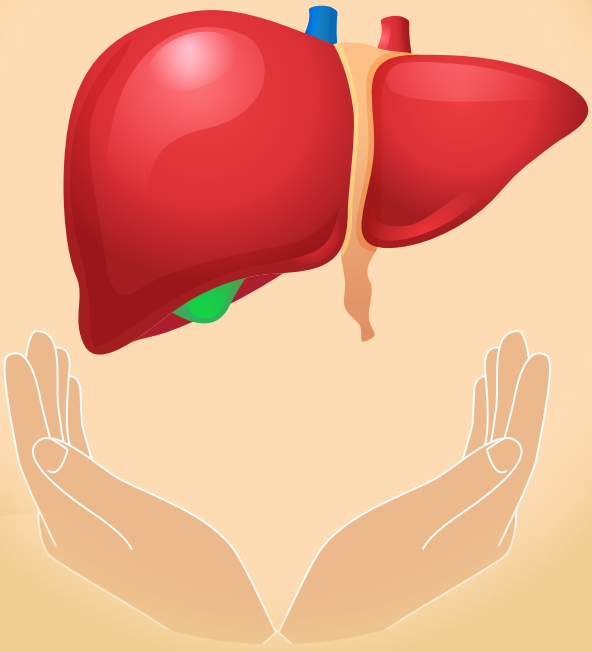
सत्यमेव जयते
Ministry of Health and Family Welfare
Government of India

NATIONAL HEALTH MISSION
राष्ट्रीय स्वास्थ्य मिशन

Technical Guidelines for

Diagnosis & management of Hepatitis B



2019

Technical Guidelines for

Diagnosis & management of Hepatitis B

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दिनांक/Dated 19 February, 2019

FOREWORD

The National Viral Hepatitis Control Programme, a new initiative under the National Health Mission, marks the beginning of the nation's journey to control Viral Hepatitis and thereby reducing mortality and morbidity attributed to it. It is envisioned that this programme wilt reach large number of persons possible harboring the infection.

This document provides implementation strategies for treatment of Hepatitis B on how to reverse this alarming trend of Viral Hepatitis B, describing a number of high-impact interventions and opportunities for their scaled-up implementation.

The recommendations in these guidelines promote the use of simple, non-invasive diagnostic tests to assess the stage of tiver disease and eligibility for treatment; prioritize treatment for those with most advanced liver disease and at greatest risk of mortality and recommend the preferred use of nucleos(t) ide with a high barrier to drug resistance for first and second-tine treatment.

I hope that these Technical and Operational Guidelines with inputs from stalwarts from across the country will enable effective roll out of Hepatitis B diagnosis and management in India. I wish National Viral Hepatitis Control Programme all success.

(S. Venkatesh)

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Preface

Viral hepatitis is a public health problem in India. Hepatitis A and E, which are water and foodbome infections, are often the cause for sporadic cases or outbreaks of viral hepatitis in India. Hepatitis B and C infections can lead to chronicity and thereafter sequelae like cirrhosis and hepatocellular carcinoma, which account for majority of hepatitis B and C related deaths.

Hepatitis B virus (HBV) infection is a significant health problem in India. Since India has one-fifth of the world's population, it possibly accounts for a large proportion of the worldwide HBV burden. It is estimated that 15 - 25% of these chronic hepatitis B cases are likely to suffer from cirrhosis and liver cancer and may die prematurely.

The Government of India launched National Viral Hepatitis Control Program (NVHCP) on the World Hepatitis Day (28th July 2018) with provision of free diagnosis and treatment for viral hepatitis through the National Health Mission.

Horizontal transmission in childhood and Mother to Child transmission of HBV are considered to be the most common mode of transmission. However, the HBV infection is both preventable by a very effective vaccine as well as treatable with oral drugs. The hepatitis B vaccine has been incorporated in the current Universal Immunization Program; the first dose is given as early as possible after birth, preferably within 24 hours for preventing perinatal HBV transmission.

The NVHCP entails free diagnostics and treatment of chronic hepatitis B and it is important to have standard diagnostic algorithm and treatment protocols that are followed across the country. These guidelines provide this standardization in a public health approach. This guidance d(])cument is the collective effort of the members of Technical Resource Group on care and support for viral hepatitis, with representation of clinicians, laboratorians and program managers from across the country, representing different sectors (government, private, academic institutes, community members, development partners). The group has taken into considerations the latest available evidence and global guidelines, and adapted them to the Indian context.

I hope; these guidelines will offer the needed technical guidance for delivering quality treatment and services for successful implementation of the program.

(RK Dhiman)

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ACRONYMS

AFP	Alfa Feto Protein
AIDS	Acquired Immuno Deficiency Syndrome
ALF	Acute Liver Failure
ALP	Alkaline Phosphatase
ALT	Alanine amino transferase
Anti-HBc	Antibody to Hepatitis B core antigen
Anti-HBe	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
NPMU	Non Steroidal Anti Inflammatory Drug
NSAID	National Viral Hepatitis Management Unit
NVP	Nevirapine
OP	Out Patient
OST	Opioid Substitution Therapy
PIP	Program Implementation Plan
PCR	Polymerase Chain Reaction
PEG	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
SPMU	State Surveillance Officer
SSO	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

CONTENTS

Background

Global

Epidemiology of Viral Hepatitis: Viral hepatitis is now recognized as a major public health challenge that requires an urgent response. Viral Hepatitis caused 1.34 million deaths in 2015, a number comparable to deaths caused by tuberculosis and higher than those caused by HIV. (1) It is estimated that worldwide, Hepatitis A Virus (HAV) infections caused approximately 11,000 deaths in 2015 (accounting for 0.8% of the mortality from viral hepatitis). (2) It is estimated that 325 million people worldwide are living with chronic HBV or HCV infection. Approximately, 1.75 million people were estimated to be newly infected with HCV in 2015, increasing the total number of people living with Hepatitis C to 71 million. (1) Every year, there are an estimated 20 million Hepatitis E Virus (HEV) infections worldwide leading to an estimated 3.3 million symptomatic cases of acute hepatitis E. It is estimated that Hepatitis E caused 44,000 deaths in 2015 (accounting for 3.3% of mortality due to viral hepatitis). (1)

India

Viral hepatitis is increasingly being recognized as a public health problem in India. HAV and 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 accounts for 10-40% of acute hepatitis and 15-45% of acute liver failure. (3)

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%. (3) Based on some regional level studies, it is estimated that in India, approximately 40 million people are chronically infected with Hepatitis B and 6-12 million people with Hepatitis C. (4) Chronic HBV infection accounts for 40% of Hepato-cellular Carcinoma (HCC) and 20-30% cases of cirrhosis in India. (3) Chronic HCV infection accounts for 12-32% of HCC and 12-20% of cirrhosis. (3) Population based syndromic and health facility based surveillance of viral hepatitis is mandated under the Integrated Disease Surveillance Programme (IDSP). A systematic review of available information from published studies and from large unpublished reliable datasets, to assess the prevalence of chronic HCV infection in the Indian population has recently been done to assess the prevalence of overall HCV infections, and by age, sex, risk factors and place in the country. This meta-analysis data estimated that India (current population approx. 1.3 billion) has 5.2-13 million anti-HCV positive persons. As the data on HCV viremia amongst the anti-HCV positive persons were not available, data from elsewhere was used to estimate that India has about 3 million to 9 million persons with active HCV infections. (5) All key and bridge population groups under the NACP for HIV infections are especially vulnerable to viral hepatitis infections too. These include groups like recipients of multiple blood/blood products transfusion, patients on hemodialysis, People Who Inject Drugs, MSM, female sex workers, sexual partners of infected people, prisoners, migrants and truckers etc. Also, high risk population for viral hepatitis include close first degree relatives and family members: mother, siblings, spouse and children, of persons affected with viral hepatitis. The other populations for both hepatitis B and C include those who have received blood or blood products especially before implementation of hepatitis C testing at a large scale in India; i.e. before 2001. Such population groups shall be treated as key populations or high-risk groups (HRGs) under the National Viral Hepatitis Control Program. Hepatitis B and C infections have long gestation periods before the disease progresses to advanced stages resulting in liver cirrhosis and liver cancer, resulting in mortality if treatment is not provided in time. Intervention to prevent advancement of the disease is particularly more challenging because during the gestation period, the disease does not manifest itself through any specific symptoms. Recent advances in diagnostics have now made it possible to diagnose people carrying viral hepatitis infections through point-of-care rapid diagnostic kits. Several new technologies and platforms are also now available for conducting confirmatory tests through viral load testing. Reliable treatment of viral hepatitis B & C is now possible with new medicines. Diagnostics and treatment services have so far been available only through the private sector in India. In absence of a public health initiative, such incidence of disease leads to high out of pocket expenditure. The Government of India has, hence, launched National Viral Hepatitis

Control Program (NVHCP) for prevention and control of viral hepatitis, with a view to provide free of charge screening, diagnosis, treatment & counseling services to all, and specially to people belonging to high-risk groups.

