HAV antibody in serum/plasma is important in diagnosis of infection, as HAV is present in blood transiently during the incubation period.

IgM antibodies against HAV are generally detectable 5-10 days before onset of symptoms and can persist for up to 6 months. Anti-HAV IgM antibodies indicate **acute infection.**

IgG antibodies against HAV becomes the predominant antibody during convalescence and remains detectable indefinitely. Anti-HAV total antibodies (IgG and IgM) or specific IgG (but anti-HAV IgM negative) indicate immunity to hepatitis A either because of **past infection or vaccination.**

The serum aminotransferases, aspartate aminotransferase (AST) and ALT increase to a variable degree during prodromal phase of illness and precede the rise in bilirubin levels.

Yellowish discoloration of sclera (jaundice) and skin is usually visible when serum bilirubin value is >2.5 mg/dL.

Management

There is no role for antiviral drugs in therapy for HAV infection. Virtually all previously healthy patients with hepatitis A recover completely with no clinical sequelae. The case fatality is very-very low (~0.1%) but is increased in advanced age and in the presence of underlying debilitating diseases.

Infection in the community is best prevented by improving social conditions especially overcrowding and poor sanitation.

Hepatitis B Infection

HBV, a double-stranded DNA virus, belongs to the family of hepadnaviruses. HBV infection is a global public health problem. Perinatal transmission and occasionally horizontal transmission early in life are most common in high prevalence areas. Sexual contact and percutaneous transmission also contribute to the transmission of HBV.

Clinical Presentation

The spectrum of clinical manifestations of HBV infection varies in both acute and chronic disease. During the acute phase, manifestations range from subclinical or anicteric hepatitis to icteric hepatitis and, in some cases, fulminant hepatitis. The incubation period for HBV varies from 30-180 days. In chronic phase, manifestations range from an asymptomatic carrier state to chronic hepatitis, cirrhosis, and HCC. Extra-hepatic manifestations can also occur with both acute and chronic infection.

Acute Hepatitis:

Approximately 70 percent of patients with acute HBV infection have subclinical or anicteric hepatitis, while 30 percent develop icteric hepatitis. The disease may be more severe in patients co-infected with other hepatitis viruses or with underlying liver disease.

Fulminant hepatitis B is unusual, occurring in approximately 0.1 to 0.5 percent of patients; it is believed to be due to massive immune-mediated lysis of infected hepatocytes. A serum sickness-like syndrome may develop during the prodromal period, followed by constitutional symptoms, anorexia, nausea, jaundice, and right upper quadrant discomfort. The symptoms and jaundice generally disappear after one to three months, but some patients have prolonged fatigue even after normalization of serum aminotransferase concentrations.

The complete eradication of HBV rarely occurs after recovery from acute HBV infection and that latent infection can maintain the T cell response for decades following clinical recovery, thereby keeping the virus under control.

The rate of progression from acute to chronic hepatitis B in immunocompetent persons is determined primarily by the age at infection. The rate is approximately 90 percent for a perinatally acquired infection, 20 to 50 percent for infections between the age of one and five years, and less than 5 percent for an adult-acquired infection.

Treatment for acute HBV is mainly supportive. In addition, appropriate measures should be taken to prevent infection in exposed contacts.

The decision to hospitalize patients should be taken on a case-to-case basis. Patients, who have a coagulopathy, are deeply jaundiced, or encephalopathy should generally be hospitalized. Hospitalization might also be considered in patients who are older, have significant comorbidities, cannot tolerate oral intake, or have poor social support systems.

In acute cases, the patients who have fulminant hepatitis or hepatitis B with underlying cirrhosis should be considered for antiviral treatment.

Chronic Hepatitis:

A history of acute hepatitis is elicited in only a small percentage of patients with chronic HBV infection. In low or intermediate prevalence areas, approximately 30 to 50 percent of patients with chronic HBV infection have a past history of acute hepatitis; such a history is lacking in the remaining patients in these areas and in the majority of patients in high prevalence areas (predominantly perinatal infection).

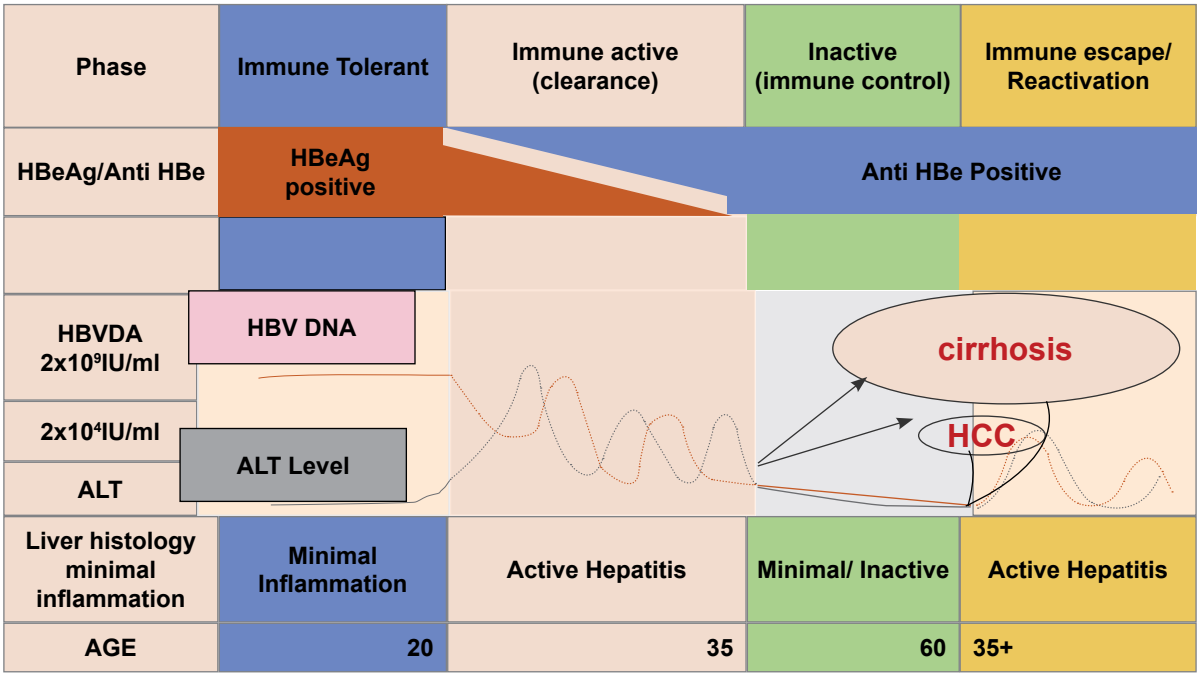
Many patients with chronic HBV are asymptomatic (unless they have decompensated cirrhosis or have extrahepatic manifestations), while others have nonspecific symptoms such as fatigue. Some patients experience exacerbations of the infection which may be asymptomatic, mimic acute hepatitis, or manifest as hepatic failure.

Physical examination may be normal, or there may be stigmata of chronic liver disease. Jaundice, splenomegaly, ascites, peripheral edema, upper gastrointestinal bleed and encephalopathy may be present in patients with decompensated cirrhosis. Laboratory tests may be normal, but most patients have a mild to moderate elevation in serum AST and ALT. During exacerbations, the serum ALT concentration may be as high as 50 times the upper limit of normal, and alfa-fetoprotein (AFP) concentrations as high as 1000 ng/mL may be seen. A progression to cirrhosis is suspected when there is evidence of hypersplenism (decreased hemoglobin, white blood cell and/ or platelet counts) or impaired hepatic synthetic function (hypoalbuminemia and/or prolonged prothrombin time/ international normalized ratio (INR).

Extrahepatic manifestations — Extrahepatic manifestations, which are thought to be mediated by circulating immune complexes, occur in 10 to 20 percent of patients with chronic HBV infection. As mentioned above, acute hepatitis may be heralded by a serum sickness-like syndrome manifested as fever, skin rashes, arthralgia, and arthritis, which usually subsides with the onset of jaundice. The two major extrahepatic complications of chronic HBV are polyarteritis nodosa and glomerular disease.

Natural Course and Phases of Chronic Hepatitis B Infection

The natural course of chronic HBV infection is determined by the interplay between virus replication and the host immune response. Other factors that may play a role in the progression of HBV-related liver disease include gender, alcohol consumption, and concomitant infection with other hepatitis virus(es). The outcome of chronic HBV infection depends upon the severity of liver disease at the time HBV replication is arrested.



This phase seen in HBV transmission at birth/1-2 years of life. HBeAg +ve and high viral load (10^7 IU/mL) but no elevation of transaminases and minimal activity in liver as there is no immunological response.	With increased immune response HBV DNA level decreases. Liver enzymes fluctuate. Active inflammation in liver ending in HBeAg negative and HBeAb +ve (HBeAg seroconversion) Ongoing activity could progress to fibrosis and liver cirrhosis with HCC.	HBeAg remains negative in 70-85% with low viral load <2 x 10^3 IU/mL with persistently normal liver enzymes but hepatitis activity may continue in some Fibrosis/ cirrhosis noted in those who had progressed in immune active phase	Progression from HBeAg negative inactive phase to HBeAg negative hepatitis B with mutation in core or core promoter region of HBV genome resulting in HBeAg negative but with continued HBV replication and progression in liver disease.

Fig.2: Natural History of Chronic HBV Infection

Modified from: Hepatitis B Virus Infection, Yun-Fan Liaw, Chia-Ming Chu, Lancet 2009; 373 : 582-92

Replicative phase: Immune tolerance — In patients with a perinatally acquired HBV infection, the initial phase is characterized by high levels of HBV replication—the presence of hepatitis B e antigen (HBeAg) and high levels of HBV DNA in serum—but no evidence of active liver disease as manifested by lack of symptoms, normal serum ALT concentrations, and minimal changes on liver biopsy.

The immune tolerance phase usually lasts 10 to 30 years, during which there is a very low rate of spontaneous HBeAg clearance.

Replicative phase: Immune clearance — The transition from the immune tolerance to the immune clearance phase occurs during the second and third decades in patients with perinatally acquired HBV infection. During the immune clearance phase, spontaneous HBeAg clearance increases to an annual rate of 10 to 20 percent.

HBeAg seroconversion is frequently, but not always, accompanied by biochemical exacerbations (abrupt increases in serum ALT). Exacerbations are believed to be due to a sudden increase in immune-mediated lysis of infected hepatocytes. They are often preceded by an increase in serum HBV DNA and a shift of HBcAg (hepatitis B core antigen) from nuclear to cytoplasmic sites within hepatocytes, suggesting that immune clearance may be triggered by an increase in viral load or a change in the presentation of viral antigens. How these changes occur is not known.

Most exacerbations are asymptomatic and are discovered during routine follow-up. However, some are accompanied by symptoms of acute hepatitis and may lead to the incorrect diagnosis of acute hepatitis B in patients who are not previously known to have chronic HBV infection. Exacerbations may be associated with an elevation in the IgM anti-HBc titer, which may lead to misdiagnosis of acute HBV infection and an increase in the serum alpha-fetoprotein concentration, which may raise concerns about the diagnosis of HCC.

Patients with severe exacerbations should be referred to specialized centers for liver transplantation and receive treatment with nucleos(t)ide analogues (NAs).

Not all exacerbations lead to HBeAg sero-conversion and clearance of HBV DNA from the serum, a phenomenon termed abortive immune clearance. These patients may develop recurrent exacerbations with an intermittent disappearance of serum HBV DNA with or without a transient loss of HBeAg. Such repeated episodes of hepatitis may increase the risk of developing cirrhosis and HCC.

Low or non-replication phase/inactive carrier state — Patients in the low or non-replicating phase/inactive carrier state are HBeAg negative and anti-HBe positive. In some patients, HBV DNA is undetectable in serum by polymerase chain reaction assays, and liver disease is in remission as evidenced by normal serum ALT concentrations and the resolution of necro-inflammation in liver biopsies. HBeAg-negative patients with a persistently normal serum ALT can still have significant histologic inflammation and/or fibrosis.

Because of the fluctuating nature of chronic HBV infection, patients should not be categorized as inactive carriers unless there are at least three ALT levels and two to three HBV DNA levels over a 12-month period of observation. Studies suggest that combined quantification of HBsAg level and HBV DNA at a single time point may help in differentiating inactive carrier phase versus HBeAg-negative chronic hepatitis. HBsAg <1000 international units/mL in an HBeAg-negative patient with serum HBV DNA <2000 international units/mL identifies the inactive carrier phase with a high diagnostic accuracy (94 percent).

HBeAg-negative chronic hepatitis — Some patients continue to have moderate levels of HBV replication and active liver disease (elevated serum ALT and chronic inflammation on liver biopsies), but remain HBeAg negative. Such patients are said to have HBeAg-negative chronic hepatitis. They have a residual wild-type virus or HBV variants that cannot produce HBeAg due to precore or core promoter genetic variations.

Patients with HBeAg-negative chronic hepatitis are older and have more advanced liver disease. They also tend to have fluctuations in HBV DNA and ALT levels.

Resolution of chronic HBV infection — Some patients with chronic HBV infection become HBsAg negative. The annual rate of delayed clearance of HBsAg has been estimated to be 0.5 to 2 percent in Western patients and much lower (0.1 to 0.8 percent) in Asian countries In most reports, patients who cleared HBsAg appeared to have a good prognosis. In the absence of other causes of liver injury, progression to cirrhosis and hepatic decompensation after HBsAg clearance is rare. However, the risk of hepatocellular carcinoma remains, and surveillance should continue in those who have HCV or hepatitis D virus (HDV) co-infection, cirrhosis, or are older than 50 years at the time of HBsAg clearance.

Laboratory Diagnosis

Laboratory testing during the acute phase reveals elevations in the concentration of alanine and aspartate aminotransferase levels (ALT and AST); values up to 1000 to 2000 international units/L are typically seen during the acute phase with ALT being higher than AST. The serum bilirubin concentration may be normal in patients with anicteric hepatitis. The prothrombin time is the best indicator of prognosis. In patients who recover, the normalization of serum aminotransferases usually occurs within one to four months. A persistent elevation of serum ALT for more than six months indicates a progression to chronic hepatitis.

Assessment and Staging of HBV Chronic infection

Routine assessment of HBsAg-positive persons is needed to guide management and indicate the need for treatment. This generally includes assessment of:

1. Serological markers of HBV infection ;
2. Measurement of HBV DNA levels; and
3. Assessing severity of liver disease by

    a. Liver enzymes

    b. Non-invasive tests (NITs) such as aspartate aminotransferase (AST)-to-platelet ratio index (APRI), FIB-4, transient elastography (FibroScan).

    c. Liver biopsy, if available

Serological markers of HBV infection

Chronic Hepatitis B (CHB) infection is defined as the persistence of HBsAg for more than 6 months. Previous HBV infection is characterized by the presence of antibodies (anti-HBs and anti-HBc). Immunity to HBV infection after vaccination is characterized by the presence of only anti-HBs.

HBeAg: It also needs to be established whether the person is in the HBeAg-positive or HBeAg-negative phase of infection (please see the table above), though both require lifelong monitoring, as the condition may change over time. In persons with CHB, a positive HBeAg result usually indicates the presence of active HBV replication and high infectivity. Spontaneous improvement may occur following HBeAg-positive sero-conversion (anti-HBe), with a decline in HBV replication, and normalization of ALT levels. This confers a good prognosis and does not require treatment. HBeAg can also be used to monitor treatment response, as HBeAg (anti-HBe) sero-conversion in HBeAg-positive persons with a sustained undetectable HBV DNA viral load may be considered a potential stopping point of treatment. However, this is infrequent even with potent NAs therapy. Some HBeAg-negative persons have active HBV replication but are positive for anti-HBe and do not produce HBeAg due to the presence of HBV variants or pre-core mutants.

Measurement of HBV DNA levels

Plasma HBV DNA concentrations quantified by real-time polymerase chain reaction (PCR) correlate with disease progression and are used to differentiate active HBeAg-negative disease from inactive chronic infection, and for decisions to treat and subsequent monitoring. HBV DNA concentrations are also used for optimal monitoring of response to antiviral therapy, and a rise may indicate the emergence of resistant variants.

Plasma HBV DNA levels should be expressed in IU/mL to ensure comparability; values given as copies/mL can be converted to IU/mL by dividing by a factor of 5 to approximate the conversion used in the most commonly used assays (i.e. 10,000 copies/mL = 2000 IU/mL; 100,000 copies/mL = 20,000 IU/mL; 1 million copies/mL = 200,000 IU/mL). The same assay should be used in the same patient to evaluate the efficacy of antiviral therapy.

Assessing severity of liver disease

A full assessment should include

- Clinical evaluation for features of cirrhosis and evidence of decompensation, and
- Measurement of serum bilirubin, albumin, ALT, AST, alkaline phosphatase (ALP), and prothrombin time; as well as full blood count, including platelet count.
- Other routine investigations include ultrasonography and alpha-fetoprotein (AFP) measurement for periodic surveillance for HCC, and endoscopy for varices in persons with cirrhosis.

Please refer to Annexure 1 for details on assessing severity of liver disease (fibrosis and cirrhosis)

Please refer to Annexure 2 for the algorithm for laboratory diagnosis of Viral hepatitis

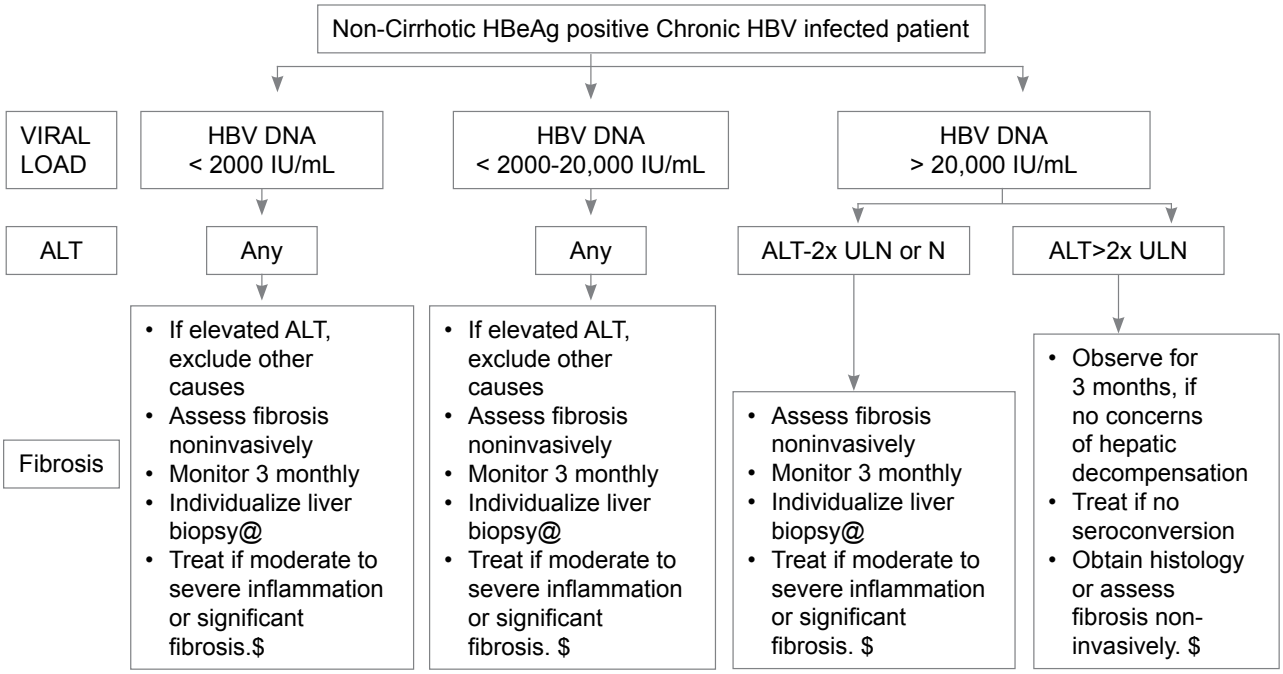
Management

Whom To Treat

It is critical to evaluate the patient carefully as treatment of hepatitis B is life-long in most cases. The clinical spectrum and phases of the chronic hepatitis B pose difficulty in deciding on whom to treat.