Introduction to the programme

India is committed to progressively move towards elimination of viral hepatitis B and C and control other virus induced hepatitis. This is in line with our global commitment towards achieving Sustainable development goal (SDG) goal 3; target 3.3 which aims to "By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water borne diseases and other communicable diseases" The Government of India is a signatory to the resolution 69.22 endorsed in the WHO Global Health Sector Strategy on Viral Hepatitis 2016-2021 at 69th WHA towards ending viral hepatitis by 2030. In India, the estimated burden of hepatitis is very high, necessitating focus on prevention and control measures to mitigate morbidity and mortality arising out of hepatitis. (6) There are several components that exist in the different programs of Government of India, such as Immunization for Hepatitis B; Swachh Bharat Mission; Safety of blood and blood products; Safe drinking water and sanitation, which are directly or indirectly related to the response to viral hepatitis. The sequelae of chronic hepatitis which includes cirrhosis and HCC poses long term burden on the health system. A recent cost benefit analysis of treating hepatitis C infection demonstrated that curing the HCV with 12-24 weeks of directly acting antivirals (DAAs) is substantially more cost effective than managing the sequelae and has better health outcomes. (7) Unsafe injection practices during health care or otherwise, remain a risk and have potential to transmit the HBV and HCV infection. Use of Reuse Prevention (RUP) syringes is a critical intervention to interrupt the chain of such transmission. India manufactures RUPs for injection in therapeutic care and mandating its use in public and private sector offers a new opportunity to address unsafe injections.

With the view to address the existing gaps in current programs, National Viral Hepatitis Control Program (NVHCP) was launched in July, 2018 on the occasion of the World Hepatitis Day, with the focus to integrate the existing programs towards awareness, prevention and treatment for viral hepatitis (A, B, C, D & E). The program proposes to address management of all types of viral hepatitis. The advent of newer and safe drugs for treatment of Hepatitis C ensuring cure makes it easier to combat it. Similarly, the available drugs for hepatitis B treatment are quite potent and safe and keep the virus suppressed for prolonged periods, reducing the risk of cirrhosis and liver cancer. The technical guideline on diagnosis and management of viral hepatitis with focus on management of Hepatitis C were published in 2018. The current guidelines are focusing on diagnosis and management of Hepatitis B along with the operational component of implementing the same under the program.

Aim

1. Combat hepatitis and achieve country wide elimination of Hepatitis C by 2030
2. Achieve significant reduction in the infected population, morbidity and mortality associated with Hepatitis B and C viz. Cirrhosis and Hepato-cellular carcinoma (liver cancer)
3. Reduce the risk, morbidity and mortality due to Hepatitis A and E.

Key objectives:

1. Enhance community awareness on hepatitis and lay stress on preventive measures among general population especially high-risk groups and in hotspots.
2. Provide early diagnosis and management of viral hepatitis at all levels of healthcare
3. Develop standard diagnostic and treatment protocols for management of viral hepatitis and its complications.

4. Strengthen the existing infrastructure facilities, build capacities of existing human resource and raise additional human resources, where required, for providing comprehensive services for management of viral hepatitis and its complications in all districts of the country.
5. Develop linkages with the existing National programmes towards awareness, prevention, diagnosis and treatment for viral hepatitis.
6. Develop a web-based "Viral Hepatitis Information and Management System" to maintain a registry of persons affected with viral hepatitis and its sequelae.

Components

The key components include:

1. Preventive component: this remains the cornerstone of the NVHCP. It will include

a. Awareness generation
b. Immunization of Hepatitis B (birth dose, high risk groups, health care workers)
c. Safety of blood and blood products d. Injection safety, safe socio-cultural practices
d. Safe drinking water, hygiene and sanitary toilets

2. Diagnosis and treatment:

a. Screening of pregnant women for HBsAg to be done in areas where institutional deliveries are < 80% to ensure their referral for institutional delivery for birth dose Hepatitis B vaccination.
b. Free screening, diagnosis and treatment for both hepatitis B and C would be made available at all levels of health care in a phased manner.
c. Provision of linkages, including with private sector and not for profit institutions, for diagnosis and treatment.
d. Engagement with community/peer support to enhance and ensure adherence to treatment and demand generation.

3. Monitoring and evaluation, surveillance and research effective linkages to the surveillance system would be established and operational research would be undertaken through Department of Health Research (DHR). Standardised M&E framework would be developed and an online web based system established.

4. Training and capacity building:

This would be a continuous process and will be supported by NCDC, ILBS and state tertiary care institutes and coordinated by NVHCP. The hepatitis induction and update programs for all level of health care workers would be made available using both, the traditional cascade model of training through master trainers and various platforms available for enabling electronic, e-learning and e-courses.

Activities

The main activities of the program would include the following:

Program management			
Prevention Awareness generation & behaviour change communication Immunization for hepatitis B – birth dose, high risk groups, health care workers Provision of safe blood and blood products Injection Safety by Use of only RUP syringes in all government HCFs Safe socio-cultural practices	Diagnosis and Treatment Diagnoisis/Screening – serological tests Confirmation – molecular tests (where required) Treatment of uncomplicated cases – at treatment centres, drug dispensation upto HWC Treatment of complicated cases at model treatment centres Laboratory capacity building and quality assurance Referral and linkages	Monitoring & Evaluation Surveillance & Research Hepatitis information and management portal Standardized M&E framework and web based portal Indicator based monitoring of the program Surveillance of acute viral hepatitis, chronic viral hepatitis and it's sequelae Review Meetings External Reviews	Training and Capacity Building Standardized training modules for all cadres of health care workers & program managers. Digital & conventional training program E learning Induction & refresher training Facilitation through tele-consulting

Targets for the NVHCP

The National Viral Hepatitis Control program has the following cumulative physical targets for the first three years:

1. Program Management:

a. National Viral Hepatitis Management Unit (NVHMU): To establish a NVHMU in the first year.

b. State Viral Hepatitis Management Unit (SVHMU) - To establish a State Viral Hepatitis Management Unit in the first year within existing state health governance structure i.e. State Health Society. This would be structured on similar lines as the NVHMU.

2. Prevention:

a. Develop and implement the protocol for ante-natal screening of pregnant women for Hepatitis B; and start screening in the first year.

b. Develop and implement tracking mechanism to ensure institutional delivery for all Hepatitis B carrier pregnant women.

c. Increase Hepatitis B zero dose immunization to over 90%

d. Implement safe injection practices in government systems immediately

e. Blood safety targets

f. To develop institutional mechanism for periodic testing of drinking water sources in coordination with Department of Drinking Water and Sanitation (DoDWS).

g. Improved IEC for prevention and checking transmission

3. Diagnosis & treatment

A. Diagnosis:

a. Set up the National Reference Laboratory by the end of first year.

b. Establish State level reference laboratories in each state by the end of first year.

c. Develop District Diagnostics centres with viral load testing capabilities by the end of first year.

d. Start first line diagnosis through Rapid Diagnostic Kits at all levels by the end of first year.

e. Test 1.6 lakh individuals in the first year, 10.1 lakh in second year and 30.1 lakh in the third year for Hepatitis

f. Start screening people belonging to high-risk groups for Hepatitis B in first year.

g. Encourage opportunistic screening for HBV and HCV of patients visiting health care facilities

B. Treatment:

a. Establish at least one Model Hepatitis Treatment Centre in each state\UT in the first year in an institution identified by the respective state\UT government. Increase the number of such centres if required (on the basis of need assessment) in consultation with the concerned state\UT government, in subsequent years.

b. Establish at least one treatment centre at district level in the public sector, preferably in a medical college or the district hospital, by the end of second year to offer access to quality assured management of Viral Hepatitis.

c. Number of new hepatitis C cases to be treated across the country: over 3 lakh patients in 3 years

d. Start treatment for Hepatitis B for people needing treatment, by the end of first year