Table 2: Whom to treat and whom to monitor

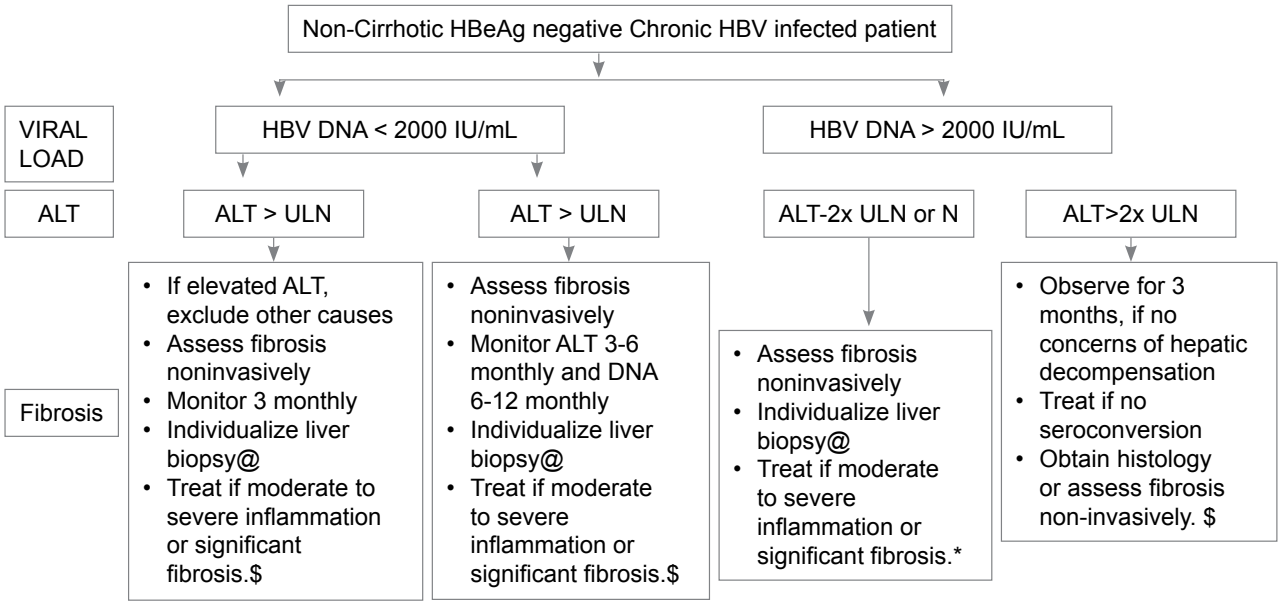
WHOM TO TREAT	WHOM NOT TO TREAT
As a priority, all adults, adolescents and children with CHB and evidence of compensated or decompensated cirrhosis should be treated, regardless of ALT levels, HBeAg status or HBV DNA levels	Antiviral therapy is not recommended and can be deferred in persons without evidence of cirrhosis, and with persistently normal ALT levels and low levels of HBV replication (HBV DNA <2000 IU/mL), regardless of HBeAg status or age. • Where HBV DNA testing is not available: Treatment can be deferred in HBeAg-positive persons aged 30 years or less and persistently normal ALT levels.
Treatment is recommended for adults with CHB who do not have evidence of cirrhosis, but are aged more than 30 years (in particular), and have persistently abnormal ALT levels and evidence of high-level HBV replication (HBV DNA >20 000 IU/mL), regardless of HBeAg status.	Continued monitoring is necessary in all persons with CHB, but in particular those who do not currently meet the recommended criteria for whom to treat or not treat, to determine if antiviral therapy may be indicated in the future to prevent progressive liver disease. These include persons without cirrhosis aged 30 years or less, with HBV DNA levels >20 000 IU/mL but persistently normal ALT;



@Biopsy if non-invasive tests suggest evidence of significant fibrosis, ALT persistently elevated, Age>35 yr or family h/o HCC or cirrhosis.$

- Moderate to severe inflammation on liver biopsy means either Hepatic activity index by Ishak activity score >3/18 or METAVIR activity score A2 or A3
- Significant fibrosis on liver biopsy means F >2 by METAVIR fibrosis score or Ishak fibrosis stage > 3
- Liver stiffness > 8 kPa (by Fibroscan) or APRI > 1.5 indicates significant fibrosis; Liver stiffness > 11 kPa (by Fibroscan) or APRI > 2.0 indicates cirrhosis

Fig.3: Treatment indications for non-cirrhotic HBeAg positive chronic HBV infected patients



@Biopsy if non-invasive tests suggest evidence of significant fibrosis, ALT persistently elevated, Age>35 yr or family h/o HCC or cirrhosis.$

- Moderate to severe inflammation on liver biopsy means either Hepatic activity index by Ishak activity score >3/18 or METAVIR activity score A2 or A3
- Significant fibrosis on liver biopsy means F >2 by METAVIR fibrosis score or Ishak fibrosis stage > 3
- Liver stiffness > 8 kPa (by Fibroscan) or APRI > 1.5 indicates significant fibrosis; Liver stiffness > 11 kPa (by Fibroscan) or APRI > 2.0 indicates cirrhosis

Fig.4 :Treatment indications for non-cirrhotic HBeAg-negative chronic HBV-infected patients

Reference: SK Sarin et al, Asian-Pacific clinical practice guidelines on the management of Hepatitis B: A 2015 update; Hepatol Int (2016) 10:1-98

There are various antiviral agents recommended for treatment of CHB. The section below deals with these drugs and their dosages in adults and children.

Table 3: Recommended drugs for the treatment of CHB and their doses in adults

	Drug	Dose
1	Tenofovir disoproxil fumarate (TDF)	300 mg once daily
2	Entecavir (adult with compensated liver disease and lamivudine naive)	0.5 mg once daily
3	Entecavir (adult with decompensated liver disease)	1 mg once daily
4	Tenofovir alafenamide fumarate (TAF)	25 mg once daily

Table 4: Recommended drugs for the treatment of CHB and their doses in children

Drug	Dose	
Tenofovir (in children 12 years of age and older, and weighing at least 35kg)	300 mg once daily	
Entecavir (in children 2 years of age or older and weighing at least 10kg. the oral solution should be given to children with a body weight up to 30kg)	**Recommended once-daily dose of oral solution (mL)**	
	Body weight (kg)	Treatment –naïve persons*
	10 to 11	3
	>11 to 14	4
	>14 to 17	5
	>17 to 20	6
	>20 to 23	7
	>23 to 26	8
	>26 to 30	9
	>30	10

*Children with body weight more than 30 kg should receive 10mL (0.5mg) of oral solution or one 0.5 mg tablet once daily

Selection of antiviral drug for CHB:

- In all adults, adolescents and children aged 12 years or older in whom antiviral therapy is indicated, the NAs which have a high barrier to drug resistance (tenofovir or entecavir) are recommended.
- In woman of childbearing age Tenofovir may be preferred as the drug of choice in the eventuality of a pregnancy. Entecavir is not recommended in pregnancy.
- Tenofovir is preferred in patients who have been exposed to lamivudine who have a potential for Entecavir resistance.
- Entecavir is recommended in children aged 2–11 years.
- Entecavir may be preferred over Tenofovir in:

Age > 60 years; bone disease due to chronic steroid use or use of other medications that worsen bone density, history of fragility fracture, osteoporosis; altered renal function with eGFR < 60 mL/min/1.73 m2 or albuminuria > 30 mg/ 24 hr or moderate dipstick proteinuria or Low phosphate (<2.5 mg/dL) or in patient on hemodialysis (Ref: EASL guidelines)

- Tenofovir alafenamide fumarate (TAF) is the drug of choice in patients with reduced renal function or bone disease bone toxicities, where entecavir is contraindicated
- Drugs with a low barrier to resistance (lamivudine, adefovir or telbivudine) are available but not recommended as they lead to drug resistance.
- Despite the inconvenience of injections and side effects PegIFN may be considered in a sub group of non cirrhotics where a finite therapy might achieve a sustained response.

Key points in counseling and preparing the patient prior to initiation of therapy

Preparing to start treatment: Patients should be counseled about the indications for treatment, including the likely benefits and side-effects, willingness to commit to long-term treatment, and need to attend for follow-up monitoring both on and off therapy; the importance of full adherence for treatment to be both effective and reduce the risk of drug resistance; and cost implications.

Measurement of baseline renal function and assessment of baseline risk for renal dysfunction should be considered in all persons prior to initiation of antiviral therapy

When To Stop Treatment

All persons with cirrhosis based on clinical evidence (or APRI score >2 in adults) require lifelong treatment with NAs, and should not discontinue antiviral therapy because of the risk of reactivation, which can also cause severe acute-on-chronic liver injury.

The discontinuation of treatment of Hepatitis B is usually not recommended and should be done at specialized centers under the guidance of the necessary expertise

Decision to discontinue therapy requires careful consideration on the risk of virological relapse, decompensation and death on discontinuation versus the financial implication of continued cost of medications and monitoring.

All patients with cirrhosis should not discontinue antiviral therapy because of the risk of reactivation which may potentially lead to decompensation and death.

Discontinuation may be considered in patients without cirrhosis:

- With persistent HBsAg loss after one year of consolidation treatment (regardless of prior HBeAg status or availability of HBV DNA levels)
- HBeAg loss and sero-conversion to Anti-HBe after completion of one year (preferably 3 years) of additional treatment with persistently normal ALT levels and undetectable HBVDNA levels.
- Careful long term monitoring for reactivation with serial 3-6 monthly HBeAg, ALT and HBVDNA levels is mandatory in those who have discontinued treatment for consideration of retreatment.

Relapse may occur after stopping therapy with NAs. Retreatment is recommended if there are consistent signs of reactivation (HBsAg or HBeAg becomes positive, ALT levels increase, or HBV DNA becomes detectable again)

Monitoring

The disease is complex and has sequelae, resolution as well as drugs side effects. Hence, three types of monitoring is necessitated

- Monitoring for disease progression and treatment response in persons with CHB prior to, during and post-treatment
- Monitoring for tenofovir or entecavir side-effects
- Monitoring for hepatocellular carcinoma

Table 5: Monitoring : Parameters and frequency

Interval (Months)	3 Months			6 Months			9 Months			12 Months		
HBeAg/Anti HBe		√	√	√	√	√	√	√	√	√	√	√
HBVDNA		√	√	√	√	√	√	√	√	√	√	√
ALT	√	√	√	√	√	√	√	√	√	√	√	√
AST										√		√
CBC (Platelet)										√	√	√
APRI/FIB4/ Fibro Scan										√	√	√
USG				√						√	√	√
Serum Creatinine											√	
eGFR											√	
Phosphate											√	
Urine Protein: Creatinine Ratio											√	

	Not on Treatment
	Treatment
	Discontinue Treatment

Monitoring for those:

Not on Treatment:

Frequent monitoring with monthly ALT and 3 monthly HBeAg/Anti HBeAg and HBVDNA quantitative would be required in those with fluctuating ALT and HBV DNA 2000-20,000 IU/mL, who are as yet not on treatment.

In active chronic B with persistently normal ALT and HBV DNA <20,000IU/mL, may be monitored annually

On Treatment:

More frequent 3-6 monthly assessment is required initially in those with advanced liver disease in the first year.

Discontinued Treatment:

Careful long term monitoring for reactivation with serial 3-6 monthly HBeAg, ALT and HBVDNA levels is mandatory in those who have discontinued treatment for consideration of retreatment.

Monitoring for disease progression and treatment response in persons with CHB prior to, during and post-treatment

It is recommended that the following be monitored at least annually:

--ALT levels (and AST for APRI), HBsAg, HBeAg, and HBV DNA levels (where HBV DNA testing is available)

--Non-invasive tests (APRI score, FIB-4 or FibroScan) to assess for the worsening of fibrosis/presence of cirrhosis, in those without cirrhosis at baseline

--If on treatment, adherence should be monitored regularly and at each visit.

More frequent monitoring is needed

- In persons who do not yet meet the criteria for antiviral therapy: More frequent monitoring for disease progression may be indicated in: persons who have intermittently abnormal ALT levels or HBV DNA levels that fluctuate between 2000 IU/mL and 20 000 IU/mL (where HBV DNA testing is available) and in HIV co-infected persons.
- In persons on treatment or following treatment discontinuation: More frequent on-treatment monitoring (at least every 3 months for the first year) is indicated in: persons with more advanced disease (compensated or decompensated cirrhosis); during the first year of treatment to assess treatment response and adherence; where treatment adherence is a concern; in HIV co-infected persons and in persons after discontinuation of treatment.

Monitoring for tenofovir and entecavir toxicity

Measurement of baseline renal function and assessment of baseline risk for renal dysfunction should be considered in all persons prior to initiation of antiviral therapy. Renal function should be monitored annually in persons on long-term tenofovir or entecavir therapy, and growth monitored carefully in children.

Measurement of baseline renal function includes: serum creatinine (Cr) levels, and calculation of creatinine clearance (CrCl)/estimated glomerular filtration rate (eGFR) using the Cockcroft–Gault (CG)

CG formula: eGFR = (140 – age) x (weight in kg) x 0.85 (if female) / (72xCr in mg/dL)

Table 6: Recommended dosage of Tenofovir in adults with renal impairment

CrCl (mL/min)	Dose
30-49	300 mg every 48h
10-29	300 mg twice weekly (every 72-96 hours)
<10 and not on Haemodialysis	No recommendation
On Haemodialysis	300 mg every7d

Monitoring for hepatocellular carcinoma (HCC)

Routine surveillance for HCC with abdominal ultrasound and alpha-fetoprotein testing every six months is recommended for:

- Persons with cirrhosis, regardless of age or other risk factors
- Persons with a family history of HCC
- Persons aged over 40 years (lower age may apply according to regional incidence of HCC), without clinical evidence of cirrhosis (or based on APRI score ≤2), and with HBV DNA level >2000 IU/mL (where HBV DNA testing is available).

Special Situations

Pregnancy

Care of the pregnant woman

All pregnant women with HBV should be evaluated for the need of treatment for hepatitis B and any associated liver disease, and given advice about prevention of transmission. Only a proportion of those with hepatitis B virus infection (pregnant or otherwise) need treatment.

Hepatitis B in a pregnant woman is not a reason for considering termination of pregnancy. Similarly, the need for caesarean delivery should be decided based on obstetric indications, and not on the presence of HBV infection.

Administration of hepatitis B vaccine to pregnant women with HBV provides no benefit either to the mother or the baby.

Care of the baby

Immunoprophylaxis of hepatitis B virus infection

The newborn baby should be administered a timely first dose (the 'birth dose') of hepatitis B vaccine (monovalent) as soon as possible after birth, ideally within 24 hours. Even within this time duration, the earlier it can be administered, the better. If, for some reason, the birth dose is not administered within 24 hours, it should still be administered as soon as it is possible and not omitted. This dose is administered intramuscularly in the anterolateral thigh. This birth dose must be followed by timely administration of 3-doses of hepatitis B-containing vaccine [e.g. monovalent hepatitis B vaccine, tetravalent combination vaccine with DPT (DPT-Hep B) or a pentavalent vaccine (DPT+Hep B+Hib)]. The hepatitis B vaccine birth dose followed by these three doses is the most effective method for prevention of mother-to-child transmission of hepatitis B.

Hepatitis B immunoglobulin (HBIG) may provide some additional protection in situations where risk of transmission is particularly high – i.e. babies born to mothers with hepatitis B who also have detectable detectable HBeAg and/or high viral load. However, additional benefit provided by it, over properly-administered hepatitis B vaccine (as described above) is small. Also, HBIG is costly and has limited availability. If a decision is taken to administer HBIG (0.5 ml or 100 international units, intramuscular), this should be done as soon after birth as possible (and within 12-24 hours) and in a limb other than the one in which hepatitis B vaccine has been administered.

Data on benefit and risks of administering anti-hepatitis B drugs to the pregnant women for prevention of mother-to-child transmission are unclear.

Breast feeding

A mother who has hepatitis B may breast feed her baby, unless there is an exuding injury or disease of the nipple or surrounding skin. The advantages of breast feeding far outweigh the risk, if any, of transmission of hepatitis B to a baby who has received hepatitis B vaccine.

Timing of testing

If it is felt that the baby needs to be tested for hepatitis B, this should be done only after 1 year of age. Any positivity before this age is difficult to interpret and may resolve spontaneously over time.

Co-morbidities

HIV and Hepatitis B Co-infection

The natural history of both diseases is affected when a person is co-infected with both HIV and Hep B and this has implications on management of both diseases. Current evidence suggests that human immunodeficiency virus (HIV) infection has an adverse impact on HBV-related liver disease progression, with higher serum HBV DNA polymerase activity, lower rates of loss of serum hepatitis B e antigen, and increased risk of cirrhosis, liver-related mortality, and hepatocellular carcinoma at lower CD4 T-cell counts. HBV infection is more likely to be chronic in those with HIV infection. In some cohorts, liver disease has emerged as a leading cause of death in HIV-infected persons co-infected with either hepatitis B or C, as mortality due to other HIV-related conditions has declined following the introduction of antiretroviral therapy (ART).

Similarly, the HBV infection also negatively impacts the progression of HIV infection leading to faster immune deterioration and higher mortality. Other studies have suggested that HBV is associated with a rapidly progressive course of HIV infection . A retrospective analysis indicated that the risk of death in 64 individuals co-infected with HIV and HBV was approximately two-fold higher than that in individuals with HIV mono infection. Prospective observational cohort among those with primary HIV infection showed that HBV co-infection is an independent predictor of immunologic deterioration in such group of patients. In another large prospective multicentre cohort by Chun et al among 2352 (PLHIV) with sero-conversion window of less than 3 years, co-infected persons with Hepatitis B were associated with two times higher risk of AIDS/death, higher among HBV co-infected patients compared to HBV mono-infected patients

The HIV-Hepatitis co-infected persons show faster CD4 decline, slower CD4 recovery following ART, increased incidence of AIDS and non-AIDS events, increased rate of ARV toxicity and increased chances of Immune reconstitution hepatitis. In one of the large cohort studies of more than 5000 co-infected persons, the relative risk of liver related deaths was found to be 17 times higher than those with HBV mono-infected patients.

Other challenges among co-infected include cross-resistance between HIV and HBV drugs, increased liver injury, either due to direct hepatotoxicity or to ART-related immune-reconstitution hepatitis, with elevation of ALT; if ART does not cover both HIV and HBV infections adequately, fulminant hepatitis is an eventuality.

Evaluation of HIV and HBV Co-infected Persons

The risk of HBV infection may be higher in HIV-infected adults, and therefore all persons newly diagnosed with HIV should be screened for HBsAg. Those found positive for HBsAg should be evaluated further following the guidelines for evaluation of those with HBV Infection. Besides routing clinical evaluation, one should look for sign of cirrhosis and hepatic decompensation like ascites and pedal oedema.

The lab investigations, besides routine haemogram and biochemistry, should specifically include Liver Function Test (LFT), prothrombin time, AFP, ultrasound and upper gastrointestinal endoscopy. The virological examination should include HBeAg, Anti-HBe antibody and HBV DNA quantitative (Real-Time PCR).

Assessment of severity of fibrosis : The assessment of degree of fibrosis and cirrhosis is important. Please refer to Annexure 1 for details.

Treatment of HIV and HBV Co-infected patients

All HIV positive patients with HBV co-infection should start dual anti HIV & HBV therapy with tenofovir based ART regimen irrespective of CD4 count, HBV viral load or status of liver disease e.g., ALT level or fibrosis stage. In HBV and HIV co-infected adults and adolescents, tenofovir + lamivudine + efavirenz as a fixed-dose combination is recommended as the preferred option to initiate ART under the National AIDS Control Program. This three drug combination includes the drugs with efficacy against hepatitis B.

Stopping Tenofovir based ART should be avoided in HIV + HBV co-infection for concern of severe hepatitis flare and decompensated following HBV reactivation.

This treatment strategy has achieved high rates of HBV DNA suppression (90%), HBeAg loss (46%) and HBsAg loss (12%) in HBeAg-positive patients after 5 years of treatment, without evidence of resistance, and reduced progression to cirrhosis with no significant differences in response in those with or without HIV co-infection . To date, no viral resistance to tenofovir in vivo has been described, although resistant strains have been identified in vitro. Although the risk of developing cirrhosis is negligible in HBV-HIV-co-infected persons on long-term tenofovir combined with lamivudine therapy, the risk of HCC persists, but is low.

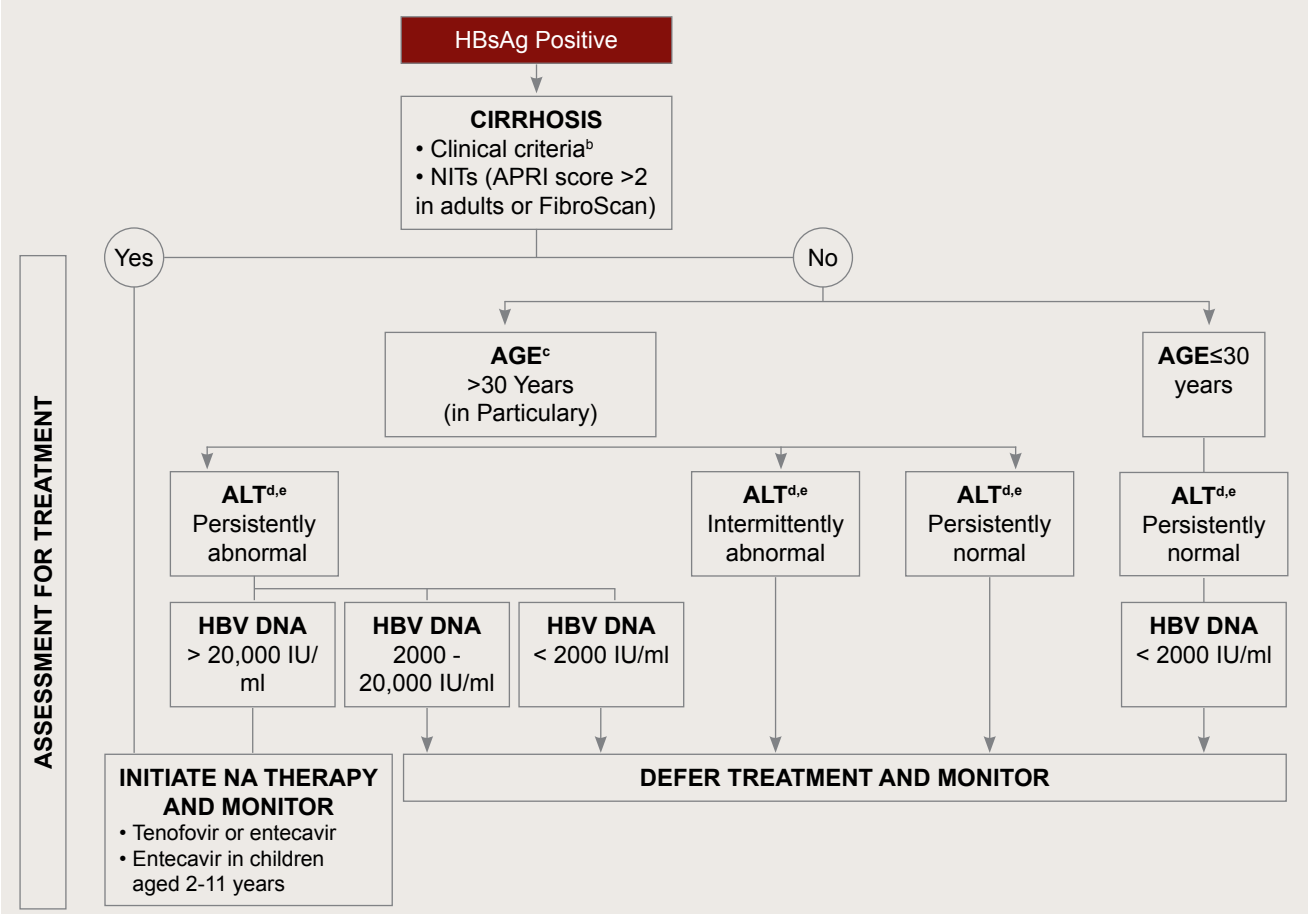
If ARVs need to be changed because of HIV drug resistance or some drug toxicity, then tenofovir and lamivudine should be continued together with the new ARV drugs unless TDF is specifically contraindicated due to its toxicity.

Prevention of HBV infection

The risk of HBV infection may be higher in HIV-infected adults, and therefore all persons newly diagnosed with HIV should be screened for HBsAg and immunized if HBsAg is negative. Those already infected with HBV (HBsAg positive) do not benefit from HBV vaccine. PLHIV who have already suffered from HBV in the past and have developed protective titre of Anti-HBs antibody (>10 mIU/mL) also do not require HBV vaccine.

Response to HBV vaccine is lower in persons with HIV or with a low CD4 count, and a meta-analysis has shown that a schedule of four double (40 µg) doses of the vaccine provides a higher protective anti-HBs titre than the regular three 20 µg dose schedule

Besides this, all infants born to HBV positive women need to be immunized within 24 hours of birth (Dose - 0) followed by 6, 10 & 14 weeks (dose – 10 µg IM) and HBIG – (0.5 ml or 100 international units, intramuscular), this should be done as soon after birth as possible (and within 12-24 hours) and in a limb other than the one in which hepatitis B vaccine has been administered.



NIT : non-invasive tests, ALT alanine aminotransferase, APRI aspartase aminotransferase-to-platelet ratio index

a Defined as persistence of hepatitis B surface antigen (HBsAg) for six months or more. The algorithm does not capture all potential scenarios, but the main categories for treatment or monitoring. Recommendations for settings without access to HBV DNA testing are provided in the relevant chapters.

b Clinical features of decompensated cirrhosis: Portal hypertension (ascites, variceal haemorrhage and hepatic encephalopathy), coagulopathy, or liver insufficiency (jaundice). Other clinical features of advanced liver disease/ cirrhosis may include: hepatomegaly, splenomegaly, pruritus, fatigue, arthralgia, palmar erythema, and oedema.

c The age cut-off of >30 years is not absolute, and some persons with CHB less than 30 years may also meet criteria for antiviral treatment.

d ALT levels fluctuate in persons with chronic hepatitis B and require longitudinal monitoring to determine the trend. Upper limits for normal ALT have been defined as below 30 U/L for men and 19 U/L for women, though local laboratory normal ranges should be applied. Persistently normal/abnormal may be defined as three ALT determinations below or above the upper limit of normal, made at unspecified intervals during a 6–12–month period or predefined intervals during 12-month period.

e Where HBV DNA testing is not available, treatment may be considered based on persistently abnormal ALT levels, but other common causes of persistently raised ALT levels such as impaired glucose tolerance, dyslipidaemia and fatty liver should be excluded.

Fig. 5: Algorithm on the management of persons with chronic hepatitis B infection[a]

Modified from WHO guidelines 2015

Hepatitis C Infection

Hepatitis C virus, which, before its identification was labeled "non-A, non-B hepatitis," is a linear, single-stranded enveloped RNA virus belonging to the flavivirus family.

Clinical Course of Hepatitis C Infection

Hepatitis C infection is usually acquired through infected syringes and needles, and transfusion of infected blood. Sexual transmission of HCV occurs infrequently in heterosexual couples. It is reported to be more common in HIV-positive persons, particularly in MSM. The risk of transmission of HCV from a mother to her child occurs in 4–8% of births to women with HCV infection, and in 10.8–25% of births to women with HIV and HCV co-infection.

HCV causes both acute and chronic hepatitis. Acute hepatitis is often clinically mild and marked by fluctuating elevations of serum aminotransferase levels; >50% likelihood of chronicity, leading to cirrhosis in >20%.

Chronic infection with HCV is usually clinically silent, and is only very rarely associated with life-threatening disease. Spontaneous clearance of acute HCV infection occurs within six months of infection in 15–45% of infected individuals in the absence of treatment. Almost all the remaining 55–85% of persons will harbor HCV for the rest of their lives (if not treated) and are considered to have chronic HCV infection.

Left untreated, chronic HCV infection can cause liver cirrhosis, liver failure and HCC. Of those with chronic HCV infection, the risk of cirrhosis of the liver is 15–30% within 20 years. The risk of HCC in persons with cirrhosis is approximately 2–4% per year.

Laboratory Diagnosis

As illustrated in figure 6, following an initial eclipse phase of 1–2 weeks when no virological or serological markers of infection may be detected, the natural course of HCV infection is characterized by the appearance of HCV RNA, then HCV core p22 Ag in the absence of an antibody response for a further 6–10 weeks. During this serological window, it has been shown that free (i.e. not complexed with antibody) HCV core antigen (HCVcAg) can be detected in a proportion of individuals. Following the development of the antibody response, HCVcAg becomes complexed with these antibodies specific for HCV.

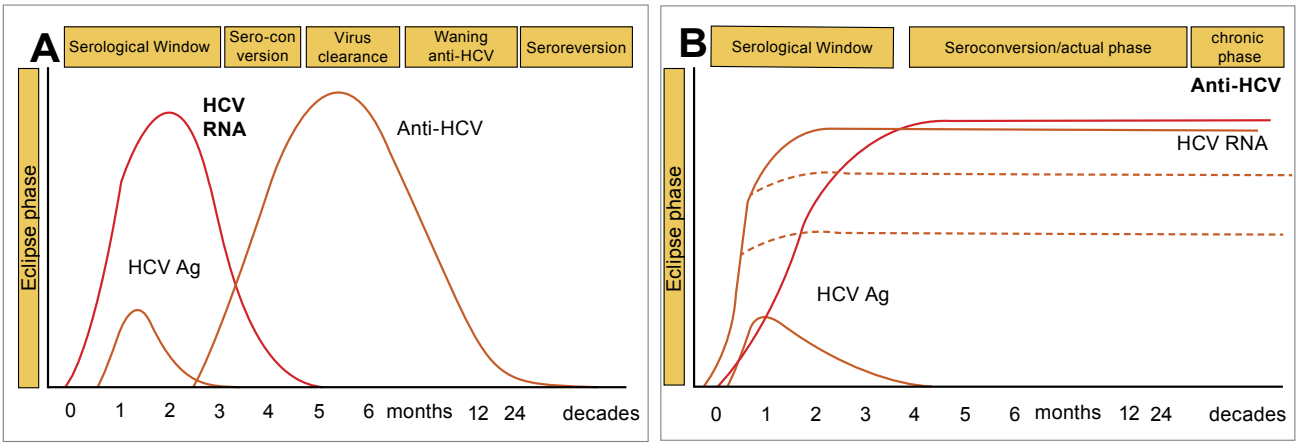


Fig.6: Approximate Time course of virological and immunological markers of HCV infection with (A) Self-resolving HCV infection, and (B) Chronic HCV infection

Ref: WHO guidelines; Feb. 2017

The standard method of diagnosis is by detection of anti-HCV antibody. Third generation immunoassays, which incorporate proteins from the core, NS3, and NS5 regions, can detect anti-HCV antibodies usually within 6 - 8 weeks of infection, i.e., from the initial phase of elevation of aminotransferases. Both rapid diagnostic tests (RDTs) and Immunoassays are available, with comparable sensitivity and specificity. This test does not differentiate between current and past infection. The test may also be false positive in some situations and the diagnosis of an individual patient should be confirmed by HCV RNA detection prior to considering treatment. Since anti-HCV antibodies from an infected mother may persist in children <18 months of age, HCV RNA detection is also used to diagnose HCV infection in this age group (after 2 months of age)

Window period. Assays designed solely to detect antibodies to HCV inevitably have a window period of infectivity in early infection, during which antibodies may be undetectable. HCV RNA is typically not used to determine exposure to HCV, in spite of its short window period (1–2 weeks after the onset of acute infection) primarily because of cost. There are some situations with occult HCV infection, i.e. HCV RNA detectable in the absence of any serological markers (i.e. HCV seronegative), which may be due to underlying immunosuppression in, for example, HIV-infected populations.

Screening for HCV infection is done using serological testing for antibodies to HCV. If positive, a Nucleic Acid Test (NAT) for HCV RNA is needed to confirm chronic HCV infection. It is important to consider the possibility of infection with other blood borne viruses in persons infected with HCV, and to offer screening for HBV and HIV in addition to HCV. Screening for other infections, for example tuberculosis (TB), is also indicated in some groups at risk, such as people living with HIV, prisoners and People who inject drugs (PWID).

The algorithm for the diagnosis of Hepatitis C infection is enclosed as **Annexure 2**

Whom To Test

Diagnostic serologic testing for HCV will be available to all people who would access the testing sites. However, the initial focus would remain on testing specific population groups that have been documented to have a higher positivity rates in different studies across India.

These focus or priority populations for testing will include but not limited to:

1. People who inject drugs (PWID)
2. Men who have sex with men
3. Female sex workers
4. People who received blood transfusion before routine testing for hepatitis C
5. People who need frequent blood transfusion, such as, thalessemic and dialysis patients
6. People living with HIV
7. Inmates of prisons and other closed settings

Treatment of Viral Hepatitis C in Adults

The spectrum of disease in persons infected with HCV extends from mild fibrosis to cirrhosis and HCC. Compensated cirrhosis may progress over time to decompensated cirrhosis associated with ascites, oesophageal and gastric varices, and eventually to liver failure, renal failure and sepsis, all of which are life-threatening. HCC may also occur at a rate of 2–4% per year in persons with cirrhosis. The diagnosis of decompensated liver disease is based on both clinical examination and laboratory monitoring, and therefore a careful medical examination of patients must be made prior to commencing therapy. The stage of disease may be assessed by liver biopsy or by using a variety of non-invasive methods.

Chronic HCV infection is the leading cause for end-stage liver disease (cirrhosis) and its complications including development of ascites, variceal bleeding, severe infections, etc, HCC and liver-related deaths worldwide. There

is substantial economic burden if HCV patients are not treated. HCV is a major cause of morbidity globally, with estimated 495,000 deaths; in India, HCV infection was estimated to be responsible for 37,000 deaths in the year 2015.

The availability of highly effective DAAs has however changed the HCV treatment paradigm, leading to hope of elimination of this infection as a public health threat by the year 2030. In a recent study, this has been demonstrated that the treatment with generic DAAs available in India will improve patient outcomes, provide a good value for money within 2 years, and be ultimately cost-saving. Therefore, HCV treatment should be a priority from a public health as well an economic perspective. Treating HCV-infected persons could prevent decompensated cirrhosis, HCC and liver-related mortalities. Treating all persons with HCV along with preventive measures will ultimately eliminate HCV infection from India.

Staging of HCV infection is important as it identifies patients with advanced disease, a group that requires enhanced monitoring and prioritization for treatment before the onset of decompensated cirrhosis. In many high-income countries, all persons with chronic HCV infection who do not have a contraindication for therapy are considered to be suitable for treatment (although many are not able to access treatment because of eligibility restrictions placed by third- party payers to reduce costs).

Clinical Assessment Before Initiating Treatment

A number of clinical considerations are important for the management of persons with chronic HCV infection. Pre-treatment evaluation of the risk of adverse events should be based on the patients clinical details, concomitant medications, and knowledge of treatment regimen to be administered.

A detailed history for alcohol consumption as well as any other medications that the patient might be taking should be taken. An alcohol intake assessment should be done for all persons with HCV infection followed by the offer of a behavioral alcohol reduction intervention for persons with moderate-to-high alcohol intake.

The risk of cirrhosis and HCC varies, depending upon certain patient characteristics or behaviors. For example, men, persons who consume excess alcohol, persons with HBV or HIV co-infection and immunosuppressed individuals are all at higher risk of developing cirrhosis or HCC. Disease associated with HCV infection is not confined to the liver. Extrahepatic manifestations of HCV include cryoglobulinaemia, glomerulonephritis, thyroiditis and Sjogren syndrome, insulin resistance, type 2 diabetes, and skin disorders such as porphyria cutanea tarda and lichen planus. Persons with chronic HCV infection are more likely to develop cognitive dysfunction, fatigue and depression. These outcomes may be associated with replication of the virus in the brain; however, the causal link between these manifestations and chronic HCV infection is not certain.

Assessment of Degree of Fibrosis

Assessing the degree of liver fibrosis is an important step in the clinical management of persons with HCV infection. Persons with cirrhosis are at increased risk of HCC and death due to liver failure. Furthermore, the selection of treatment regimens can depend on the presence or absence of cirrhosis.