4. Training:

a. Ensure all trainings to operationalize state reference laboratories and Model Treatment Centres by the end of first year.

b. To develop capacities of state\UT teams for training of personnel at the district laboratories and treatment centres.

c. To develop IT driven institutional mechanisms for offering online counselling and courses to personnel at all levels. The program will also explore facilitation through tele consulting where required.

d. To develop capacities of functionaries in Community Health Centre, Primary Health Centre and Health and Wellness Centre (CHC, PHC and HWCs) to implement diagnostic and treatment support protocol appropriate at that level

5. Monitoring and evaluation, surveillance and research:

a. To develop and operationalize the Viral Hepatitis Information Management System (VHIMS) for

i. Maintaining a registry of patients

ii. Tracking of patients for ensuring treatment adherence and compliance.

iii. Developing dashboards and reports for monitoring of the Program.

b. Co-ordinate with the National Viral Hepatitis Surveillance Program

i. Surveillance of acute viral hepatitis

ii. Surveillance of chronic viral hepatitis

iii. Surveillance of sequelae of chronic viral hepatitis

c. Research: Identify evidence based operational research and implement in collaboration with DHR

Hepatitis B

Hepatitis B is a potentially life-threatening liver infection caused by the hepatitis B virus (HBV). It is a major public health problem worldwide including India. HBV is spread predominantly by per-cutaneous or mucosal exposure to infective blood and various body fluids. Common modes of transmission of infection include perinatal mother to child transmission, infected needles, transfusion of infected blood and blood products and sexual mode.

Hepatitis B can be either acute or chronic, and the associated illness ranges in severity from asymptomatic to symptomatic, progressive disease. The risk of complication correlates with the age of acquisition of infection i.e. neonate acquiring infection from mother has nearly 90% chance of developing chronicity. People with chronic hepatitis B are at increased risk of developing hepatic decompensation, cirrhosis, and hepatocellular carcinoma. Chronic hepatitis B (CHB) – defined as persistence of hepatitis B surface antigen (HBsAg) for six months or more after acute infection with HBV– is a major public health problem. Based on the prevalence of HBsAg, different areas of the world are classified as high (≥8%), intermediate (2-7%) or low (<2%)HBVendemicity. Published literature suggests that India falls under the category of intermediate endemicity zone.

Viral hepatitis B is preventable through the intramuscular administration of a safe and effective vaccine. Prevention of perinatal /vertical transmission is possible through hepatitis B vaccination at birth. In India,under Universal immunization program(UIP), hepatitis B immunization includes birth dose for hepatitis B vaccine andsubsequentthree doses of vaccine at 6, 10 and 14 weeks. Health care workers and high-risk groups by virtue of their occupation and behavior are more vulnerable to acquiring infection.

Routine assessment of HBsAg-positive persons is needed to guide HBV management and indicate the need for treatment. This generally includes assessment of: measuring aminotransferase levels to help determine liver inflammation and stage of liver fibrosis by non-invasive tests (NITs) such as aspartate aminotransferase (AST)-to-platelet ratio index (APRI). Serum HBV DNA levels/viral load quantified by real-time polymerase chain reaction (PCR) correlate with disease progression and are used for decisions to treat and subsequent monitoring.

Since majority of infected people remain asymptomatic, and often present with advanced disease, early diagnosis is critical to timely initiation and scale up of treatment for viral hepatitis B. Inadequate public and health-care provider awareness; the asymptomatic nature of infection during the early stages, lifelong treatment and access to quality diagnostics are some of the challenges to scaling up management of viral hepatitis B.

Antiviral agents active against HBV are available, and have been shown to suppress HBV replication, prevent progression to cirrhosis, and reduce the risk of HCC and liver-related deaths. However, currently available treatments fail to eradicate the virus in most of those treated, necessitating potentially lifelong treatment. These drugs need to be made available and used such that timely intervention will prevent the onset of advanced liver disease.

Prevention strategies including needle exchange in people who injects drugs (PWID), barrier contraception need to be promoted in key affected populations, including persons who inject drugs, men who have sex with men (MSM), and sex workers; prevention of HBV transmission through immunization of health care workers need to be ensured in health-care settings. Voluntary blood donation and universal screening of blood and blood products for transfusion will also help in prevention strategies.

In view of the above, it is pertinent to address all aspects of HBV prevention, care and treatment of persons with CHB infection under the NVHCP. This will provide opportunities to save lives improve clinical outcomes of persons living with CHB, reduce HBV incidence and transmission, and stigma due to disease.

Hepatitis B Virus

HBV, a double-stranded DNA virus, belongs to the family of hepadnaviruses. 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.

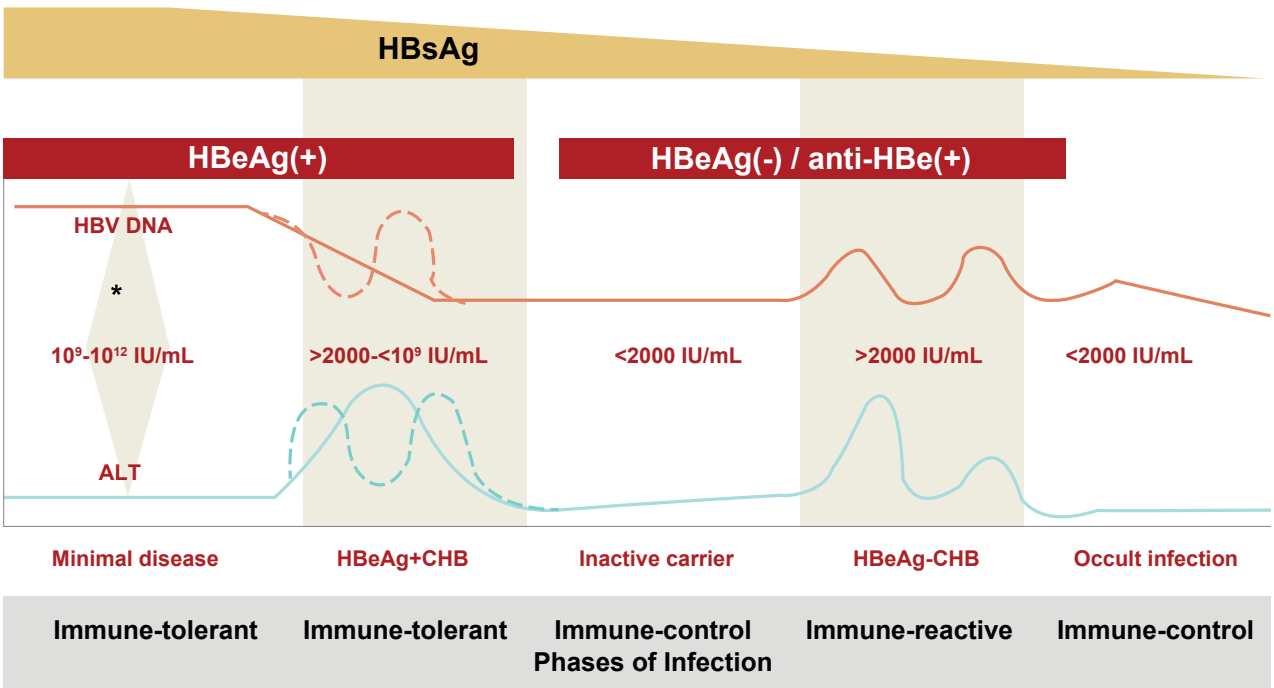
The disease can manifest both in acute and chronic forms and varies from asymptomatic to symptomatic progressive disease.

The spectrum of disease and natural history of chronic HBV infection are diverse. In some people, CHB is inactive and does not lead to significant liver disease. In others, it may cause progressive liver fibrosis, leading to cirrhosis with end-stage liver disease, and a markedly increased risk of hepatocellular carcinoma (HCC), independent of the presence of cirrhosis – usually many years after initial infection. Longitudinal studies of untreated persons with CHB show an 8–20% cumulative risk of developing cirrhosis over five years. In those with cirrhosis, there is an approximately 20% annual risk of hepatic decompensation and the annual incidence of hepatitis B-related HCC is high, ranging from <1% to 5%. Untreated patients with decompensated cirrhosis have a poor prognosis, with 15–40% survival at five years. Several host and viral factors, especially coinfections with HIV, HCV and hepatitis D virus (HDV), together with other cofactors such as alcohol use, may increase the rate of disease progression and risk of developing HCC.