Please refer to Annexure 1 for assessment of degree of fibrosis and cirrhosis

Baseline and follow-up Investigations

The directly acting antivirals are much better tolerated by patients, as they have fewer adverse events and thus less need for early discontinuation of therapy. However, there remains the need for laboratory monitoring in patients with cirrhosis, those with significant comorbidities and those treated with ribavirin therapy. A summary monitoring schedule framework for the treatment of patients is shown in Table below. If blood parameters become abnormal on therapy, increased monitoring and dose adjustment may be required. Clinical judgement based on the patient's clinical details such as presence of HIV co-infection, cirrhosis or renal impairment, potential Drug –Drug Interactions and clinical well-being during treatment may necessitate more frequent monitoring

Table 7: Monitoring schedule framework for the treatment of patients

Time	Regimen: Only DAAs (non-cirrhotic usually)			Regimen: DAAs and Ribavirin (cirrhotic usually)		
	CBC, S.Creatinine, LFT	Adherence and side effects	HCV RNA	CBC, S.Creatinine , LFT	Adherence and side effects	HCV RNA
Baseline	Yes		Yes	Yes		Yes
Week 1				Yes	Yes	
Week 2				Yes	Yes	
Week 4	Yes	Yes		Yes	Yes	
Week 8				Yes	Yes	
Week 12				Yes	Yes	
Week 12 after completion of treatment (SVR-12)			Yes	Yes		Yes

CBC, complete blood counts; LFT, liver function tests; SVR, sustained viral response

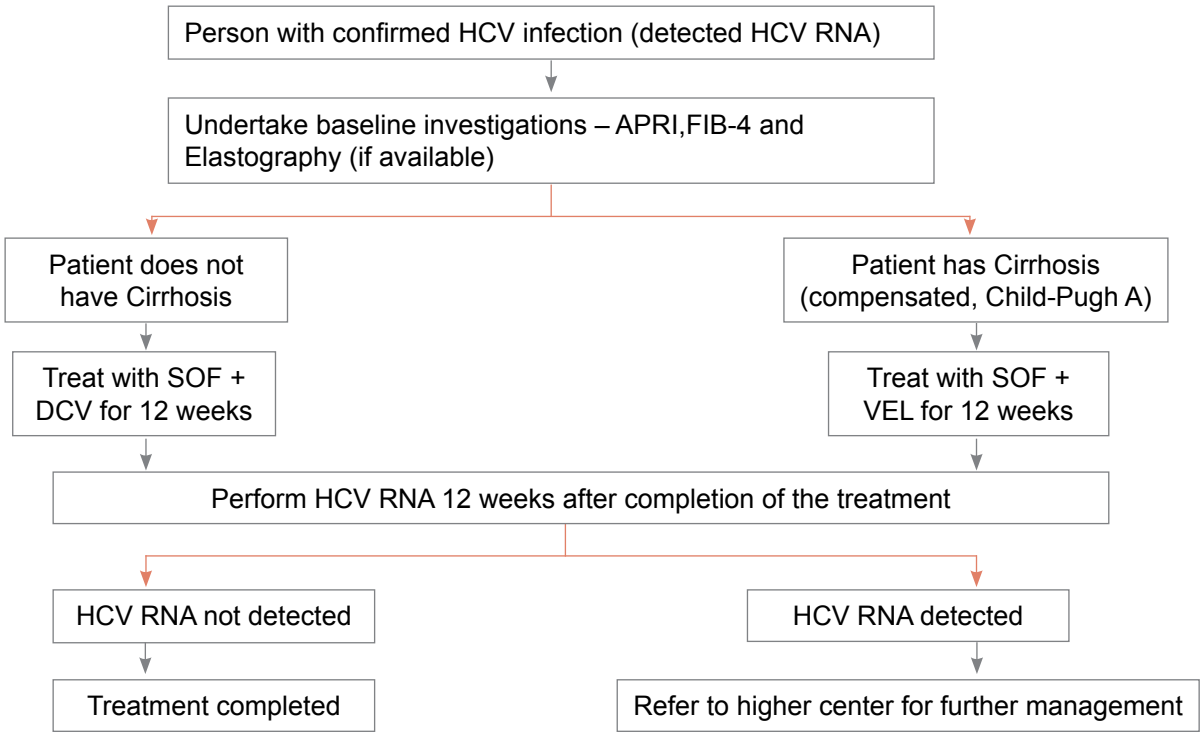
Whom To Treat

Any individual diagnosed to have infection with hepatitis C virus (viremia +) needs treatment. The duration of treatment will depend on the several situations such as, cirrhosis versus non-cirrhosis, presence of decompensation (ascites, variceal bleeding, hepatic encephalopathy, or infection(s), treatment naïve versus treatment experienced (to peg IFN, DAAs, etc).

What Regimen To Use

DAAs are the recommended first line treatment in India. The combination of the DAAs and the duration of treatment will depend on presence or absence of cirrhosis and on the genotype of the virus.

The following algorithm will provide guidance on selection of regimen and the duration in treatment naïve hepatitis C patient .



SOF, sofosbuvir; DCV, daclatasvir; VEL, velpatasvir

Fig. 7: Algorithm for guidance on selection of regimen and duration of treatment in hepatitis C naïve patient .

Table 8: Regimens recommended

Regime type	Category of patients	Regime recommended	Duration of Treatment
I	Patient without cirrhosis(uncomplicated)	Sofosbuvir(400mg) & Daclatasvir(60mg)*	84 days (12 wks)
II	Patient with cirrhosis- compensated (Child-Pugh A)	Sofosbuvir(400mg) + Velpatasvir(100mg)	84 days(12 wks)
III	Patient with cirrhosis- decompensated (Child-Pugh B and C)**	Sofosbuvir(400mg) + Velpatasvir (100mg) & Ribavirin(600-1200mg**)	84 days(12 wks)
		In Ribavirin intolerant patients - Sofosbuvir(400mg) + Velpatasvir(100mg)	168days (24 wks)

dose adjustments in PLHIV, renal insufficiency, etc.* * Refer to the Model Treatment Center (MTC)*

Table 9: Dosage of recommended DAA

Name of drug	Dosage
Sofosbuvir	400 mg once a day
Daclatasvir	60mg once a day
Sofosbuvir + Velpatasvir	Sofosbuvir(400mg) + Velpatasvir (100mg) once a day
Ribavirin	800-1200 mg (to be decided based on weight, hemoglobin level, renal function and presence of cirrhosis)

Counseling Messages for Screening Test Results:

All patients should be provided information on the meaning of their test results by the attending clinicians/ trained health care workers/peer counselors:

Providing Pre-test information: through media such as posters, brochures, websites and short video clips shown in waiting rooms. This would include information on viral hepatitis and the benefits of testing for hepatitis B or C; the meaning of a positive and negative test result; a brief description of prevention options; confidentiality of the test result; the practical implications of a positive test result, including the when and where of treatment available.

Post-test information/counseling for a non-reactive hepatitis C screening test:

- Explain the meaning of the non-reactive antibody test, ensuring that the patient understands a negative antibody test does not protect him/her from future infection in the event of risk taking behaviors.
- Discuss that if the patient was recently exposed (6 months), he/she may be in a window period and recommend repeat screening in 6 months, and provide information on hepatitis C prevention, risk and harm reduction.
- Encourage the patient to make healthy choices and to get vaccinated against hepatitis B, if appropriate.

Post- test counseling and linkages to treatment services for a reactive hepatitis C screening test:

- Explain the meaning of the reactive antibody test and counsel on the need for diagnostic testing (hepatitis C RNA test) to confirm a diagnosis of chronic hepatitis and other tests for staging of liver disease.
- Explain that the patient is most likely chronically infected and provide basic hepatitis C disease and treatment information. Make an active referral to the viral hepatitis treatment units.
- Discuss the importance of minimizing risk behaviors to avoid transmitting hepatitis C infection to others, and encourage notification and screening of needle sharing and sexual partners.
- Encourage and offer HBV and HCV testing for family members, including children, and sexual partners.
- Discuss healthy liver practices, including stopping or reducing alcohol intake and getting vaccinated against hepatitis A and B, if appropriate.

Adherence counseling by trained pharmacist: 1) Pill count: the total number of pills/doses dispensed and the total number of pills/doses returned at monthly visits for each drug for the entire treatment duration for all patients; 2) Patient self-reports: it helps to determine reasons for non-adherence

Though the majority of patients can be initiated the treatment for hepatitis C, there are several situations in which it is recommended to refer the patient to a specialized center. These include:

a. Patients with decompensated cirrhosis
b. Treatment experienced patients
c. Patients on chemotherapy with deranged liver enzymes
d. Patient with impaired renal function
e. Patient with HCC
f. Paediatric patients
g. Thalassemic patients

Side Effects of Drugs Used in Treatment

New DAA regimens are well tolerated by patients. Certain regimens have been shown to be safe for use in patients with decompensated liver cirrhosis and those who have undergone liver transplantation. However, close monitoring is required in these patients and it is recommended that such regimens be undertaken only in units with the expertise to manage these patients and treat complications if they arise.

Daclatasvir: The common adverse reactions associated with this drug are fatigue, headache and nausea, seen in studies that have either used the drug in combination with sofosbuvir with or without ribavirin.

Sofosbuvir with or without ledipasvir: Both drugs have been well tolerated by patients. They are reasonably well accepted by patients, with low rates of discontinuation in clinical studies. Fatigue, headache, insomnia and nausea are the most common adverse events reported. Recent evidence has emerged of significant bradyarrhythmias associated with sofosbuvir in patients also taking amiodarone and therefore it is contraindicated in these patients.

Sofosbuvir with Velpatasvir: Both drugs have been well tolerated by patients. Headache, fatigue, anemia, nausea, insomnia, diarrhea, weakness, rash and depression are the most common adverse events reported, which are at as similar frequency to placebo-treated patients.

Dose adjustment of ribavirin

Anaemia is a common, predictable side-effect of ribavirin therapy and dose adjustment is often required. Patients whose haemoglobin 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 haemoglobin 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 haemoglobin decreases by ≥2 g/dL during any 4-week period. In addition, for these patients, if the haemoglobin 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 m2 should not be treated with ribavirin and those on haemodialysis must have the dose lowered to 200 mg per day or take it three times per week. Increased monitoring is required in this group. 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.

Drug Interactions with DAA

The following tables provide common drug interactions of the commonly used DAA.

Therapy with DAAs: contraindications/warnings

There are few contraindications to treatment with DAAs. The cytochrome P450 (CYP)/P-glycoprotein (P-gp) inducing agents, such as **carbamazepine and phenytoin, are contraindicated with all regimens.** Simultaneous use lead to significantly reduced concentrations of DAAs, which may lead to virological failure.

Other concomitant medicine-related interactions are discussed in table ..... The University of Liverpool website, www.hep-druginteractions.org, is a good resource for checking for drug interactions with DAA.

Sofosbuvir should be used with caution in patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) at MTC .

Table 10: Contraindications to therapy with Ribavirin

Absolute Contraindication	Relative Contraindication
• Pregnancy or unwillingness to use contraception • Breastfeeding women • Severe concurrent medical disease, including severe infections • Poorly controlled cardiac failure • Chronic obstructive pulmonary disease • Previous ribavirin hypersensitivity • Co-administration of didanosine	• Abnormal haematological indices: » Hemoglobin <10 g/dL » Neutrophil count <1.5x10^9/L » Platelet count <90x10^9/L • Serum creatinine >1.5 mg/dL • Haemoglobinopathies (sickle cell disease or thalassaemia) • Significant coronary artery disease

Annexure-3 highlights drug interactions between DAA and some commonly prescribed medications. The University of Liverpool website, www.hep-druginteractions.org, is a good resource for checking for drug interactions with DAAs.

Special Situations and co-morbidities

Treatment of Patients with Decompensated Cirrhosis

DAAs can cause severe complications when prescribed to persons with decompensated cirrhosis (presence of ascites, jaundice, history of hepatic encephalopathy and variceal bleed or Child-Pugh score ≥7 [Class B and C], http://www.hepatitisc.uw.edu/page/clinical-calculators/ctp). Therefore, they should be used only in settings where specialized care for managing such cases is available. Therefore refer all these patients to a specialized center for further evaluation, HCV genotype estimation should be done in all patients. Following regimens would be used to treat these patients (Table 11).

Table 11: DAAs in the Treatment of Decompensated Cirrhosis *

	All Genotype
Ribavirin tolerant	Daily fixed-dose combination of SOF (400 mg) + VEL (100 mg) + weight-based RBV** x 12 weeks
Ribavirin intolerant	Daily fixed-dose combination of SOF (400 mg) + VEL (100 mg) x 24 weeks

SOF: sofosbuvir; VEL: velpatasvir; RBV: ribavirin. * to be managed at model treatment center (MTC), **Ribavirin should be administered orally with food twice daily, with the dose determined according to body weight (1000 mg daily in patients with a body weight of <75 kg and 1200 mg daily in patients with a body weight ≥75 kg). Ribavirin should be started at lower dose (600 mg perday) then gradually increase to the máximum tolerated dose.

Management of Treatment Experienced Patients

Refer all these patients to a specialized center for further evaluation, especially analysis for resistance associated substitutions (RAS), endoscopy, imaging (TPCT, CEMR, etc), etc. HCV genotype estimation should be done in all patients. These patients would be treated by regimens as shown in Table 12.

Table 12: DAAs in the Management of Treatment Experienced Cirrhotic and Non-cirrhotic Patients.

Treatment failure regimen	No cirrosis / Compensated cirrhosis	Non-Genotype 3	Genotype 3
Peg IFN+RBV Or SOF+RBV	No cirrhosis	Daily fixed-dose combination of SOF (400 mg) + VEL (100 mg) x 12 weeks	Daily fixed-dose combination of SOF (400 mg) + VEL (100 mg) x 12 weeks
	Compensated cirrhosis	Daily fixed-dose combination of SOF (400 mg) + VEL (100 mg) x 12 weeks	Daily fixed-dose combination of SOF (400 mg) + VEL (100 mg) + weight-based ribavirin* x 12 weeks
SOF+DCV/LDV	No cirrhosis	Daily fixed-dose combination of SOF (400 mg) + VEL (100 mg) + weight-based ribavirin x 24 weeks	Daily fixed-dose combination of SOF (400 mg) + VEL (100 mg) + weight-based ribavirin x 24 weeks
	Compensated cirrhosis	Daily fixed-dose combination of SOF (400 mg) + VEL (100 mg) + weight-based ribavirin x 24 weeks	Daily fixed-dose combination of SOF (400 mg) + VEL (100 mg) + weight-based ribavirin x 24 weeks

SOF: sofosbuvir; RBV: ribavirin, VEL: velpatasvir.

*Ribavirin should be administered orally with food twice daily, with the dose determined according to body weight (1000 mg daily in patients with a body weight of <75 kg and 1200 mg daily in patients with a body weight ≥75 kg). Ribavirin should be started at lower dose (600 mg perday) then gradually increase to the maximum tolerated dose.

Reference Gane EJ, Shiffman ML, Etzkorn K, Morelli G, Stedman CAM, Davis MN, Hinestrosa F, Dvory-Sobol H, Huang KC, Osinusi A, McNally J, Brainard DM, McHutchison JG, Thompson AJ, Sulkowski MS; GS-US-342-1553 Investigators. Sofosbuvir velpatasvir with ribavirin for 24 weeks in hepatitis C virus patients previously treated with a direct-acting antiviral regimen. Hepatology. 2017 Oct;66(4):1083-1089. doi: 10.1002/hep.29256. Epub 2017 Aug 26. PubMed PMID: 28498551.

People who inject drugs

Globally, approximately 67% of PWID have evidence of anti-HCV antibodies. PWID are at increased risk of HCV-related disease and transmission, as well as for all-cause morbidity and mortality, and therefore require specialized care and should be considered as a priority for HCV treatment. In reality, many PWID with HCV infection are unaware that they are infected and HCV treatment rates among them are very low. This is due to a number of reasons, including the criminalization of drug use, as well as discrimination and stigma in health care settings. When caring for PWID, the central tenets of respect and non-discrimination should be followed, and additional adherence and psychological support given as required.

Screening

As a population with a high prevalence of HCV infection, all PWID should be offered screening for HCV as an integral component of a comprehensive package of harm reduction interventions. Repeated screening is required in individuals at ongoing risk of reinfection, and the possibility of reinfection after spontaneous clearance or successful treatment should also be considered. Those who have been previously infected should be re-tested at least annually using HCV RNA testing, as the antibody remains positive after the first infection.

HCV case-finding and treatment in specialist drug dependency services has also been shown to be cost-effective in high-income settings. The higher the treatment rates, the more cost-effective HCV case-finding becomes, as more of those identified will be treated, and a greater population impact would be seen. Screening for HBV and HIV is also recommended in PWID.

Care

Treatment of HCV in PWID requires integration of services, as other health care needs, including treatment for HIV and TB as well as drug and alcohol dependency, are often also present. Harm reduction strategies, including the provision of OST and sterile injection equipment, are required in order to prevent acquisition of HCV and other blood borne viruses such as HBV and HIV.

At all times, avoidance of discrimination or stigmatization of PWID is essential. Care should be given only with informed consent. Moreover, acceptability of services is a vital component of health care, and peer interventions may help with reducing injecting drug use and promoting safer injection practices. PWID are at risk of infection with HBV and should be vaccinated using the rapid vaccination regimen.

Interventions in PWID offer important area of synergies with the National AIDS Control Programme (NACP) and the different intervention can be delivered using the targeted interventions.

Persons with HIV/HCV Co-infection

Persons with HIV/HCV co-infection generally have more rapid progression of liver fibrosis, especially those with a CD4 cell count of <200 cells/mm3. Furthermore, even among patients in whom ART leads to successful control of HIV infection (i.e. undetectable HIV viral load), the risk of hepatic decompensation among co-infected patients is higher than among patients with HCV mono infection. For these reasons, all persons with HIV/HCV co-infection should be considered for HCV treatment.

Evaluation of HIV and HCV Co-infected persons

The assessment of those with HCV/HIV includes clinical evaluation – history, physical examination for jaundice, hepato-splenomegaly, ascites, cirrhosis/decompensation and laboratory tests including LFT, prothrombin time, complete haemogram, AFP, etc. Other tests required are abdominal ultrasound, endoscopy, assessment of liver fibrosis (APRI/FIB 4/fibro-Scan- please refer Annexure 1, and HCV RNA quantitative assay.

Treatment of HIV and HCV Co-infection

In the past, treatment of HIV and HCV co-infected persons with interferon and ribavirin combination therapy was difficult, as many patients had to discontinue treatment due to side-effects such as depression or weight loss as well as severe anaemia, thrombocytopenia and neutropenia. Furthermore, SVR rates in patients with co-infection were lower than among HCV-mono infected patients.

Outcomes of HCV therapy with DAAs in persons with HIV co-infection are comparable to those with HCV mono infection. Thus, DAA therapy has substantially simplified the treatment of persons with HIV and HCV co-infection.