The detailed guidelines for the natural history, phases of chronic HBV infection and co-morbidities have been address in the National guidelines for Diagnosis and management of viral hepatitis, 2018 by NVHCP, NHM and should be referred to.

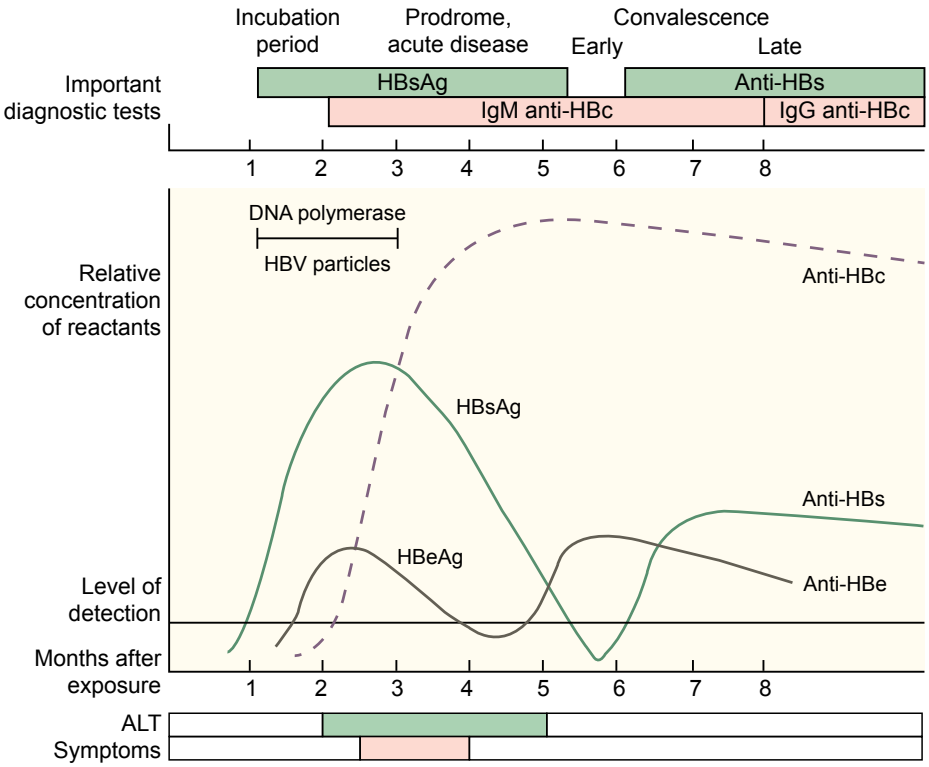
Diagnosis of Hepatitis

Chronic HBV infection is a dynamic process reflecting the interaction between HBV replication, hepatocytes and the host's immune response. The natural history of chronic HBV infection has been schematically divided into four phases, as depicted in figure below, taking into account the presence of HBeAg, HBV DNA levels, alanine aminotransferase (ALT) values and eventually the presence or absence of liver inflammation. The risk of progression to cirrhosis and HCC is variable and is affected by the host's immune response.



Source: Santantonio T, Fasano M, Current concepts on management of chronic hepatitis B. http//dx.doi.org/10.5772/54759

Clinical progression along with associated serological events in acute HBV infection



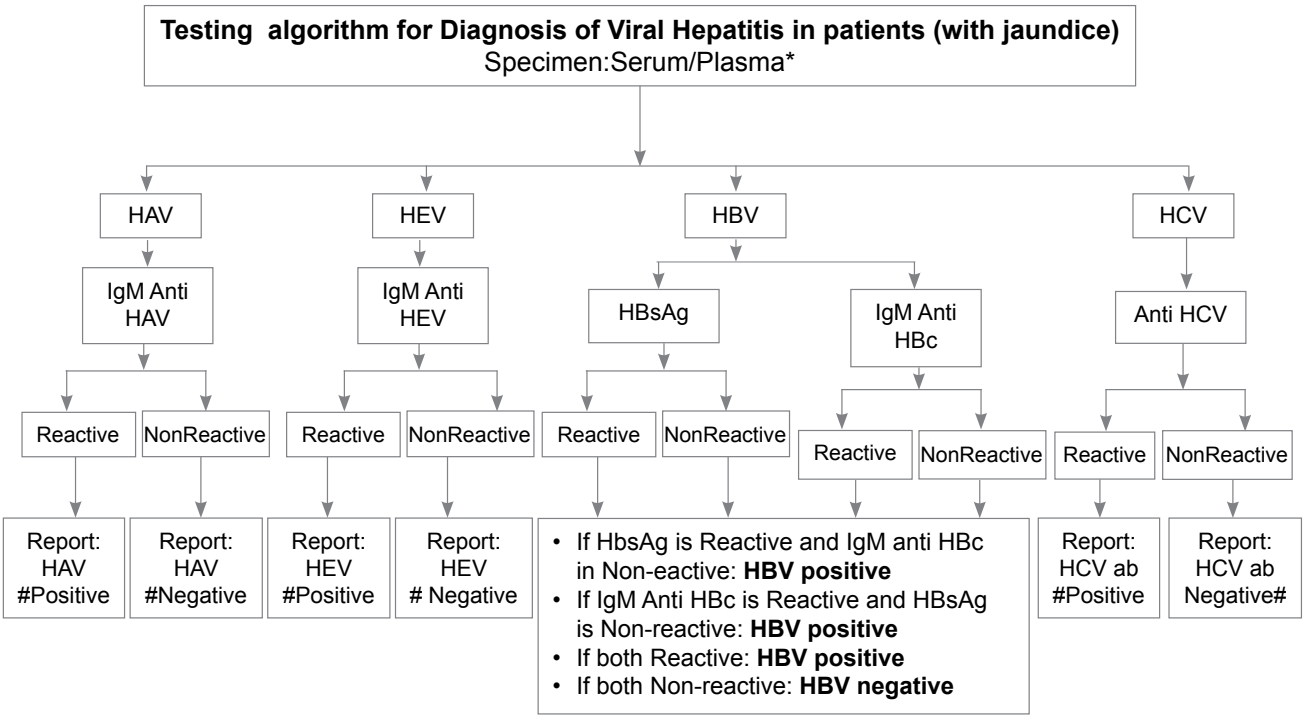
Source: Karen C. Carroll, Stephen A. Morse, Timothy Meitzner, Steve Miller: Jawetz, Melnick, and Adelberg's Medical Microbiology, 27th Edition, Mc-Graw Hill Education.

Interpretation of HBV markers

The following table depicts the combination of various serological markers of hepatitis B and the interpretation of these findings.

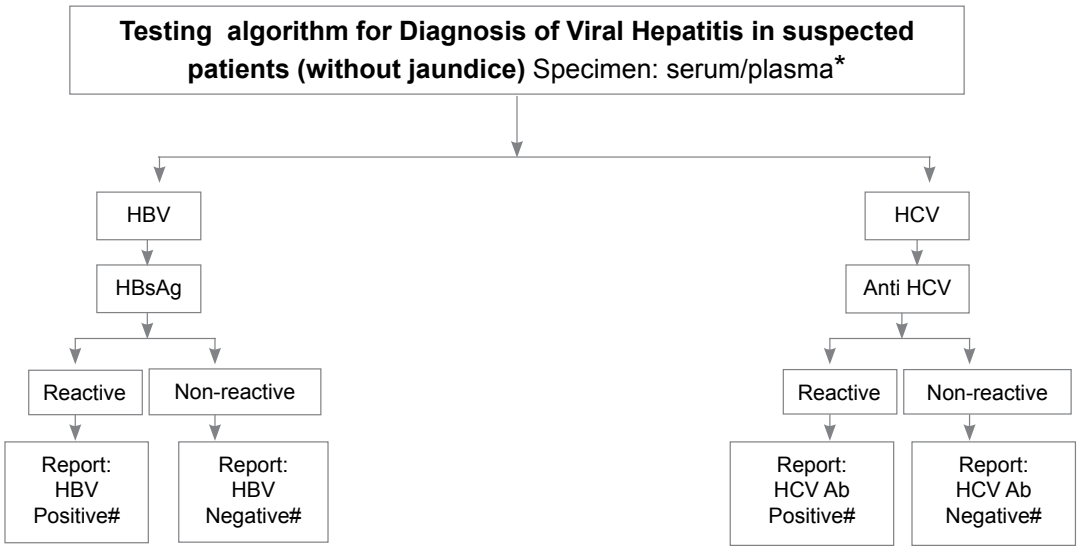
Table 1: Common serologic patterns of hepatitis B infection and their interpretation

HBsAg	Total anti-HBc	IgM anti-HBc	Anti-HBs	Interpretation
-			-	Never exposed
-	+	-	+	Past natural infection, cleared, immunity achieved
-	+	-	-	Past natural infection, cleared, anti-HBs has waned over time
-	+	-	-	Immunity due to vaccination
-	-	-	+	Recent infection, recovered, immunity achieved
-	+	+	+	Acute infection, ongoing
+	+	-	-	Chronic infection (ongoing)



Serum samples to be used for serological and biochemical testing, to be aliquoted and stored at - 20°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 hepatitis C RNA estimation and two archived at - 80°c for quality assurance



** Serum samples to be used for serological and biochemical testing, to be aliquoted and stored at - 20°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 - 80°c for quality assurance

Whom to treat

The persistence of HBsAg beyond 6 months defines the person to have a chronic hepatitis B.There is no need to confirm with second HBsAg test in completely asymptomatic patients or those with features of fibrosis/cirrhosis/HBV flare. Those with acute hepatitis or a recent risk factor (180 days) for HBV infection should undergo a repeat HBsAg testing after 6 months to confirm chronicity.

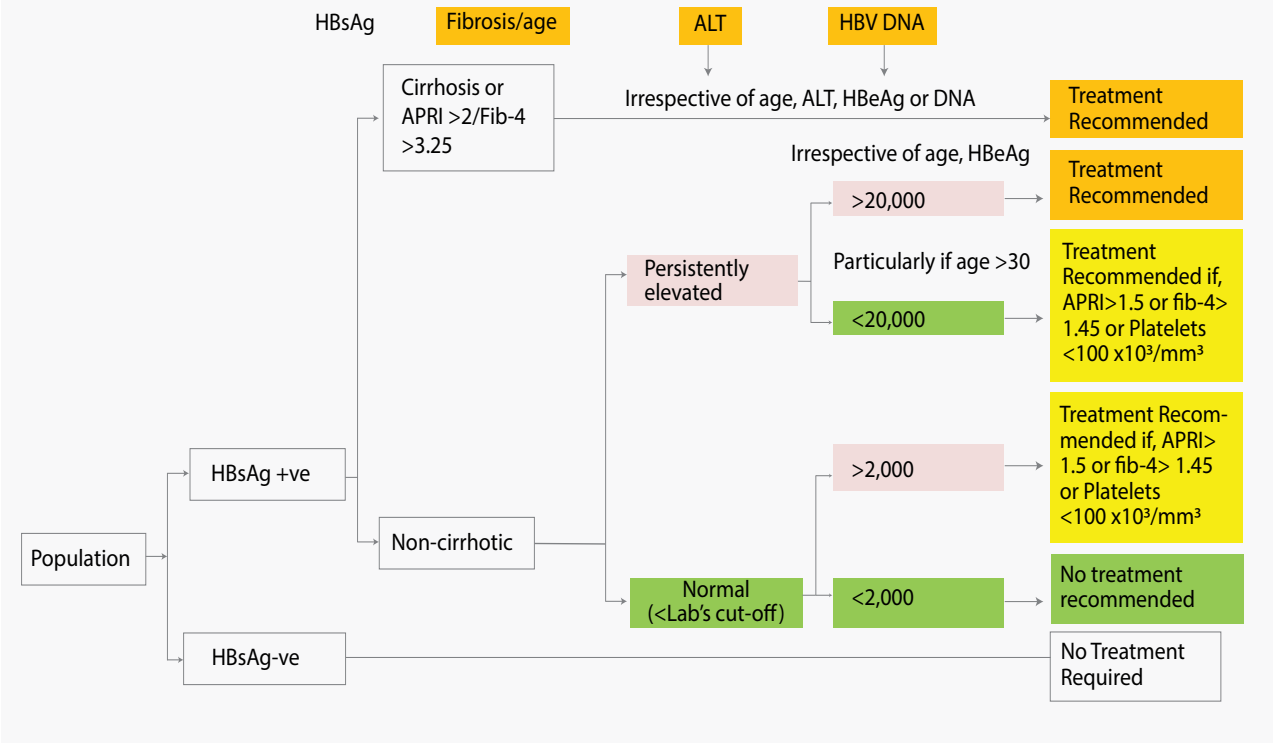
The decision to identify the people who need treatment rely upon the presence of cirrhosis, fibrosis, levels of liver enzymes and platelet count. The HBeAg is not required for assessing the eligibility to initiate treatment and hence will not be used in the program.

The persistently elevated ALT under the program is defined as at least 2 values four weeks apart in the last 6 months, which are above the upper limit of normal.

The extent of fibrosis / cirrhosis can be established using several methods. It is recommended to use the non-invasive techniques (NIT) like APRI and FIB-4 for assessing the extent of fibrosis. An APRI score of 2 or more or a FIB-4 more than or equal to 3.25 is suggestive of cirrhosis. The APRI score more than 1.5 or FIB-4 score more than 1.45 correlates with significant fibrosis (Stage F2). Transient elastography(FibroScan) may be done in settings where they are available and cost is not a major constraint (Conditional recommendation).A mean cut-off of ≥12.5 kPa may be used to diagnose cirrhosis and ≥8.0 to diagnose significant fibrosis.The details on evaluating the status of cirrhosis can be seen in Annexure 1 that details on the assessment of the severity of liver disease

Based on the various parameters, the following algorithms should be used to identify people who need treatment.

Chronic Hepatitis B Infection : whom to treat



HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e-Antigen; APRI, AST to platelets ratio index; FIB-4, fibrosis-4

Treatment: what to treat with?

There are various antiviral agents recommended for treatment of CHB. The details are described in the National Treatment guidelines. However, the following table summarizes the recommendations:

Table 2: Recommended drugs for the treatment of CHB and their doses in adults

S.NO.	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 3: 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 10 mL (0.5 mg) 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 nucleotide analogues (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).
- 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.

The formulations for children are not currently approved, as and when they become available and approved, the above recommendation will be useful.

Monitoring the treatment

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

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

Baseline Investigations: At first visit, we need to do complete blood counts (CBC), HBsAg, APRI, LFT (at least ALT & AST), ultrasound (USG) of abdomen and HBV DNA.. There should be baseline HIV screening where possible of all people testing positive for HBsAg or anti-HCV.

Follow up Investigations: The person should be followed up regularly and the ALT levels have to be monitored every six months. The HBV DNA should be done for each person every year. The APRI/FIB-4 scoring should be done every 6 months and hence the lab investigations needed should be accordingly undertaken. Renal function tests should be monitored every six months, or earlier if deemed necessary by the treating physician for monitoring drug toxicity.

Referral to model treatment centers

Majority of patients will be covered with these regimens recommended in these guidelines. However, a few cases might need some variants from these regimes (like patientsneeding TAF, patients needing and eligible for pegylated interferon, patients with malignancy on chemotherapy, patients with family history of cirrhosis or HCC attributable to HBV infection, patients with virological failure, acute liver failure and acute liver injury and jaundice/flare up cases, reactivation cases etc). These special cases will be a very small fraction of the overall disease burden and have to be managed at the Model Treatment Center. A summary guidance for MTC is enclosed as Annexure 2

Hepatitis B infection and pregnancy

Perinatal transmission is the major route of HBV transmission, In the absence of prophylaxis, a large proportion of viraemic mothers, especially those who are seropositive for HBeAg, transmit the infection to their infants at the time of, or shortly after birth. The risk of perinatal infection is also increased if the mother has acute hepatitis B in the second or third trimester of pregnancy or within two months of delivery. Although HBV can infect the fetus in utero, this appears to be uncommon and is generally associated with antepartum hemorrhage and placental tears. The risk of developing chronic infection is 90% following perinatal infection (up to 6 months of age) but decreases to 20–60% between the ages of 6 months and 5 years.

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 aspect of mid-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+HepB+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 detectableHBeAg 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. Under the program, HBIG will be made available and should be administered for preventing mother to child transmission of HBV (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 anterolateral aspect of mid-thigh 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.

HBV Infection in Pregnancy

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 as detailed in above section.

Hepatitis B in a pregnant woman is not a reason for considering termination of pregnancy. Similarly, the presence of HBV infection is not an indication for caesarean delivery, which should be based on obstetric indications only. Administration of hepatitis B vaccine to pregnant women with HBV provides no benefit either to the mother or the baby.