There are fewer Drug-Drug Interactions (DDIs) between DAAs and ARV medicines, and SVR rates with DAA-based therapy among persons with HIV co-infection are higher than 95%, even for those with prior HCV treatment failure or advanced fibrosis. Therefore, there is no longer a need to consider HIV/HCV co-infected patients as a special, difficult-to treat patient population. The need to check for DDIs between HIV and HCV medications, however, needs to be emphasized.

It is advisable to first initiate treatment for HIV and achieve HIV suppression before starting HCV treatment, although there are some circumstances where it may make sense to treat HCV infection first and then initiate therapy for HIV. This could include persons with moderate-to-severe fibrosis at risk of rapid liver disease progression if the HIV infection is not associated with significant immunosuppression at the time of treatment. Also, in view of the short duration of HCV treatment, the risk of DDIs between HCV and HIV medicines and the increased risk of ART-related hepatotoxicity in the presence of HCV infection, treating HCV infection first can simplify subsequent ART depending on the regimen available locally.

Potential harmful effects of ARV drugs include their hepatotoxic effects. Several studies have shown that hepatotoxicity as a result of ART may be worsened in the presence of concomitant HCV infection. However, the highest rates of hepatotoxicity have been observed with ARV drugs that are no longer commonly used or recommended, including stavudine (d4T), didanosine (ddI), nevirapine (NVP) or full-dose ritonavir (600 mg twice a day) . For most HIV/HCV co-infected persons, including those with cirrhosis, the benefits of ART outweigh concerns regarding drug-induced liver injury. Raised liver enzymes may be the result of ART-induced drug toxicity and/ or opportunistic infections, making interpretation of liver enzyme elevations more problematic than for patients with HCV infection alone. ALT and AST should be monitored at 1 month after ART initiation and then every 3–6 months. A significant elevation of AST/ALT should prompt careful evaluation for other causes of liver function impairment (e.g. alcoholic hepatitis, hepatobiliary disease), and may require short-term interruption of the ART regimen or specific drug suspected of causing the elevation.

Daclatasvir is associated with significant drug interactions with many NNRTIs and PIs, and its concomitant use requires caution, dose adjustments or consideration of alternative DAAs. The dose of daclatasvir will be 30 mg with ATV/r and 90 mg with EFV. Ledipasvir (LDV) and sofosbuvir have shown reduced potential for drug interactions with ARV drugs due to their use of different metabolic pathways. A complete list of drug-drug interactions is available at www.hep-druginteractions.org.

Table 13: Drug Interactions Between Direct-Acting Antivirals and Antiretroviral Drugs

Selected HIV Drugs	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Sofosbuvir/ Velpatasvir
3TC	√	√	√	√
ABC	√	√	√	√
FTC	√	√	√	√
TDF	√	√	√ Monitor for TDF toxicity.	√ Monitor for TDF toxicity.
Unboosted ATV	√	√	√	√
ATV/r or ATV/c	√ ↓ DCV dose to 30 mg/day	√	√ If a PI/r or PI/c is used with TDF, ↑ TDF concentrations are expected. If co-administration is necessary, monitor for TDF-associated toxicities.*	√ If a PI/r or PI/c is used with TDF, ↑ TDF concentrations are expected. If co-administration is necessary, monitor for TDF-associated toxicities.*
DRV/r or DRV/c	√	√		
LPV/r	√	√		
EFV	√ ↑ DCV dose to 90 mg/day	√	√ If used with TDF, monitor for TDF toxicity.	X
NVP	√ ↑ DCV dose to 90 mg/day	√		X
RAL	√	√	√	√

ATV/r = atazanavir/ritonavir; ATV/c = atazanavir/cobicistat; DAA = direct-acting antiviral agents; DRV = darunavir; DRV/r = darunavir/ritonavir;; DTG = dolutegravir; DSV = dasabuvir; EFV = efavirenz; FTC = emtricitabine; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivir; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate;
*Consider alternative HCV or ART to avoid increases in TDF exposure. If co-administration is necessary, monitor patient for TDF-associated adverse reactions.
Key to Symbols:
√ = ARV agents that can be used concomitantly
X = ARV agents not recommended

(Ref: Guidelines for the Use of Anti-retroviral Agents in HIV-1-Infected Adults and Adolescents; Downloaded from https://aidsinfo.nih.gov/guidelines on 6/27/2018)

Management of Cirrhotic Patients after HCV clearance in SVR 12

HCV infection can be considered cured in non-cirrhotic patients who have achieved a SVR 12 after 12 weeks of completing the treatment. Thus no follow-up is required.

Patients with a history of excessive alcohol drinking, obesity, type 2 diabetes, hypertension etc should be periodically subjected to a thorough clinical assessment as needed.

In patients with cirrhosis who have achieved cured (successful treatment), long-term post-SVR follow-up studies have demonstrated that there is a persistence of risk of developing HCC, although it is significantly reduced compared to untreated patients or patients who did not achieve an SVR. Thus, HCC surveillance in these patients must be indefinite. These patients with liver cirrhosis who have achieved SVR should remain under surveillance for HCC every 6 months by ultrasound, and for oesophageal varices by endoscopy if varices were present at pre-treatment endoscopy.

There is increased risk of reinfection (1-8%) following successful HCV among patients at high risk, such as PWIDs or men who have sex with men, etc. Thus the risk of reinfection should be explained to the patient in order to positively modify risk behavior. Following SVR 12, the monitoring for HCV reinfection should be recommended in these patients with ongoing risk behavior. If reinfection is identified during post-SVR follow-up, then retreatment is indicated.

Persons with chronic kidney disease

There is an unmet need for DAA treatment in patients with severe renal disease (eGFR <30 mL/min/1.73 m2) and those requiring haemodialysis. Sofosbuvir, which is used in many approved regimens, does not have the safety and efficacy data to support its use in these situations.

Patients receiving ARV drugs in combination with tenofovir and sofosbuvir may require enhanced renal monitoring.

Given the complex management needs for this group, these patients should be referred to higher and specialized center for appropriate management.

Persons with HBV/HCV co-infection

It is important to check for the presence of HBV infection before starting HCV treatment. HBV and HCV co-infection may result in an accelerated disease course; HCV is considered to be the main driver of disease. Persons co-infected with HBV and HCV can be treated with antiviral therapy for HCV; SVR rates are likely to be similar to those in HCV-mono infected persons. During treatment and after HCV clearance, there is a risk of reactivation of HBV, and this may require treatment with concurrent anti-HBV antiviral therapy. DDIs must be checked before initiating treatment.

Persons with TB/HCV co-infection

People at increased risk of infection with HCV are also often at increased risk of infection with TB. Therefore, screening for active TB should be part of the clinical evaluation of patients being considered for HCV treatment.

If the patient does not have any one of the following symptoms – current cough, fever, weight loss or night sweats – TB can be reasonably excluded; otherwise, the patient should undergo further investigations for TB or other diseases.

Most of the DAAs interact with metabolic pathways in the liver, which increases and/or decreases the drug level of DAAs when co-administered with antimicrobial medicines such as rifabutin, rifampin and rifapentine. Therefore, concurrent treatment of HCV infection and TB should be avoided. Active TB should generally be treated before commencing therapy for HCV. Furthermore, in persons with HCV infection being treated for TB, it is important to monitor liver function tests, as the risk of anti-mycobacterial -induced hepatotoxicity is

higher in patients with TB/HCV co-infection than in those with TB mono infection, although the risk of severe hepatotoxicity is rare.

Concurrent treatment of HCV infection and multidrug-resistant TB is particularly complicated because of many DDIs between DAAs and second-line antimicrobials. There are limited data on the management of persons co-infected with HCV, HIV and TB, but such cases need sound clinical judgement in order to reduce the additive side-effects, pill burden and DDIs. Baseline liver function tests for individuals with chronic liver disease are encouraged prior to initiating treatment for latent TB infection. For individuals with abnormal baseline test results, routine periodic laboratory testing should be carried out during the treatment of latent TB infection.

Women of child-bearing age

None of the DAAs have been evaluated among pregnant women. Thus, women with childbearing potential should be counseled that they require effective contraception during treatment and for six months after completion of therapy. Safety of DAAs in pregnancy has not been established. Ribavirin is associated with fetal abnormalities. DAAs are thus contraindicated in pregnant women and those with child bearing potential unless effective contraception (i.e. two forms of contraception) can be guaranteed during treatment and, for women taking ribavirin, for 6months after completing therapy. Pre-treatment pregnancy tests should be conducted prior to treatment initiation.

Hepatitis E

Hepatitis E virus (HEV) is a non-enveloped single stranded RNA virus belonging to Hepevirus. This agent is transmitted almost exclusively by the fecal oral route. It is an outbreak prone disease with an incubation period of around 2-10 weeks.

Clinical Presentation

The illness usually begins after the incubation period of 14-70 days as an acute viral syndrome with mild fever, marked loss of appetite, aversion to food, upper abdominal discomfort ,nausea and/vomiting. Within a few days of onset of these non-specific symptoms jaundice can appear with the resolution of these non-specific symptoms. Jaundice usually persists for 1-6 weeks and then gradually resolves. In children, most HEV infections occur without any symptom or as a mild illness without jaundice. In contrast, in adults, acute hepatitis E may have a prolonged cholestatic phase with significant itching. Acute liver failure may be seen in a small proportion (0.4-5%) which is higher in pregnant women normally within a week of onset of symptoms.

Laboratory Diagnosis

Cases of hepatitis E are not clinically distinguishable from other types of acute viral hepatitis. Diagnosis is strongly suspected in appropriate epidemiologic settings e.g. occurrence of several cases in localities in known disease-endemic areas, in settings with risk of water contamination, if the disease is more severe in pregnant women and if hepatitis A has been excluded.

Definitive diagnosis of hepatitis E infection is based on the detection of specific IgM antibodies to the virus in a person's blood. In acute hepatitis with clinical jaundice, the serum bilirubin levels are above 2.5mg/dL and serum ALT is more than 10 times the upper limit of normal.

Management of Viral Hepatitis E

There is no specific treatment capable of altering the course of acute hepatitis E. As the disease is usually self-limiting, hospitalization is generally not required. Hospitalization is required for people with fulminant hepatitis and symptomatic pregnant women.

Immunosuppressed people with chronic hepatitis E benefit from specific treatment using ribavirin, an antiviral drug. In some specific situations, interferon has also been used successfully.

Special Situations

Certain population sub-groups are at a higher risk for severe disease following HEV infection. These include pregnant women, persons with pre-existing liver disease and persons with immunosuppression. During HEV epidemics, fulminant hepatitis occurs with a disproportionately high rate among pregnant women. Overall case-fatality rates from hepatitis E have ranged from 0.1% to 4%; however, case-fatality rates among pregnant women are much higher, being 10%-25%.

It is important to recognize patients with acute hepatitis E occurring in these special situations as sick patients who need hospitalization.

Management of acute viral hepatitis during pregnancy

The patient is preferably managed in a hospital with ICU facilities and blood banking to provide adequate blood product support, in addition to Obstetric services.

- Monitor blood pressure, exclude toxaemia of pregnancy.
- Permit oral intake, maintain adequate hydration.
- Monitor closely for development of signs of acute liver failure.

Premature induction of labor has no proven role in preventing or treating ALF.

If spontaneous premature rupture of membranes or premature labor occur, one should: Give vitamin K (10 mg IV, repeat after 24 h), monitor fetal heart rate, arrange blood (may need if postpartum bleeding occurs). If the fetus is >34-36 weeks, consider induction of labour, otherwise manage conservatively. For premature rupture of membranes, give antibiotic prophylaxis.

In case of intrauterine death, induction of labor (misoprostol or oxytocin) should be considered in a patient not in acute liver failure. However, if the mother has acute liver failure, labour should not be induced.

Oxytocin should be used after delivery, to prevent post-partum bleeding. If bleeding occurs, use oxytocin infusion; if needed, ergometrine or misoprostol can be used. Use blood transfusion, if necessary.

For baby, assess for hypothermia and hypoglycaemia, and treat if present. Administer vitamin K, give normal vaccines and initiate breast feeding (if the mother can nurse).

Diagnosis and management of acute liver failure

Acute liver failure: Definition

Acute liver failure (ALF) is defined as a severe injury to a previously normal liver, presenting initially as jaundice, and then altered mental state (hepatic encephalopathy) within 4 weeks of the onset of jaundice. Hepatic encephalopathy manifests as mental changes, restlessness, reversal of sleep pattern, altered consciousness and/or persistent vomiting. It is often associated with cerebral edema, which may manifest as slowed heart rate, high blood pressure and irregular respiration. Less commonly, coagulopathy may develop with bleeding from one or more body sites.

ALF can be complicated by secondary bacterial infection (leading to sepsis), renal failure, multi-organ failure, and carries a high risk of death.

How to suspect

The development of one or more of the following should lead to suspicion of impending acute liver failure, or of severe acute hepatitis:

- Severe or persistent nausea and vomiting
- Mental state changes: excessive sleepiness, irritability, agitation, disorientation, confusion, abnormal behaviour or decreased level of consciousness
- Spontaneous bleeding (nasal, oral, vaginal, diarrhoea, vomiting)
- Repeated episodes of hypoglycemia
- Fever not possible to manage with tepid sponging
- Dehydration or inability to maintain oral hydration, or not passing urine

Differential diagnosis

In such patients, other diseases (e.g. severe malaria, dengue infection, leptospirosis, other less common systemic infections, sepsis, cholangitis, liver abscess, drug toxicity) may need to be excluded by clinical or laboratory evaluation.

Management

Patients with manifest or suspected ALF should be hospitalized. Hospitalization may also be considered in persons with acute hepatitis who are at high risk of developing ALF (e.g. pregnant women with hepatitis E in the last trimester, or those with underlying chronic liver dysfunction). The patient is preferably managed in ICU or high dependency unit.

Treatment should focus on:

a. General care of seriously ill or unconscious patient, including

   i. Close observation and monitoring of vital signs, changes in sensorium and bleeding, urine output, etc

   ii. Quiet surroundings; head of the bed elevated at ~30^{O} with head in neutral position

   iii. Nil by mouth, maintenance of fluid and electrolyte balance by intravenous route, while avoiding over-hydration and hyponatremia (these can worsen cerebral edema)

   iv. Steps to prevent bed sores and corneal injury

   v. Monitoring of blood sugar, and prevention and treatment of hypoglycaemia

b. Treatment of symptoms, including

   i. Fever: Sponging, paracetamol if needed

   ii. Vomiting: Domperidone

   iii. Itching: Calamine lotion

c. Patients with encephalopathy should receive lactulose (via nasogastric tube – thin tube, placed gently to avoid injury and bleeding) 30 ml 2-3 times per day initially, later adjusted to produce 2-3 soft stools daily (avoid diarrhea). Mannitol (0.5-1.0 g/Kg IV) may be considered in case of prominent cerebral edema, provided urine output is good. In such patients, transfer to a hospital with intensive care facilities may need consideration.

d. Vitamin K may be administered if coagulopathy is prominent (10 mg IV/d X 3 days)

e. Prevention and treatment of complications

i. Bacterial infections: consider prophylactic antibiotic, look for and treat early.

ii. Stress ulcers/bleeding: H2 receptor antagonist or proton pump inhibitor

iii. Bleeding: blood or fresh frozen plasma transfusion

iv. Seizures: diazepam

v. Shock: IV fluids

vi. Hypoxia: Oxygen

The following should be avoided or used with caution:

a. Invasive procedures that carry the risk of bleeding
b. Hepatotoxic drugs
c. Drugs that increase the risk of bleeding (e.g. aspirin, NSAIDs)
d. Sedative drugs
e. Corticosteroids

Specific anti-viral agents have no role in management, except possibly in case of acute severe hepatitis B.

Referral of a Patient with Acute Liver Failure to a Tertiary Care Center

When to refer?

- When the patient develops any degree of alteration in sensorium and INR is above 1.5

Where to refer?

- Transfer the patient to a specialized intensive care with the skills to provide airway and ventilator management (tertiary care unit)
- Facility for liver transplantation is available (if patient is willing)

How to transport the patient?

- Transfer without delay along with a trained health care personnel
- Detailed discussion between the transferring and receiving physicians/team is essential before the transfer
- In the scenario of an evolving hepatic encephalopathy - intubate and sedate to ensure a controlled and safe transfer
- Appropriate fluids should be available for ongoing volume resuscitation
- Patient should be maintained normoglycaemic
- Vasopressors should be drawn-up and available.
- Mannitol should be available for management of raised intracranial pressure during transit.

SECTION 2

OPERATIONAL GUIDELINES* TO ROLL OUT TREATMENT OF HEPATITIS C

(*Operational guidelines for roll out of treatment of hepatitis B will be disseminated subsequently)

Introduction

The Government of India has decided to launch the integrated initiative for Prevention and Control of Viral Hepatitis with provision of free treatment for hepatitis C through the National Health Mission. To roll out the treatment for hepatitis C with a public health approach, the present section has been developed for facilitating the operationalization of the treatment of Hepatitis C across the country and intends to address the operational aspects of the same.

Organization of Services

The services will be delivered through designated treatment sites that are located within an existing public health facility, including tertiary care facilities followed by district hospitals. The extent of services will depend upon the availability of the expertise and resources in the selected sites. There will be 15 sites that will be identified as Model Treatment centers (MTC). These will also act as places for referral, capacity building and mentoring for the other treatment centers (TC). Selection of the Model treatment Center sites will be done by the central unit for viral hepatitis, with concurrence of states being the implementing agency.

Guidelines for the Organization of Services

Objectives and functions of the Treatment Sites

The management of hepatitis C has been simplified over the last few years since the introduction of Directly Acting Antivirals. The main objective of the treatment site under the initiative is to enhance the access to treatment for hepatitis C.

Model Treatment Centre (MTC) and Treatment Centre (TC): The treatment for hepatitis C will also involve management of patients that present with a range of clinical presentations, cirrhotic and non-cirrhotic, treatment naive or treatment experienced, special situations like renal impairment etc. Hence, to effectively manage the patients with HCV infection, it is planned to have a tiered approach for service delivery. All the treatment centers will have the capacity to deliver the DAA in uncomplicated cases (and few other scenarios as per the national technical guidelines). They could be situated in public health care facilities like the medical colleges, district hospitals etc. However, the cases that need more specialized care will be referred to higher centre that have the requisite capacity and experience to manage the complicated cases (e.g. decompensated cirrhosis, thalessemics with HCV infection, HCV infection in renal impairment etc.). These health care facilities with specialized services for diagnosis and management (like availability of Gastroenterologist/hepatologist, Doppler, CT scan, MRI scan etc.) are termed as Model Treatment center. Hence, the MTC will perform all the functions of a treatment centre , will also receive in-referrals and also be the centers for training, mentoring and conducting operational research under the initiative.

As the complications of chronic viral hepatitis are vast, the scope of initiative will be restricted to the use of directly acting antivirals in treatment of hepatitis C as per the prescribed regimens.

Functions of the Model Treatment Center:

1. To ensure Screening/ Diagnosis in suspected cases of Hepatitis C Infection
2. Treatment & Management of Hepatitis C infection
3. In referrals for cases screened / diagnosed elsewhere, for the management of viral hepatitis
4. Management of complicated cases referred from other treatment centers.
5. Management of cases under special categories as per national guidelines(eg: thalassemics, patient with treatment failure etc.)
6. Ensure compliance and completion of treatment

7. Training and mentoring of other treatment sites
8. Operational research

Functions of the Treatment Center :

1. To ensure Screening/ Diagnosis in suspected cases of Hepatitis C Infection
2. Treatment and Management of uncomplicated Hepatitis C infection
3. In referrals for cases screened/diagnosed elsewhere, for the management of viral hepatitis.
4. Out referrals to MTC for clinical management of hepatitis as per national treatment guidelines.
5. Ensure compliance and completion of treatment

Selection criteria and steps for setting up a Treatment Site

Each site will be selected by the state, based on the burden of disease according to available evidence in form of studies, outbreaks, case reports, blood bank data etc. Once the sites are identified and proposed, a joint team will visit the facility and assess its feasibility for delivery of services, adequacy of needed space and man power and willingness of the institute to set up such center. The team that will undertake the feasibility visit should ideally comprise of the state and district officials of the initiative, central unit officials and other invited partners. The report of feasibility visit should be prepared, signed and kept with the state officials. The format for feasibility visit is attached as Annexure 4

Inclusion criteria for consideration as a potential treatment site include:

1. Established evidence of case load for Viral hepatitis C infection or its sequel
2. Evidence of high hepatitis burden in catchment area
3. Commitment and Willingness of the Institute to have a center and consequent agreement to follow the SOP and protocols under the initiative
4. Availability of required infrastructure
5. Availability of appropriate human resource for clinical and laboratory management, as well as other services routinely.

Infrastructure

The institution will be responsible for providing essential infrastructure for setting up the center. The institution should identify adequate space from where the services can be delivered, preferably in vicinity of OPD services. It should be clearly displayed at several places in the hospital for the ease of access by the patients especially in the blood bank premises, STI clinics, HIV/ICTC centres etc. There should be services available every day preferably, and have definite timings displayed boldly across the facility. It will be the responsibility of the institution to provide basic furniture like chairs, tables, cabinet/almirah etc., space for storage of drugs, and have necessary electrical and other fixtures. It has to be noted that no separate allocation will be made for infrastructure and state has to bear the costs if any.

Human Resource

The services will be delivered through the existing health system and the institution will have to nominate a nodal officer who would be responsible for the day to day functioning of the centers. Ideally, this could be the Head of department of Internal Medicine/Gastroenterology/Hepatology (or a person deputed /nominated by HOD) in tertiary centers and the physician in district hospitals and elsewhere. The patients should be seen by the attending physician from the system and the documentation of the patient data and management should be recorded in the formats that are made available under the program. To assist the delivery of services in a uniflow system and to ensure efficacy, the treatment centers will be provided the following staff under the program in a phased manner:

Staffing provided by the program

Table 14: Staff at the treatment sites.

S No	Model Treatment centers
1	Medical Officer – 1
2	Pharmacist -1
3	Data Entry Operator – 1
4	Peer Support -1

S No	Treatment centers
1	Pharmacist -1
2	Data Entry Operator – 1
3	Peer Support -1

Since the Model Treatment centers will also undertake additional tasks like training, mentoring, operational research and conducting review meetings with state and central unit, they will be provided one contractual position of level of Medical Officer(MO).

To facilitate the diagnosis and laboratory monitoring of treatment, the initiative will strengthen the laboratories to deliver services as per the national guidelines. The laboratories so established (preferably in the same institute as the treatment center) will have the following manpower that the program will provide in a phased manner, as per the level of facility.

Table 15: Staff at the state laboratory.

S No	Manpower at State laboratories
1	Technical Officer – 1
2	Data Entry Operator – 1
3	Laboratory Technician – 1

Table 16: Staff at the district laboratory.

S No	Manpower at District laboratories
1	Laboratory technician -1

The staff should be recruited by the institution as per the norms and procedures followed for recruitment of contractual staff as per the guidelines of the National Health Mission (NHM). The remuneration for all these staff shall be in accordance to the state NHM norms. There should be an in-built system of appraisal of such staff from time to time.

Terms of Reference for various staff at Treatment site

1. Nodal Officer

a. Overall responsibility of the functioning of the centre, reporting to state / central unit, participation in review meeting, coordinate and develop referral system and linkages with other departments of the hospital
b. Ensure that patient are not discriminated in the hospital and are not denied admission/ care.
c. Ensure that all ethical practices including confidentiality are maintained.
d. Ensure availability of adequate stock of quality drugs as per defined targets at all times
e. Ensure reporting of any short expiry drug in a timely manner to allow timely relocation and avoid financial loss
f. All administrative matters relating to the centre including sanctioning of leave of contractual staff, annual performance appraisal of the staff etc. as per guidelines
g. Ensure adherence to the highest standards of quality and excellence in patient care
h. Review and monitor the functioning of the centre periodically and in depth and ensure submission of reports as required.
i. Act as Focal point for interaction with central unit/ State program management officials etc.

2. Medical officer (MO) of Model Treatment Center (MTC)

Qualification: The MO should be a Medical graduate (MBBS) with 5 years of experience in clinical care preferably related to infectious diseases. S/he must be registered in the concerned state Medical Council. A candidate with higher education will be preferred.

Job Responsibilities

a. S/he is the functional team leader of the centre under the overall guidance of the Nodal officer. The MO has to supervise the administrative and medical functions of the centre on a day- to- day basis and provide leadership to staff to work as a cohesive team and deliver the services effectively
b. S/he should examine the patients, advise required investigations, review the investigations and prescribe the treatment.
c. Refer difficult/ complicated cases to the Nodal Officer or other specialist for further expert opinion and interventions including admission and inpatient care, if required
d. Monitor the consumption and availability of drugs, and alert the concerned authorities in case of impending shortage well in advance so as to enable adequate replenishment without disruption of services
e. S/he must ensure that all records, registers, cards are updated on a daily basis and reports are sent to the concerned authorities on time. All reports should be checked by the MO before taking approval from the Nodal Officer for sending them to the concerned authorities
f. S/he has to ensure that the guidelines for running and maintaining the centre are abided by.
g. Facilitate and coordinate trainings in the centre.
h. Ensure that a daily due list is prepared for the patients expected to visit and a follow up action is taken to contact the defaulting patients.
i. Any other duty assigned by Nodal Officer/ Initiative.

3. Pharmacist

Qualification: The pharmacist should hold a Degree in Pharmacy from a recognized institute. If candidate with degree is not available, diploma holder in pharmacy with 3 years of experience in health care institution can be considered. S/he must be registered in the concerned state pharmacy council.

Job responsibilities of Pharmacist:

a. S/he has to work under the guidance and supervision of nodal officer/MO
b. Dispense drugs with proper counseling / interaction with patient
c. Advise the patients and family about the importance of adherence during each visit
d. Counsel the patient on possible drug toxicities and report the same, if significant
e. Do pill count and report any adverse effects of drugs Also, confirm the next visit date and inform the patient
f. Maintenance of the drug stores
g. Maintain and update drug stock and drug dispensing registers regularly every day. Inform the concerned medical and nodal officer in case of any discrepancy. Duly take signature of nodal officer every fortnightly in the stock register
h. Ensure that the centre has enough stock of drugs for at least 3 months and inform the concerned authority about any near expiry or excess stocks well in time for relocation to other sites and ensure FEFO protocol is followed
i. Physical verification of the drugs under the supervision of the nodal officer and/or the MO
j. Besides all the above, any other duty assigned by nodal officer.

In case pharmacist is not available/on leave, the nodal officer in consultation with the head of institute will make any alternative arrangement so that the functioning does not suffer and regular staff of the facility must also be integrated for service delivery.

4. Data entry operator

Qualification: The Data entry operator should be a graduate with Diploma in Computer Applications (from a recognized institute or university) or 'O' Level course from DOEACC. S/he has to undergo training under the initiative in monitoring and evaluation tools (M & E) of the programme aimed to build the capacity of the person in recording data, preparing and sending reports and maintaining records properly.

Job responsibilities of Data Entry Operator:

1. S/he has to work under the guidance and supervision of MO and/or nodal officer
2. Ensure that all data recording and reporting is updated
3. Print and share all circulars/information sent by central unit/States to the Nodal Officer/MO and maintain a file for the important orders/communication
4. Maintain the attendance register for the centre staff and get it verified by the nodal officer everyday and by the Nodal Officer at the end of the month
5. Maintain the HR file including the bio-data of the staff, copies of certificates, appointment letters, contractual service agreement, performance appraisal report, training details, remuneration etc.
6. Prepare and send all the monthly reports prescribed by central unit after approval of Nodal Officer
7. Assist in analysis of data under the supervision of the Nodal Officer
8. Any other duty assigned by nodal officer.

5. Peer supporter

Qualification: The peer supporter should be a person preferably with or recovered from the disease (hepatitis B or hepatitis C) , with a minimum of intermediate (12th) level education. S/he must also have sound knowledge of the local language and working knowledge of English.

Job responsibilities of peer supporter:

a. S/he has to work under the guidance and supervision of nodal officer /MO
b. Be the first interface with patient at centre
c. Ensure entries in the visit register
d. Be a peer educator for patients at centre and provide psycho-social support to newly registered patients
e. Provide assistance to patients enrolled at the centre, within the hospital (OP and IP)
f. Discuss the importance of adherence to treatment and need of viral load at 12 weeks post treatment (SVR) with the patients , Keep track of drug adherence of patients , counseling them on the importance of regularity of visits and timely investigations
g. Follow up the patients and assist in patient retrieval, where necessary and as far as possible
h. Any other duty related to the initiative assigned by nodal officer/MO

Terms of Reference for various staff of the Laboratories

Laboratory In-charge (State Lab)

Designated Microbiologist of the Institution, or Pathologist in the absence of Microbiologist

Job Responsibilities

a. Supervises the work of Laboratory personnel
b. Verification and signing of reports generated in the laboratory
c. Ensuring that all job responsibilities are adhered to by all the laboratory personnel
d. Management of funds with relation to laboratory

e. Ensure participation in and review of EQA
f. Ensure training and competence of all the laboratory personnel

Technical officer (State Lab)

Qualification: MSc Medical Microbiology with 1 year experience in clinical laboratory services. Candidates with PhD Medical Microbiology from recognized university with 3 months experience in clinical laboratory services will be preferred.

Job Responsibilities

a. Supervises the work of Laboratory technician under the guidance of the Laboratory In-charge.
b. Molecular testing where available
c. Preparation of SOPs and work instructions.
d. Verification of reports generated in testing laboratory
e. Preparation of quality control (QC) samples
f. Preparation & distribution of proficiency panels (PT) panels
g. Inventory and financial document management in lab.
h. Maintaining and monitoring timely calibration / verification of all devices and ensuring that all monitoring and measurements are done with devices having valid verification / calibration status.
i. Adherence to Biosafety guidelines.
j. Maintenance of records and logs in laboratory.
k. Disposition of nonconforming products in her area of operation.
l. Help in the conduct of teaching and training programs.
m. Participate in surveillance activities of programme, through NCDC
n. Onsite field visit to district lab for mentoring and quality assurance.
o. Reporting to laboratory In-charge
p. Any other duty assigned by laboratory In-charge

Laboratory Technician (State/District Laboratory):

Qualification: DMLT two year course or certificate in MLT for one year or B.Sc in MLT from recognized university.

Job Responsibilities

a. Collect / receive specimens in the laboratory.
b. Assist in sample transportation to referral laboratory as and when required.
c. Performs tests for hepatitis markers and preparation of reports.
d. Storage and maintenance of serum samples as per guidance.
e. Confirmation of reference samples from state medical college labs and compilation of reports.
f. Perform regular internal quality control testing ,EQA and their documentation
g. To maintain essential records in the laboratory
h. Inventory preparation for equipment and reagents.
i. Indent for supplies to the Laboratory through Lab In charge and ensure sufficient stock of Laboratory consumables is available.
j. Participate in trainings and workshops conducted.
k. Assist in molecular testing of samples where required.
l. To maintain cleanliness in and safety and follow proper biomedical waste disposals.
m. Any other work/ activity assigned from time to time.

Data Entry Operator(State laboratory):

Qualification: The Data Entry Operator should be a graduate with Diploma in Computer Applications (from a recognized institute or university) or 'O' Level course from DOEACC. S/he has to undergo training under the initiative in monitoring and evaluation tools (M & E) of the initiative aimed to build the capacity of the person in recording data, preparing and sending reports and maintaining records properly.

Job responsibilities of Data Entry Operator:

1. S/he has to work under the guidance and supervision of nodal officer (Microbiologist)
2. Ensure that all data recording and reporting is updated for all activities under the program, including surveillance of viral hepatitis, if the lab is also participating in the surveillance program for viral hepatitis
3. Print and share all circulars/information sent by central unit/States to the Nodal Officer and maintain a file for the important orders/communication
4. Maintain the attendance register for the program staff and get it verified by the nodal officer (daily/ end of the month)
5. Maintain the HR file including the bio-data of the staff, copies of certificates, appointment letters, contractual service agreement, performance appraisal report, training details, remuneration etc
6. Prepare and send all the monthly reports prescribed by central unit after approval of Nodal Officer
7. Assist in analysis of data under the supervision of the Nodal Officer
8. Any other duty assigned by nodal officer.

Training

Trainings are important for any new initiative as well as for building the capacity of the service delivery points for an effective implementation. To ensure standardized and uniform quality of service delivery, there will be capacity building of the different cadres of staff in the program, using standardized training modules and facilitator guides. The following table summarizes the proposed trainings.

Table 17: Proposal for trainings.

Cadre of Health care worker	Number of days	Responsible agency	Remark
multi-specialty team at Institute	1	Institutional nodal person with head of institution and SVHMU	Sensitization about program and its contents/approach
Medical Officers	3	NVHMU for standardized manual; SVHMU for implementation and monitoring	Induction training
Medical Officers	2	NVHMU for standardized manual; SVHMU for implementation and monitoring	Refresher trainings as deemed necessary
Pharmacist	2	NVHMU for standardized manual; SVHMU for implementation and monitoring	
Peer supporter	1	NVHMU for standardized manual; SVHMU for implementation and monitoring	
Lab technicians	3	NVHMU for standardized manual; SVHMU for implementation and monitoring	Also include EQA
Technical Officer labs	3	NVHMU for standardized manual; SVHMU for implementation and monitoring	Also include EQA
Data Entry Operator	2	NVHMU and SVHMU	

Logistics

The drugs provided for the treatment centers will be provided through the state as per the laid down procedures and as per the list of drugs indicated in the treatment algorithm in the technical guidelines for clinical management of hepatitis. It will be ensured that no stock out/expiry happens in any circumstance, once the center starts functioning. A provision of 10% buffer stock needs to be maintained all the time as per the laid down procedure. These drugs should be kept under safe custody and proper storage conditions shall be maintained. The nodal person of the center should undertake physical verification of the stocks periodically and the stock registers should be regularly updated and duly signed by the pharmacist and nodal officer.

Financial management

The treatment center will be provided funds as per the pattern of assistance under the initiative through the state management unit of the NHM. The institute must handle the funds allocated for the purpose it is meant for and generate a statement of expenditure (SOE) from time to time as per the policy and procedures laid down by the state.

Table 18A and 18B below details the pattern of assistance:

Table 18A:Pattern of assistance for Model Treatment Centers.

Budget Head	Number	Total (Annual), in INR	Remarks
Nodal Officer	1	Regular cadre	From Regular cadre
Medical Officer	1		As per state NHM norms for each personnel. To be transferred from SVHMU of NHM
Pharmacist	1		
Data Entry operator	1		
Peer support	1		
Total (HR)			
Grant-in-aid for Hepatitis A and Hepatitis E case management		100,000	To be transferred from SVHMU to MTC
Meeting/ Training	6	128,000	
Contingency (photocopy/internet/ communication/ Resistance testing in selected cases/ Printing M & E tools/ Tablets for M & E if needed) any other operational costs etc.)		300,000	

Table 18B:Pattern of assistance for Treatment Centers.

Budget head	Number	Total (Annual), in INR	Remarks
Human Resource			
Nodal Officer	1	Regular cadre	From Regular cadre
Pharmacist	1		As per state NHM norms for each personnel. To be transferred from SVHMU of NHM
Data Entry operator	1		
Peer support	1		
Total (HR)			
Grant-in-aid for Hepatitis A and Hepatitis E case management		100,000	To be transferred from SVHMU to TC
Meeting/ Training	6	24,000	
Contingency (photocopy, internet/ communication/ Resistance testing in selected cases/ Printing M & E tools/ Tablets for M & E if needed) any other operational costs etc)		50,000	

Patient Flow at the Treatment Centers

The following sections elaborate on the flow of patient at the treatment center and also can be used to guide the smooth functioning of the staff.