Chronic Hepatitis B in children and adolescents

CHB is usually benign and asymptomatic in children. In addition, there are low curative response rates with both NAs (necessitating long-term therapy) and IFN treatment, and concerns over long-term safety and risks of drug resistance. For these reasons, a conservative approach to treatment is generally indicated, unless there are other criteria for treatment, such as cirrhosis or evidence of severe ongoing necro-inflammatory disease on liver biopsy. Although the majority of children will not require antiviral therapy, early identification and monitoring of children at risk for progression of liver disease guided by liver histology and a family history of HCC remains important. The use of NITs and identification of appropriate cut-offs have not yet been defined in children. Only conventional IFN, lamivudine and adefovir have been evaluated for safety and efficacy, but children generally have a similar response as adults. IFN cannot be used in infants aged less than 1 year. The FDA has approved tenofovir for use in adolescents and children above the age of 12 years for HBV treatment. Therefore, treatment options for children below 12 years, and especially below 2 years, remain limited. Studies with NAs are ongoing to better define treatment strategies.

Co-morbidities

HBV with HCV co-infection

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.

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, liverrelated 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 coinfection 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.

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.

HBV and HDV co-infection

HDV a defective RNA virus infects persons who are infected with HBV since they require HBV to complete its life cycle. Prevention and control of HDV requires prevention of HBV infection through hepatitis B immunization, although there is no protection against HDV for those already HBV infected. Management of HBV will automatically prevent or manage co-infection as well as super-infection.

HBV and tuberculosis co-infection

Groups at increased risk of infection with HBV are also at risk of infection with TB, largely because they live in regions of the world that are endemic for both infections. Drug-induced liver injury with elevation of aminotransferases is three- to six fold higher in persons co-infected with HBV, HCV or HIV who are receiving anti-tuberculosis drugs, due to hepatotoxicity with isoniazid, rifampicin and pyrazinamide.

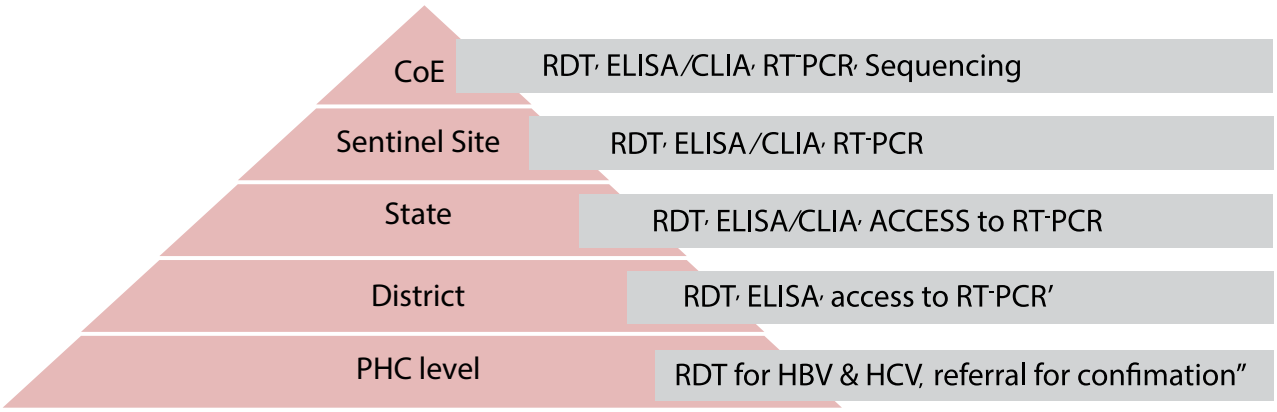
Organization of services

The diagnosis and management of hepatitis B infection requires availability of appropriate , quality assured testing for screening, confirmed diagnosis and monitoring of treatment,and at the same time, since the treatment is life long, it also demands that the treatmentbe efficacious and at the same time accessible for a chronic disease management, with strong linkages and referral mechanisms. The organization of laboratory services and the treatment services therefore, needs to be extremely strategically organized and coordinated.

Laboratory services

A variety of tests are required to establish a diagnosis of viral hepatitis and its further management. These include platelet count, estimation of liver enzymes and specific serological tests and molecular tests (HBV DNA and HCV RNA). The initiative envisages a tiered network of existing laboratories taking into account their existing competencies and capacities in order to attain a quality assured test result.

The specific tests for viral hepatitis offered in the NVHCP across public health laboratories are summarized below.



Whom to test

Diagnostic serologic testing for hepatitis B will be available to all people who would access the testing sites. However, theinitial focus would remain on testing specific population groups that remain more vulnerable to acquiring infection. These include the key populations under the NACP, and PLHA. It is important to screen them and vaccinate those who are not found to be infected with hepatitis B.

A large number of adults who get infected will clear the infection and a small proportion will remain chronically infected. Therefore, it becomes important to link those who are identified while routine screening for other purposes (eg, pre-operative screening, the persons screening positive in blood banks for donations).The transmission of mother to child also accounts for the major mode of transmission of hepatitis B. Screeningof pregnant women , including 'direct in labour' pregnant women remain important to ensure that they get diagnosed and appropriate management can be offered to them as well for preventing mother to child transmission of HBV. Family members/siblings of the infected person and their sexual partners should also be offered testing for hepatitis B infection.

Treatment services

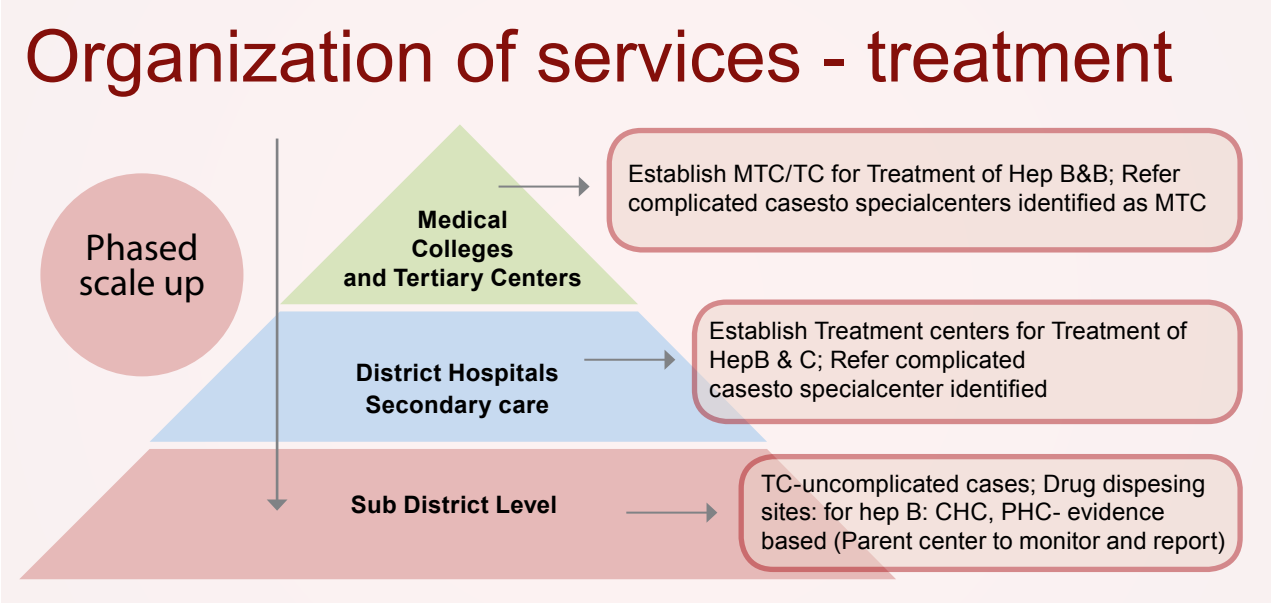
The services will be delivered through designated treatment sites that are located within an existing public health facility, including tertiary care facilities followed by district hospitals. The extent of services will depend upon the availability of the expertise and resources in the selected sites. There will be some 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.

The NVHCP has already rolled out the treatment of Hepatitis C. The sites that have been identified as MTC and TC for the hepatitis C, will also be delivering the services for hepatitis B. The human resources provided by the program for hepatitis C will also be delivering the services for hepatitis B under same pattern of assistance.