There are two components:

1. Enrollment of the patient into care
2. Follow up visits of the patient

Enrollment of the patient: The patients who present to the center could either have a definite diagnosis or might have suspected infection. In case the person is found to have hepatitis C infection by the anti-HCV test (from a government facility), they should be confirmed with HCV RNA as per the diagnosis algorithm in the national guidelines. Every person who has a detectable HCV RNA is eligible to receive treatment after taking consent (annexure 9)

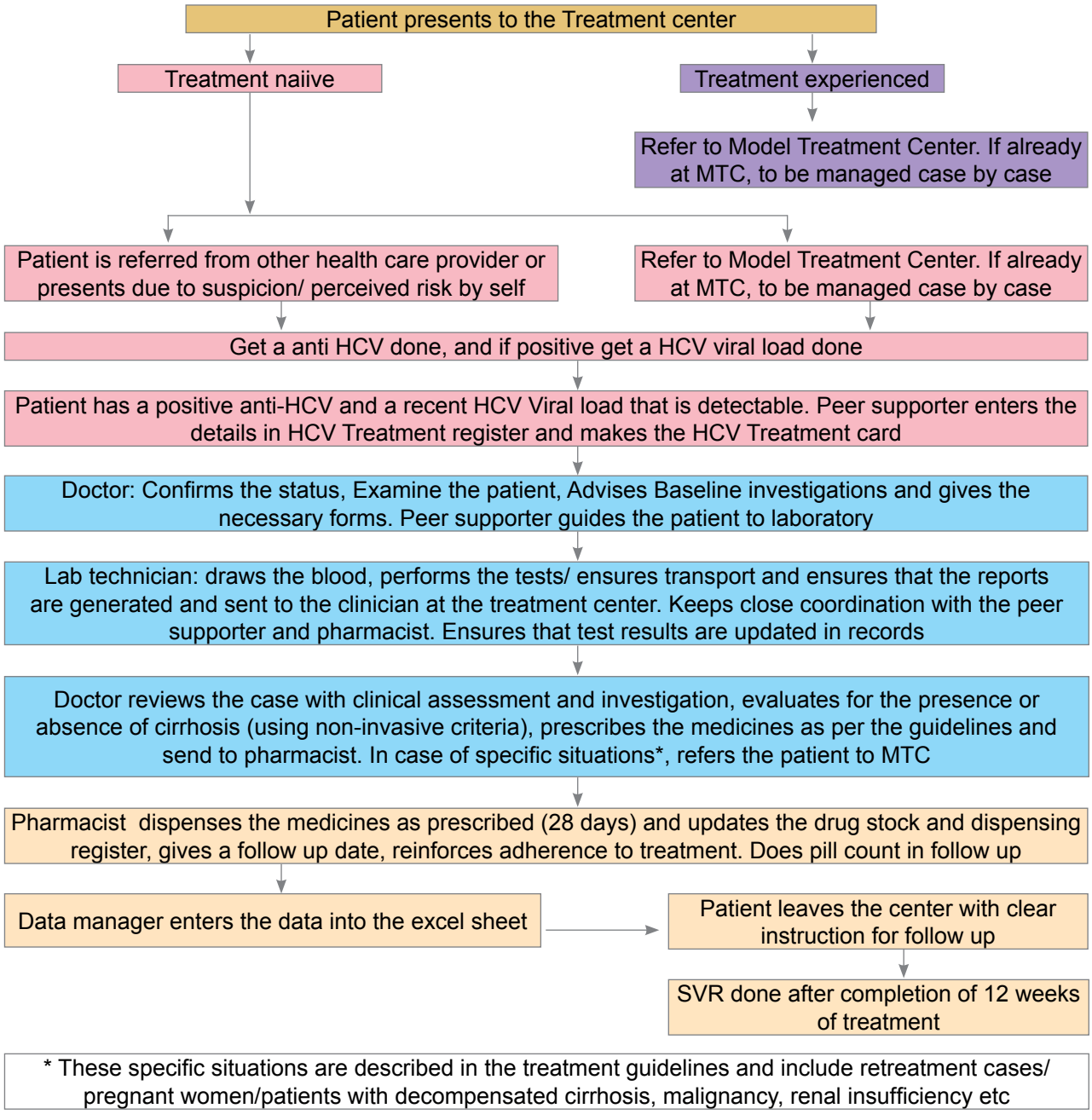


Fig.8: Patient Flow at the Treatment Centers

Every patient found anti HCV positive is registered in care for onward enrolment and has to be confirmed with a detectable HCV viral load for being eligible for treatment. Cases where anti-HCV is positive but no HCV viral RNA is detected do not have an active HCV infection and do not need treatment. Sequential entries for all the registration are to be maintained in the hepatitis C Treatment Register (Annexure 6). Once confirmed, the testing and treatment card for the patient is made. It is made in two sets: one to be kept at the center and other given to the patient. The center should take an address proof (Aadhaar card as UID is mandatory) from the patient. The confidentiality of the information provided by the patient is to be protected at all cost. Any divulgence of such information will have penal implication as per law for anyone responsible for such divulgence. The testing and treatment card will capture patient demographic information diagnosis and treatment details (Annexure 5).

The sections on name and demographic details are filled by the peer supporter while enrolling. The section on the clinical parameters and the laboratory investigations are filled by the treating doctor. The service provider signs the card at the respective places mentioned. The data entry operator maintains the digitize format of the same.

The details are also entered at each visit as and when they are advised. The follow up entries help in monitoring the disease progress, counseling of the patient for regular treatment, review of adherence of the patient to therapy. The drugs will be dispensed for 28 days. However, the pharmacist should ensure that the patient is given a follow-up day after 25 days. This will ensure that the patient does not land in a situation where s/he is out of drug stock. At every visit, the pharmacist should also count the remaining drugs (pill count) to have an idea if any doses have been missed. The patient should be instructed to bring the bottle of DAA with her/him at every visit so that the pharmacist can perform pill count, collect the old bottle and issue a new one.

The complicated cases, as defined in the technical guidelines, should be referred to the MTC. At the MTC, the drugs should be dispensed and once the patient is stable and the treating doctor is confident that the patient can be managed at the nearest treatment site, then the drug dispensation can be done at the nearest site. However, the patient should be referred back to MTC in case it is deemed necessary for appropriate management.

The uncomplicated cases, as defined in the technical guidelines, should be initiated treatment at the treatment center. Once the patient is stable and the treating doctor is confident that the patient can be managed at the nearest treatment site, then the drug dispensation can be done at the nearest site. However, the patient should be referred back in case it is deemed necessary for appropriate management.

Table 19: Summary of the key actions to be undertaken for patient management and record maintenance and the responsible person.

Visit Number	Key activity (but not limited to)	Responsible person
First visit and baseline, after confirmation of active hepatitis C infection	Ascertain Diagnosis of active Hepatitis C (anti HCV as well as HCV RNA)	Attending doctor
	Enter patient details in Hepatitis C Treatment Register and demographic details in treatment card	Peer Supporter
	Take a detailed history and examination	Attending Doctor
	Categorize presence/Absence of Cirrhosis and fill relevant section in Treatment card	Attending Doctor
	Select Regimen and start treatment	Attending Doctor
	Explain patient on adherence and follow up date	Peer supporter and pharmacist
	Dispense prescribed medicines	Pharmacist
	Get the baseline investigations done and furnish report to center	Doctor, Lab technician
Follow up visit	Educate on adherence and regular follow up	Doctor ,Peer supporter and pharmacist
	Dispense prescribed medicines	Pharmacist
	Check for any side effects	Attending Doctor
	Get any investigations needed as per technical guidelines, prescribe the medicines	Attending Doctor
	Update investigations in treatment card	Lab technician, Doctor
End of Treatment	Counsel on Treatment completion and need for SVR after 12 weeks of completing treatment	Doctor, peer supporter
	Recheck the contact details including phone	Peer supporter
For all visits	Update the record from the register and card to the excel based sheet	Data entry operator

Ideally, there should be no expiry at any center. However, in the event there is expiry of some medicines under the program, they should be discarded as per the hospital policy. The process should be documented with details on the quantity of drug, batch number and should be signed by three regular government employees including the nodal officer of the center. In case there is no institutional policy for discarding the medicines, from the central and state unit for viral hepatitis under NHM must be sought through a written communication clearly mentioning the absence of such institutional policy. Justifications and reasons for the same must be recorded in writing and kept for review by supervising authorities

Monitoring and Evaluation of the Treatment sites

The treatment sites and the laboratory will be reviewed regularly by the nodal officers for the site level day to day functioning. In addition, the district/state and National officials will also undertake supervisory site visits for supportive supervision and mentoring. The suggested frequency of the monitoring and mentoring visits are:

Table 20: Frequency of visit to the treatment sites.

Level	Frequency of visit
National	Annual
State	Quarterly
District	Once monthly

During the visits, the officials should try and provide on spot trouble shooting wherever needed, should provide clarification, assess the HR availability and required infrastructure, check the completeness and quality of records and reports submitted and randomly check the drug stocks (physical stocks vs the reported stocks)

Additionally, review meetings will be conducted that will provide a platform for experience sharing and review the progress.

Recording tools

The following recording tools are to be used under the program:

1. Site Feasibility Form: Annexure 4
2. Patient Treatment card : Annexure 5
    a. to be maintained at center
    b. Patient Treatment card (for the patient to retain)
3. Hepatitis C Treatment register: Annexure 6
4. Drug stock and dispensing register: Annexure 7a and 7b
5. Excel based tool for comprehensive record in the documents above.

Reporting tools

There will be a monthly report that each laboratory and treatment center will have to collate and submit to the state and national officials. The reporting will be in a standard format that will be developed by NCDC and initially, it will be paper / excel based and later there will be plan to digitalize the same.

The monthly reporting format is attached as Annexure 8

Information from the prescribed records and registers is compiled and used in filling up various monitoring reports which are forwarded to State Surveillance Officer (SSO) and other officials at state (NHM) and central level at central unit. Monthly reports from centres should be forwarded by 5thof every month to SSO and other state level officers by email. The reports at the state level should be compiled into a state report, the facility level reports have to be checked and feedback should be provided to centers.

The responsibility of information collection, reporting, management and analysis rests at four levels:

1. The **treatment sites** for creation and maintenance of patient records and files, operational information and reporting to state and NCDC through monthly reports and special studies

2. **State NHM, SSO and Program management unit** for analysis and consolidation of information, quality control, assessments, supportive supervision and guidance, feedback and dissemination of information to state-level stakeholders; for Programme Implementation Plans (PIPs)

3. **Central unit** for compilation of reports, analysis, evaluation and dissemination of information back to State NHM and to national and international stakeholders for advocacy and planning.

Responsibility of reporting, flow of information and frequency of reporting is summarized below:

Table 21: Flow of information and frequency of reporting.

Level	Reporting form	Person responsible for reporting	Reporting to	Frequency of Submission	Submission date by
Facility (Treatment)	Monthly Report of Center	Nodal Officer	SVHMU for Hepatitis and SSO	Monthly	5th of every month
State PMU	Consolidated report of the state	SSO / Program I/C	Central unit	Monthly	10th of every month

Independent evaluation of the program will also be planned and organized by National Program Management Unit. Key gaps identified during implementation of the program and innovative interventions would also be planned through operational research and will follow the established procedures under the guidance from the central unit.

Table 22: Monitoring Indicators for the Hepatitis C initiative.

S No	Indicator	Baseline	Target for Year 1	Source of reporting/data / verification and level
Input indicators				
1	Number of Treatment sites approved for Hepatitis C	0	15	Reports from centers
2	Are National guidelines and SOPs developed?	N/A	Yes	Program Documents; At NVHMU
3	Is there a standard Training curriculum developed?	N/A	Yes	Program Documents; At NVHMU
Process Indicators				
4	% of Treatment sites with 100% manpower as mentioned in the program	0	80%	Report from treatment center
5	Number of Persons receiving treatment for HCV in the country	NA	100,000	Analysis report at central unit
6	Number of functional Treatment sites in country who are managing Hepatitis C under the program	0	15	Monthly Reports from Treatment site
Outcome indicators				
	% of patients who achieved SVR 12 (Treatment completed)			

Annexure 1: Assessing severity of liver disease

A full assessment should include

- » Clinical evaluation for features of cirrhosis and evidence of decompensation, and
- » Measurement of serum bilirubin, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and prothrombin time; as well as full blood count, including platelet count.
- » Other routine investigations include ultrasonography and alpha-fetoprotein (AFP) measurement for periodic surveillance for HCC, and endoscopy for varices in persons with cirrhosis.

Liver enzymes: Aminotransferase levels may fluctuate with time, and single measurements of ALT and AST do not indicate disease stage. Usually, the ALT concentrations are higher than those of AST, but with disease progression to cirrhosis, the AST/ALT ratio may be reversed. Tests of liver synthetic function and/or portal hypertension include serum albumin, bilirubin, platelet count and prothrombin time. A progressive decline in serum albumin concentrations, rise in bilirubin and prolongation of the prothrombin time are characteristically observed as decompensated cirrhosis develops.

Liver biopsy: Liver biopsy has been used to ascertain the degree of necro-inflammation and fibrosis, and to help guide the decision to treat. There are several established methods of scoring histology and measuring activity (necroinflammation) separately from stage (fibrosis). However, limitations of biopsy include sampling error, subjectivity in reporting, high costs, the risks of bleeding and pneumothorax, discomfort to the patient, and the need for training and infrastructure. The pathological features of CHB on liver biopsy depend upon the stage of the disease, host immune response and degree of virus replication.

Table 23: Metavir staging for liver biopsy.

Metavir Stage	F0	F1	F2	F3	F4
Definition	No Fibrosis	Portal fibrosis without septa	Portal fibrosis with septa	Numerous septa without cirrhosis	Cirrhosis

Non-invasive tests (NITs): Though **liver biopsy remains the gold standard,** non-invasive methods for assessing the stage of liver disease are supplanting it due to the limited availability and accessibility to liver biopsy and have been validated in adults with CHB. Blood and serum markers for fibrosis, including APRI and FIB-4, or transient elastography (FibroScan) performed to rule out advanced fibrosis.

APRI (AST-to-platelet ratio index) and FIB 4 are recommended as the preferred non-invasive tests (NIT) to assess for the presence of cirrhosis (APRI score >2: FIB 4 >3.25 in adults). Transient elastography (e.g. FibroScan) may be the preferred NITs in settings where they are available and cost is not a major constraint.

APRI and FIB-4 can be readily calculated by the following formulae

APRI = * (AST/ULN) x 100) / platelet count (10^9/L)
FIB-4 = (age (yr) x AST (IU/L)) / (platelet count (10^9/L x [ALT (IU/L)1/2])

For APRI, ULN signifies the upper limit of normal for AST in the laboratory where these investigations were undertaken. For example, in a patient with an AST of 92 IU/L (where laboratory ULN for AST is 40 IU/L) and a platelet count of 80x109/L, the APRI would be: (92/40)x100/80 = 2.87. This value is >2 and is consistent with the presence of cirrhosis.

The optimal cut-off values for different NITs that correlate with specific stages of liver fibrosis have been derived and (in the case of APRI and FIB-4) also validated. APRI and FIB-4 use two cut-off points for diagnosing specific fibrosis stages, as the use of a single cut-off would result in suboptimal sensitivity and specificity. A high cut-off with high specificity (i.e. fewer false-positive results) is used to diagnose persons with fibrosis (i.e. greater than or equal to a particular stage [e.g. ≥F2]), and a low cut-off with high sensitivity (i.e. fewer false-negative results) to rule out the presence of a particular stage of fibrosis. Some persons will fall in the indeterminate range of test results (i.e. their score will be between the low and the high cut-off) and will need future re-testing and evaluation.

	APRI (low cut-off)	APRI (high cut-off)	FIB-4	Transient elastography (FibroScan)*
Cirrhosis (METAVIR F4)	1.0	2.0	-	>11–14 kPa
Significant fibrosis (METAVIR ≥F2)	0.5	1.5	1.45 (low) 3.25 (high)	>7–8.5 kPa

*There are no validated exact cut-offs for specific stages of fibrosis with FibroScan. This table presents the range of the most commonly used cut-offs for F4 and ≥F2 stages of fibrosis in CHB. A mean cut-off of 12.5 kPa may be used to diagnose cirrhosis and guide treatment decisions, after taking into account key limitations. (Reference : Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection., WHO, 2015)

Ascertaining the Degree of Cirrhosis

The degree of cirrhosis is important to be ascertained before the treatment is initiated. The Child–Pugh Score is a system for assessing the degree of liver disease, and classified patients as Class A, B, or C based on clinical and laboratory criteria. Those with Class C have the most severe liver disease. Some HCV regimens are contraindicated among persons with Child-Pugh Class B and C or decompensated cirrhosis.

The following table depicts the Child Pugh Score:

Table 24: The Child Pugh Score.

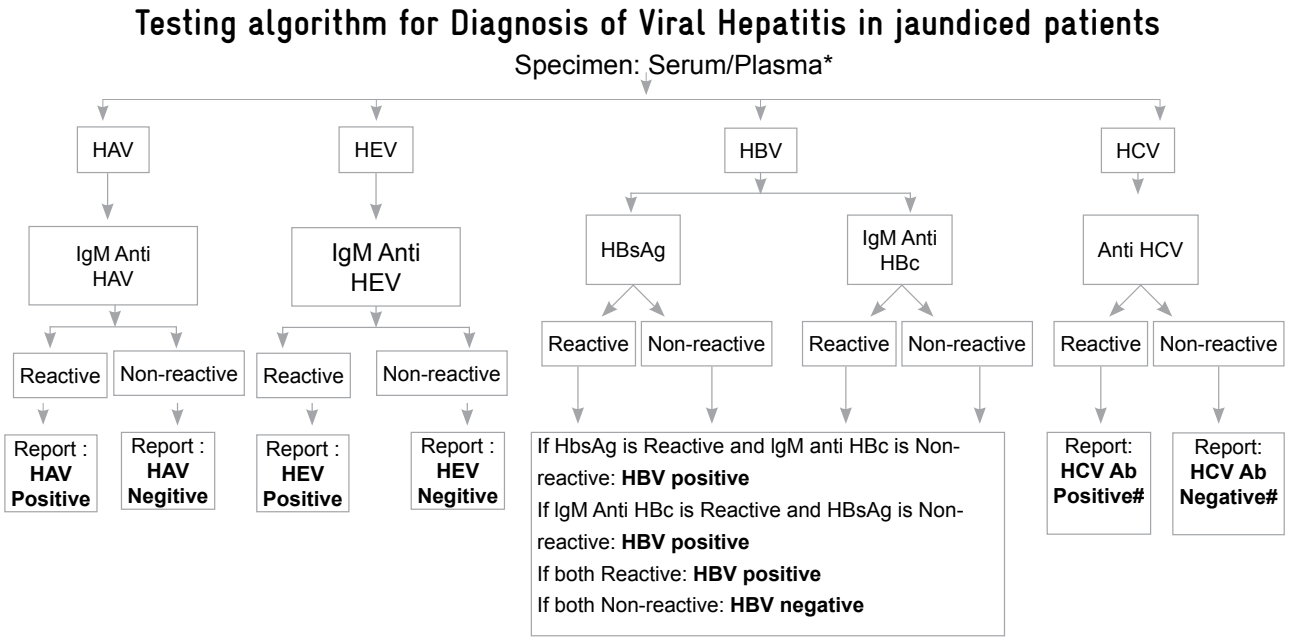
Points	1	2	3
Encephalopathy	None	Minimal (grade 1 or 2)	Advanced (grade 3 or 4)
Ascites	Absent	Controlled	Refractory
Total bilirubin (μmol/L) (mg/dL)	<34 (<2)	34–51 (2–3)	>51 (>3)
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (seconds) or PT-INR	<4 or <1.7	4–6 or 1.7–2.3	>6 or >2.3

Child–Pugh Class A: 5-6 points

Child–Pugh Class B: 7-9 points

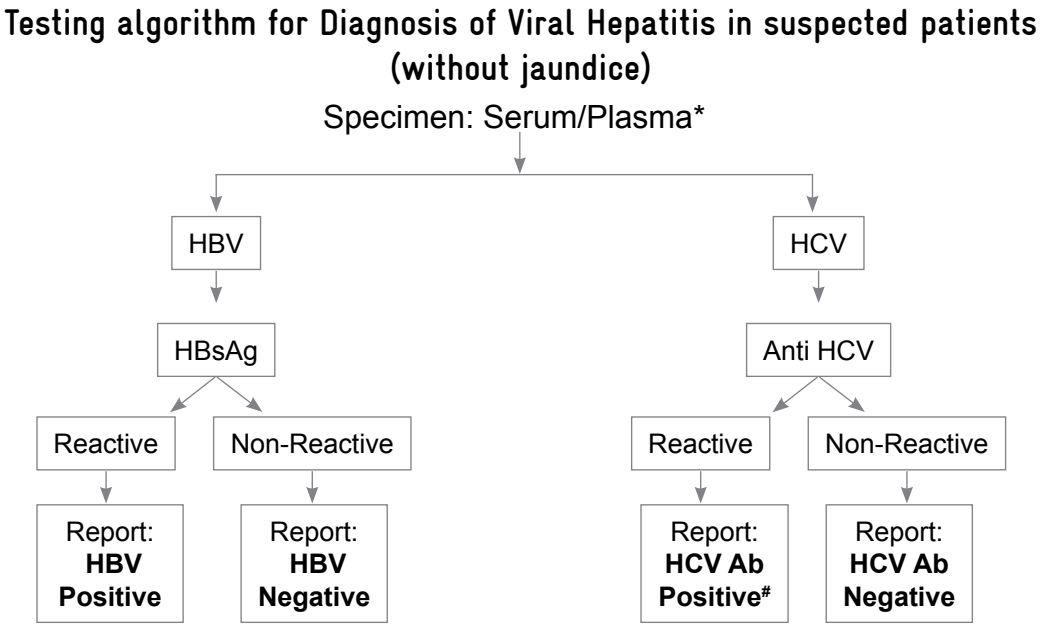
Child–Pugh Class C: 10-15 points

Annexure 2: Algorithm for the Laboratory Diagnosis of Viral Hepatitis



** Serum samples to be used for serological and biochemical testing, to be aliquoted and stored at -20⁰ C for retesting for quality purposes, dispute etc.*
#All HCV antibody (Ab) positive to be referred to treatment centre. Plasma samples to be collected and aliquoted in 3 sterile cryo vials. One vial to be used for quantitative hepatitis C RNA estimation and two archived at -80⁰ C for quality assurance

Fig.9: Testing algorithm for Diagnosis of Viral Hepatitis in jaundiced patients



** Serum samples to be used for serological and biochemical testing, to be aliquoted and stored at -200 C for retesting for quality purposes, dispute etc.*
#All HCV antibody (Ab) positive to be referred to treatment centre. Plasma samples to be collected and aliquoted in 3 sterile cryo vials. One vial to be used for quantitative hepatitis C RNA estimation and two archived at -800 C for quality assurance

Fig.10: Testing algorithm for Diagnosis of Viral Hepatitis in suspected patients (without jaundice)

Annexure -3: Drug interactions between DAA and some commonly prescribed medications

Table 25: Drug interactions between DAA and some commonly prescribed medications.