Objectives and functions of the treatment sites

The management of hepatitis C has been simplified over the last few years since the introduction of DAAs. However, the treatment for hepatitis B remains a life long treatment for most individuals who need treatment. The main objective of the treatment site under the NVHCP is to enhance the access to treatment for hepatitis B and C.

Model Treatment Centre(MTC) and Treatment Centre (TC): The treatment for hepatitis B will 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 HBV infection, it is planned to have a tiered approach for service delivery.



All the treatment centers will have the capacity to initiate / dispense the treatment for hepatitis B 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 center that have the requisite capacity and experience to manage the complicated cases (e.g. decompensated cirrhosis, thalessemicsetc.). 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 center, will also receive in-referrals and also be the centers for training, mentoring and conducting operational research under the initiative.

To minimize the travel costs, the treatment center can undertake the analysis of data and identify places where there is clustering of cases for hepatitis B treatment. They can identify these sites as Drug Dispensing Units(DDU) under them, in consultation with the state NVHCP. The DDU would be established in a phased manner. DDUs will cater to cohort of patients who are stable (as per the treating physician) for dispensing of drugs. Such patients can therefore be followed up at MTC/TC every 3-6 monthly. Once the DDU are planned, a detailed SOP for the drug supply, eligibility and reporting will have to be ensured. There should be no minimum number of patients for cohort and willingness of the patient to be linked to DDU should be considered before deciding so.

As the complications of chronic viral hepatitis are vast, the scope of initiative will be restricted to the treatment of the hepatitis B infection and ensure linkages to the other programs and schemes for managing the sequel of chronic hepatitis. Such schemes include (but not limited to) - Ayushman Bharat, NHPS, state specific schemes for patient support etc

Functions of the Model Treatment Center:

1. *To ensure Screening/ Diagnosis in suspected cases of Hepatitis B &C Infection*
2. *Treatment & Management of Hepatitis B &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 B &C Infection
2. Treatment and Management of uncomplicated Hepatitis B &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

Functions of Drug Dispensing Units

1. 1) To ensure Screening/ Diagnosis in suspected cases of Hepatitis B &C Infection
2. To dispense the drugs to stable patients transferred from the MTC/TC.
3. Encourage testing of partners and at risk people for acquiring infection with Hep B & C
4. Out referrals to MTC/TC for clinical management of hepatitis as per national treatment guidelines and for regular annual monitoring for people at their center
5. Ensure compliance to treatment, regular adherence support.

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 manpower 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 3

Inclusion criteria for consideration as a potential treatment site include:

1. Established evidence of case load for Viral hepatitis B &/or C infection or its sequel
2. Evidence of highviral 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 centers 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 attending physician

should see the patients 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

Staffing provided by the program

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.

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

S No	Treatment centers
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. It is of utmost importance that the centers identified as MTC and TC deliver the services for both hepatitis B and C

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 center 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 center 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 center under the overall guidance of the Nodal officer. The MO has to supervise the administrative and medical functions of the center 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 center are abided by.

g. Facilitate and coordinate trainings in the center.

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/ NVHCP.

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.Basic Knowledge of computers is desirable.

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 center 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 center 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 center

c. Ensure entries in the visit register

d. Be a peer educator for patients at center and provide psycho-social support to newly registered patients

e. Provide assistance to patients enrolled at the center, 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)

Microbiologist designated by 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 anddistribution 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. She/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.

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 5A and 5B below details the pattern of assistance: Table 5A: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.
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 provided from SPMU
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 4: Trainings proposed for various health care workers under NVHCP

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 SPMU	Sensitization about program and its contents/approach
Medical Officers	3	Central unit for standardized manual; SPMU for implementation and monitoring	Induction training
Medical Officers	2	Central unit for standardized manual; SPMU for implementation and monitoring	Refresher trainings as deemed necessary
Pharmacist	2	Central unit for standardized manual; SPMU for implementation and monitoring	
Peer supporter	1	Central unit for standardized manual; SPMU for implementation and monitoring	
Lab technicians	5	Central unit for standardized manual; SPMU for implementation and monitoring	Also include EQA
Technical Officer labs	3	Central unit for standardized manual; SPMU for implementation and monitoring	Also include EQA
Data Entry Operator	2	Central and state unit	

Table 5B: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.
Data Entry operator	1		
Peer support	1		
Total (HR)			
Grant-in-aid for Hepatitis A and Hepatitis E case management		100,000	To be provided from SPMU
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	

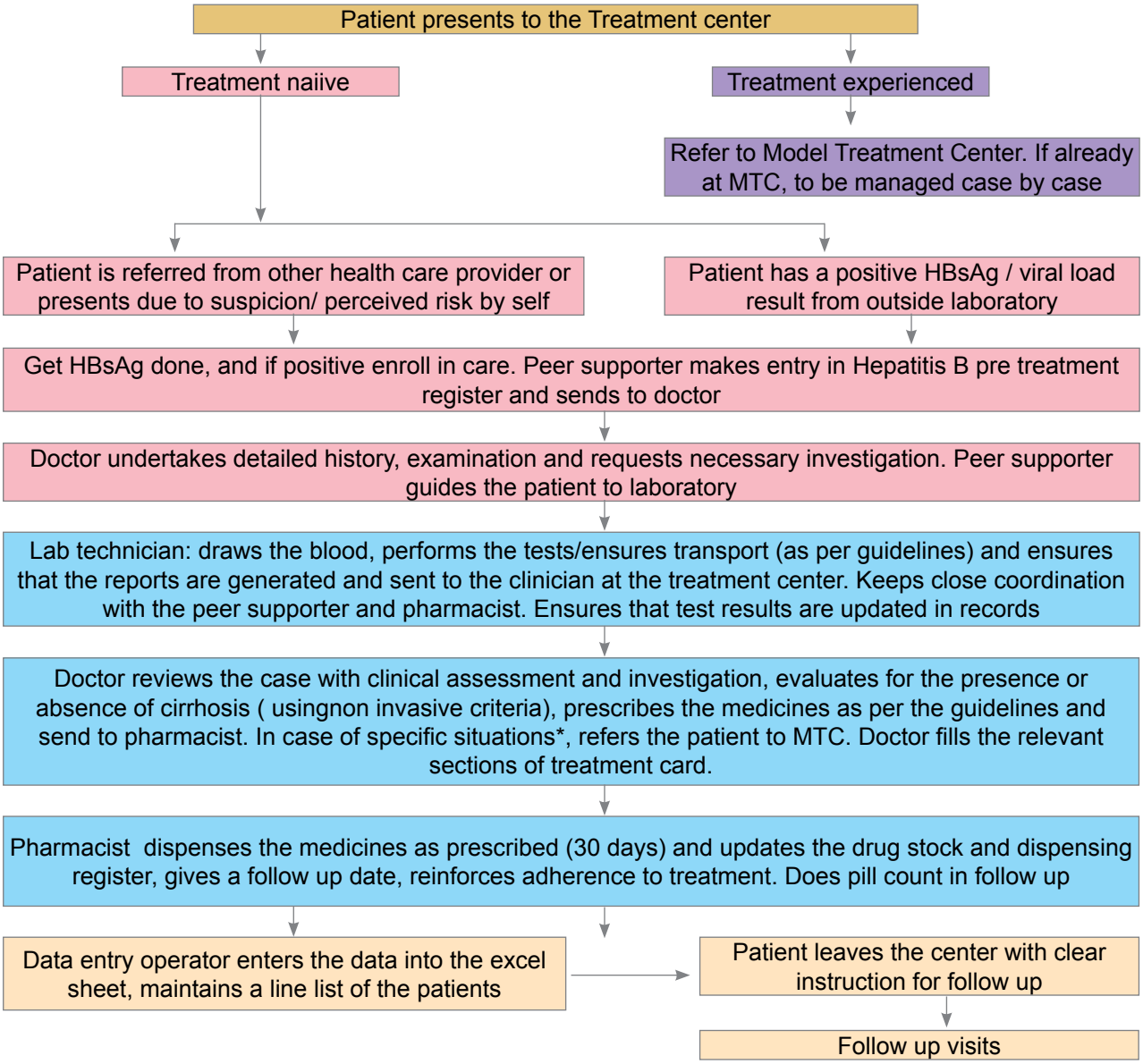
Patient flow at the treatment centers

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 B infection by the HBsAg (from a government facility), they should be confirmed with another HBsAg,if needed, at least after 6 months as per the diagnosis algorithm in the national guidelines.