	Sofosbuvir	Daclatasvir	Sofosbuvir/ Ledispavir	Sofosbuvir/ Valpatasvir
Immunosuppressants				
Azathioprine	No interaction	No interaction	No interaction	No interaction
Cyclosporine	No interaction	No interaction	No interaction	No interaction
Everolimus	No interaction	Potential interaction	Potential interaction	Potential interaction
Mycophenolate	No interaction	No interaction	No interaction	No interaction
Sirolimus	No interaction	No interaction	No interaction	No interaction
Tacrolimus	No interaction	No interaction	No interaction	No interaction
Antiretrovirals				
Zidovudine	No interaction	No interaction	No interaction	No interaction
Tenofovir	No interaction	No interaction	Potential interaction	Potential interaction
Lamivudine	No interaction	No interaction	No interaction	No interaction
Efavirenz	No interaction	Potential interaction*	Potential interaction	Significant interaction
Nevirapine	No interaction	Potential interaction	No interaction	Significant interaction
Abacavir	No interaction	No interaction	No interaction	No interaction
Protease inhibitors	No interaction	No interaction	No interaction	No interaction
Lipid lowering drugs				
Statins	No interaction	Potential interaction	Potential interaction	Potential interaction
Fibrates	No interaction	No interaction	Potential interaction	Potential interaction
Ezetimibe	No interaction	No interaction	No interaction	No interaction
Cardiovascular drugs				
Amiodarone	Significant interaction	Significant interaction	Significant interaction	Significant interaction
Digoxin	No interaction	Potential interaction	Potential interaction	Potential interaction
Clopidogrel	No interaction	Potential interaction	No interaction	No interaction
Dabigatran	No interaction	Potential interaction	Potential interaction	Potential interaction
Atenolol	No interaction	No interaction	No interaction	No interaction
Propranolol	No interaction	No interaction	No interaction	No interaction
Carvidolol	Potential interaction	Potential interaction	Potential interaction	Potential interaction
Amlodipine	No interaction	Potential interaction	Potential interaction	Potential interaction
Diltiazem	No interaction	Potential interaction	Potential interaction	Potential interaction
Nifedipine	No interaction	Potential interaction	No interaction	No interaction
Enalapril	No interaction	No interaction	No interaction	No interaction

Annexure 4: Feasibility Visit for Setting Hepatitis Treatment Center

Checklist for Feasibility of Hepatitis Treatment Center			
1	Name of the town / District/ City:		
2	Type of Hospital: (Medical College/ District Hospital / Other tertiary care)		
3	Name of the Medical Superintendent or IC of the institution		
4	Names of the identified Nodal officer by Institute		
5	Date of Feasibility Visit		
6	Members of the Visiting Team		
a			
b			
c			
d			
7	Complete postal address of the Hospital with Pin Code		
8	Contact details of the Nodal person (mobile and email)		
	BACKGROUND INFORMATION		
1	Is the Institution willing to set up a center for hepatitis treatment	Yes	No
2	Is the In-charge keen on establishing services?	Yes	No
a	Willing to allocate necessary space	Yes	No
b	Willing to have nodal person for treatment and lab services	Yes	No
c	Integrate the functioning and follow the National guidelines and protocols , including recording and reporting	Yes	No
3	What is the annual OPD of the hospital		
4	Is there super-speciality(Gastroenterology/ Hepatology)	Yes	No
5	How many cases of acute hepatitis are seen annually (explore last years report)		
6	How many cases of hepatitis B and C are seeking care (explore previous reports)		
7	Is there a blood bank in institute? What is sero-positivity for hepatitis B and hepatitis C in last three years (record year wise)	Yes	No
8	If this is a district hospital, where are patients referred or usually go for complicated cases?		
9	Do you have a HIV related service?		
a	ICTC	Yes	No
b	ART center	Yes	No
c	Opioid Substitution Center	Yes	No
d	Involvement with Prison	Yes	No
8	Is the institution implementing any other program under NHM? Please mention name(s)	Yes	No
	INFRASTRUCTURE		
1	Location of the proposed centre (is it in vicinity to OPD services)	Yes	No
	Is there an ICU	Yes	No
2	Number of rooms		
a	Doctors	Yes	No
b	Pharmacist	Yes	No
c	Data Entry Operators	Yes	No
d	Drug Storage & Pharmacist	Yes	No
e	Lab Technician	Yes	No
f	Peer supporter	Yes	No
3	Is institution willing to provide necessary furniture (chairs, tables, Almirah etc)	Yes	No
4	Will the center have access to internet	Yes	No

HUMAN RESOURCES			
1	Does the institution have the required capacity to manage chronic hepatitis Cases?	Yes	No
a	Gastroenterologist/Hepatologist	Yes	No
c	Physician (Internal Medicine)	Yes	No
d	Pediatrician	Yes	No
e	Microbiologist	Yes	No
f	Pathologist	Yes	No
g	Obstetrician	Yes	No
h	Others (Mention)		
LABORATORY CAPACITY / INVESTIGATIONS FACILITY			
1	Does the institute have a capacity to do HCV RNA	Yes	No
2	Does the Institution have facility to do HCV Screening test (immunoassay - please specify)	Yes	No
3	Are the following investigation routinely available	Yes	No
a	Complete Blood Count / Hemogram	Yes	No
b	Renal Function test	Yes	No
c	Liver Function Test (please ask for each test)	Yes	No
d	Blood Sugar	Yes	No
e	INR	Yes	No
f	Platelet count	Yes	No
g	Pregnancy Test	Yes	No
h	X Ray	Yes	No
I	Ultra Sound abdomen with Doppler	Yes	No
J	Fibroscan	Yes	No
k	CT scan		
l	MRI		
m	Endoscopy		
n	Liver Biopsy	Yes	No
o	Others		

S No	Key Issues Identified	Follow-up Actions suggested

FINAL RECOMMENDATION OF THE TEAM (Please tick)	
Recommended to Select Site for Opening Hepatitis Treatment Site	
Not Recommended to Select Site for Opening Hepatitis Treatment Site	

Signature of the Feasibility Visit Team: 1.....

2.....

3.....

4.....

Annexure 5: Patient Testing & Treatment Card

PATIENT TESTING & TREATMENT CARD

Registration Details

Hospital ID Number

Patient ID under program

Date of starting DAA : …./……./…….

Basic Demographic Information

Name : …… Age : …… Gender : M F TG

Address

Contact number

Aadhaar Number

Date of Anti-HCV testing Rapid ELISA Other

Date of HCV Viral Load Result

Previous Exposure to Hepatitis C Treatment Yes No

If yes, details

DAA Interferon

Details

Is there Cirrhosis at Registration	No	Compensated	Decompensated

Criteria for evaluating cirrhosis (At least one)

Ultrasound …/……../…… :Date

Fibroscan …… (LSM Value (in kPa …/……../…… :Date

APRI* ……Score …… Platelet Count ……AST …/……../…… :Date

FIB-4* ……ALT …… AST …… Age /……../…… :Date

……Score …… Platelet Count

If Decompensated cirrhosis, select basis

CP Score Variceal Bleed Ascites Encephalopathy

Regimen Prescribed	Duration of Treatment	
	12 weeks	24 weeks

Patient not treated at this center but transferred to higher center

Date ……..Place……

*mandatory. The center must do both APRI and FIB-4 scoring.

Baseline and Follow Up Investigations										
S No	Date of Visit	Hemoglobin	Platelet Count	ALT	AST	S. Bilirubin	S Albumin	INR	HCV Viral Load	Other-1 (USGetc)
1										
2										
3										
4										
5										

Follow Up Visits									
Visit Number	Date of Visit	Pills Left	Any New Complaints or side effects	Any other medications	Any Remark	Next Follow up date	Signature of Doctor	Signature of Pharmacist	Patient's Signature/ Thumb Impression
1									
2									
3									
4									
5									

Treatment Outcomes						
SVR Achieved (Date)	Failure (write HCV RNA quantity)	Relapse		Lost to Follow up	Death	Other

Annexure 6: Hepatitis C Treatment Register

Month: **Year:**

	1	2	3	4	5			6	7	8		9	10	11	12 Follow up Date and status (Months)						13	14	15	16	17
S. No.	Registration Number	Name of Patient	Age	Sex M/F/ TG	Patient's address	District	Contact number	Guardian / Care Giver name and contact number, if any	Prior treatment history	Date of ANTI-HCV testing	Date of HCV RNA testing*	Pre Treatment HCV RNA Level	Regimen started * I, II, III	Date of start of treatment	1	2	3	4	5	6	Date of completion of Treatment	Due Date of SVR 12	SVR Done on	Result of SVR	Remarks, if any**
1									☐ Y ☐ N																
2									☐ Y ☐ N																
3									☐ Y ☐ N																

*HCV RNA is done only if ANTI-HCV is positive. In case HCV RNA is not detectable, please put a line across the rest of the fields from 10-16

** In the remarks, please mention the status of patient (died, lost to follow up, stop treatment due to medical reasons, transferred out, referred to higher center). For any of these, also mention date.

Annexure 7a: DAA Stock register

Important: Separate page to be maintained for each drug.

Summary should be filled on the last day of the month.

Name of the drug / Regimen _____

Date	A	B				C	D	E	F	Remarks
	Opening Stock	Stock Received				Stock transferred out officially	Stock dispensed (consumption)	Stock expired / discarded	Balance stock	
		Quantity	batch number	Expiry date	Manufacturing date					

Monthly summary:

Stock at the start of the month / Opening Stock (A):

Stock received during the month (B):

Stock transferred out officially during the month (C):

Reusable stock returned during the month (D):

Stock dispensed (consumed) during the month (E):

Stock expired/discarded during the month (F)

Stock at the end of the month (F) = (A+B) – (C+D+E):

Annexure 7b: Drug Dispensation Register

Important: Separate page to be maintained for each day. Date: _____/_____/_____

Sl. No.	Patient Name	Patient Registration Number	Number of Tablets Dispensed			Patient Signature
			Regimen 1	Regimen 2	Regimen 3	
Total tablets Dispensed						

* Specify other drugs used.

Signature of the pharmacist/drug dispenser: _____

Annexure 8: Monthly reporting format

1.Name of Centre _____ 2. Code Number _____

3. Name of the District _____

4. Name of the State _____

5. Name of the Site Incharge _____

6. Report for the period [ ] [ ]
month year

7. Number of Hepatitis C infected people seeking care at the treatment center (Registering in Care)	adult male	adult female	children <18 years	total
7.1 Cumulative number of persons registered in Hepatitis C care at the beginning of this month				
7.2 Number of new persons registered in during this month				
7.3 Cumulative number of persons registered at the end of this month = 7.1 + 7.2				
8. Initiation of Treatment	**adult male**	**adult female**	**children <18years**	**total**
8.1 Cumulative number of patients ever started on Treatment (Number at the beginning of this month)				
8.2 Number of new patients started on Treatment during this month				
8.3 Number of patients on Treatment "transferred in" during this month				
8.4 Cumulative number of patients ever received Treatment (Number at the end of this month) = 8.1+ 8.2 + 8.3				
9. Treatment status (at the end of the month) out of all patients ever started on treatment (8.4)	**adult male**	**adult female**	**children <18years**	**total**
9.1 Cumulative number of patients who have completed treatment				
9.2 Cumulative number of patients who are currently taking treatment (9.2=9.1-(9.3+9.4+9.5+9.7+9.8)				
9.3 Cumulative number of patients who "transferred out"				
9.4 The number of all patients whose treatment status in this month is “stopped treatment” due to medical reasons				
9.5 Cumulative Number of patients who are lost to follow-up (LFU)				
9.6 The number of patients who did not return to the (Defaulter) and missed their doses in this month				
9.7 Total number of patients Referred to Higher center for further management				
9.8 number of deaths reported				
10. Sustained Virologic Response	**adult male**	**adult female**	**children <14 years**	**total**
10.1 Cumulative number of patients who are eligible for SVR (i.e have completed 12 weeks after end of treatment)have completed 12 weeks treatment (Out of 9.1)				
10.2 Cumulative number of patients who have undergone SVR out of the eligible patient (out of 10.1)				
10.3 Cumulative number of undetectable HCV RNA (out of 10.2)				

11. REGIMENS AT THE END OF THE MONTH		
Regimen	**a) Number of ADULTS alive and on treatment**	**b) Number of CHILDREN alive and on treatment**
Others		
Total number of patients		

12. DRUG STOCKS								
12.1 Drug Stock Status (use separate sheet if required)								
Generic Drug Name	a) Opening stock	b) Stock received during month	Add expiry date	d) Consumption during the month	e) Expiry during the month	f) stock on last day of the month	g) Amt. reqst for 3 mo. based on existing stock	h) Issues / Comments
Other								

12.2 Was there a stock-out of DAA this month? Yes ☐ No ☐

Signature of Nodal Officer: Date:

Addendum for Lost to Follow up		
S No	Reason for lost to follow up	Number of Patients
Total*		

*Total should match 9.5

Addendum for Deaths		
S No	Reason for Death	Number of Patients
1	Liver related causes	
2	Due to causes not related to liver disease	
Total*		

*Total should match 9.8

Guidance on Monthly report:

1. Section 7 captures all the registrations at the treatment center. It will come from the hepatitis C Treatment Register.
2. Out of all the registrations, there will be a significant proportion that will have undetectable viral load and will not need treatment. The section 8 captures the details on those who were started treatment. This will also come from hepatitis C Treatment Register.
3. Section 9.3 to 9.8 will be taken from Remarks column of the hepatitis C Treatment Register
4. Section 11 will come from hepatitis C Treatment Register or from drug dispensing register
5. Section 12 will come from drug stocks register

Annexure 9: Consent form

INDIVIDUAL'S CONSENT FORM FOR TESTING AND MANAGEMENT OF VIRAL HEPATITIS

I, _____ (full name), daughter/son of _____ _____ (full name) age _____ resident of (address) _____ _____ have read/have been read over and explained (circle appropriate) the accompanying guidance and have understood the information provided to me related to the investigations and proposed management required (if available)

I understand that the purpose of these tests is to:

- Establish my Viral Hepatitis status,
- Evaluate the presence of liver disease which may be associated with Hepatitis infection.
- I can allow the program to archive my specimen for further molecular testing related to viral hepatitis only in the interest of public health, provided that any information/data/detail relating to or emanating from my molecular sample shall not be divulged to any third party under any circumstances. A breach of this condition shall automatically forfeit my consent and the program's right to retain such information and shall further render them liable to penal action and compensation.

I understand that if a diagnosis of Chronic Hepatitis B/C is confirmed, I will be offered treatment as per the provisions in the initiative. I give my consent to the proposed management offered by the initiative subject to strict protection of my information.

Patient Signature: _____ DATE: _____

Staff member name obtaining consent: _____

Staff signature: _____ DATE: _____

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LIST OF CONTRIBUTORS

Dr R. K. Dhiman - Gastroenterologist, PGIMER, Chandigarh

Dr Rakesh Aggarwal - Gastroenterologist, SGPGI, Lucknow

Dr C. E. Eapen - Hepatologist, CMC, Vellore

Dr Samir R. Shah - Hepatologist, Global Hospital, Mumbai

Dr Narayanasamy K - Hepatologist, MMC, Chennai

Dr Praveen Malhotra - Gastroenterologist, PGIMS, Rohtak

Dr Mamta Manglani - Paediatric hemato-oncologist, LTMMC & GH, Sion, Mumbai

Dr Srijaya S - Gastroenterologist, GMC, Trivandrum

Dr T. Jiten Singh - Physician, RIMS, Imphal

Dr Mohd. Shaukat - Advisor, Dte GHS, MoHFW, Delhi

Mr Mehmood Pracha - Senior Advocate, Delhi

Dr Sujeet Kumar Singh - Director, NCDC, Delhi

Dr R. S. Gupta - DDG CST, NACO, Delhi

Dr Sandhya Kabra - Additional Director, NCDC, Delhi

Mr Sella Senthilm - Assistant Drug Controller, Office of DCG(I), Delhi

Mr Abou Mere - Representative, Community Organisation

Dr Aparajita Ravi Sondh - State Surveillance Officer, IDSP, Haryana

Dr Nicole Seguy - CD team leader, WHO (India)

Dr Vimlesh Purohit - NPO (HIV & Hepatitis), WHO (India)

Dr Rekha Jain – Consultant, Delhi

Dr Partha Rakshit - Deputy Director, NCDC, Delhi

Dr Hema Gogia - Deputy Assistant Director, NCDC, Delhi

Dr Preeti Madan - EIS Officer Cohort 5, NCDC, Delhi