Every patient found HBsAg positive (without acute features like jaundice) is registered in care. There is no need to confirm with second HBsAg test in completely asymptomatic patients or those with features of fibrosis/cirrhosis/HBV flare. Those with acute hepatitis or a recent risk factor (within 180 days) for HBV infection should undergo a repeat HBsAg testing after 6 months to confirm chronicity.

Once enrolled, each patient has to undergo clinical and laboratory assessment to determine the eligibility for treatment with antivirals. All the patients who are HBsAgpositive have to be enrolled in the Hepatitis B Care register (Annexure4). Once a person becomes eligible and started the treatment, the name is transferred to the hepatitis B Treatment register(Annexure5).This means that those people who are not yet eligible for treatment should be followed in the Hepatitis B Care register. Once the treatment starts, the entry are only to be made in the Hepatitis B Treatment register.

The Hepatitis B testing and treatment card will capture patient demographic information diagnosis and treatment details (Annexure 6).

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.

Follow up: The drugs will be dispensed for 30 days for initial 6-12 months. The first follow up date should be given after 25 days and then after every 30 days. This is to ensure that the patient will always have a buffer stock for 5 days and will not miss the dose in case s/he misses the scheduled appointment. Once the treating doctor is confident that the patient has been stabilized, the drug dispensation can be done for upto 3 months. The patient should be instructed to bring the bottle of medicines with her/him at every visit so that the pharmacist can perform pill count, collect the old bottle and issue a new one. Since this is a life long treatment once started, each staff interacting with the patient should provide counseling on the need for regular treatment.

The complicated cases, , 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, 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 6:Summary of the key actions to be undertaken for patient management, record maintenance and the responsible person.

Visit Number	Key activity (but not limited to)	Responsible person
First visit and baseline, after confirmation of Chronic HBV infection	Ascertain Diagnosis of Chronic HBV infection	Attending doctor
	Enter patient details in Hepatitis B Enrollment 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 (treatment site	Lab technician, Doctor
Follow up visit	Educate on treatment adherence and regular follow up	Doctor ,Peer supporter and pharmacist
	Dispense prescribed medicines	Pharmacist
	Check for any side effects	Attending Doctor, pharmacist
	Get any investigations needed as per technical guidelines, prescribe the medicines	Attending Doctor
	Update investigations in treatment card	Lab technician, Doctor
	Recheck the contact details including phone number and pincode / post office	Peer supporter / data entry operator
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 Hepatitis B treatment

Introduction

A robust monitoring and evaluation framework is vital for the program. The day to day operations of the program rely on the system established for monitoring and evaluation since Hepatitis B treatment is a lifelong treatment. The effective functioning of M&E systems relies on the ownership and responsibility of stakeholders regarding the information they provide to the systems, the feedback and it's use for policy making.In addition to the dat a collected from the service delivery points (diagnosis and management of viral hepatitis, etc.), the NVHCP will also coordinate with the existing programs and schemes that contribute towards the response to viral hepatitis B and this would be compiled for monitoring a comprehensive program update at national level.

Objectives of the monitoring and evaluation framework

- Guide monitoring of the Hepatitis B management at all levels-national, state & district
- To identify the core indicators for Hepatitis B that will allow key stakeholders in country to evaluate and measure NVHCP in all its components of Hepatitis B management.
- To facilitate collection and analysis of standardized data through appropriate reporting mechanisms at all levels.
- Enhance the availability and quality of data by using the required reporting formats with relevant data field.
- To build capacity of the Viral Hepatitis Management Units at National, State and district level and the service delivery points to regularly and systematically track progress of implementation and adherence of treatment of Hepatitis B under NVHCP.

Timeliness is a key feature of an efficient delivery system. A computerized data management system under the 'National Viral hepatitis Control Program' would facilitate automated data transfer, data validation, monitoring and evaluation. Data will therefore, be entered in standard data formats at the source, in software capable of handling multilevel entries and validation. Standard formats for recording and reporting prescribed by the NVHMU are annexed. The relevant data of the service delivery points needs to be shared within the centre, maintaining confidentiality.

In addition to the data collected from the service delivery points (diagnosis and management of viral hepatitis, etc.), the NVHCP will also coordinate with the existing programs and schemes that contribute towards the response to viral hepatitis B and this would be compiled for monitoring a comprehensive program update at national level.

Monitoring indicators

S No	Indicator	Baseline	Target forYear 1	Source of reporting and level
Input indicators				
1	Number of sites offering treatment for Hepatitis B	0	650	Reports from SVHMU
2	Are National guidelines and SOPs developed for management of Hepatitis B?	N/A	Yes	NVHMU
3	Is there a standard Training curriculum developed for management of Hepatitis B?	N/A	Yes	NVHMU
Process Indicators				
4	of State laboratory sites which % have been trained on the SOPs for labs with respect to diagnosis of Hepatitis B under the program	N/A	100%	NVHMU and SVHMU
5	of Treatment sites which have been % trained on the SOPs on Management of Hepatitis B under theprogram	N/A	100%	NVHMU and SVHMU
Output Indicators				
6	Total number of patients eligible for treatment for Hepatitis B put on treatment	N/A		NVHMU and SVHMU
7	Proportion of newborns who received % birth dose of Hepatitis B vaccine			NVHMU, SVHMU with inputs prom Universal Immunization Program

Data sources

TData sources will include State and District health units, service delivery points and healthcare-facilities. The NVHCP has some components that involve coordination with other existing programs and schemes. Data will be obtained from the respective programs/schemes/ministries for data triangulation and relevant intervention.

Data storage

Proper record keeping of client results is vital. As per the guidelines, all documents must be stored for at least 5 years or as per state/ institutional guidelines whichever is longer.

Recording and reporting at various levels and flow of information

Every health facility/service delivery point needs a system of recording the required data. Making records system systematically & regularly will help to follow up on defaulters, loss to follow up, treatment interruption and solve issues of non-adherence. Data generated & collected at service delivery point i.e. treatment site and state and district laboratory will be sent to the DVHMU, SVHMU and NVHMU through monthly reports. At State & National level, the data will be aggregated and analyzed, and feedback will be provided.

Responsibility of reporting, flow of information and frequency of monthly format reporting

Level	Reporting form	Person Responsible for reporting	Reporting to	Frequency of submission	Submission date by
SVHMU	Consolidated report of the state	Program I/C; or state nodal officer	NVHMU	Monthly	10th of every month
DVHMU	Consolidated report of the district including district hospitals, sub-district hospitals, CHC,PHC, SC, H&WC	Program I/C; or district nodal officer	SVHMU	Monthly	7th of every month
Model Treatment Centre	Monthly report	Nodal Officer of TC/MTC	SVHMU	Monthly	5th of every month
Treatment centre			SVHMU (through DVHMU if treatment centre is located at district hospital/ (sub-district level	Monthly	5th of every month
State Laboratory	Monthly report	Nodal officer of state laboratory	SVHMU	Monthly	5th of every month
District Laboratory	Monthly report	Nodal officer of district laboratory	DVHMU	Monthly	5th of every month
		DVHMU	SVHMU	Monthly	7th of every month

Review meetings & supervisory visits

The treatment sites and the laboratory will be reviewed regularly by the nodal officers for 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 according to the supervisory checklist in the annexure. Review meetings of the SVHMU officials will be organized on a quarterly basis to assess physical and financial progress, discuss constraints in implementation of the NVHCP and identify solutions to key barriers and bottle necks. Key gaps identified during the implementation of the NVHCP will also be addressed through planned operational research.

The suggested frequency of the monitoring and supervisory visits is:

Frequency of visit to the treatment sites

Level	Frequency of visit
National	Annual
State	Quarterly
District	Once monthly

Evaluation

The purpose of the evaluation is to examine NVHCP in the context of the health system and its broader surroundings. The evaluation looks at the program's strengths and weaknesses, the efficiency and effectiveness of its activities and its impact on disease. It also assesses the program's capacity to adapt to new demands, both those generated from health sector reform and decentralization, as well as those arising in response to the population's need for access to new drugs and technologies.

Outcome of the program will be assessed through framework of evaluation. It is envisaged that the program will undergo process evaluation, mid-term evaluation and end evaluation. It will be carried out by independent agency. The evaluation will be conducted in two stages after two to three years of roll out of the program. Panel of institutions will be identified to conduct evaluation.The evaluationresults will be used to maintain, correct, or modify program activities.

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.

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) are 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 (109/L)
FIB-4 = (age (yr) x AST (IU/L)) / (platelet count (109/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 validated in case of APRI and FIB-4. 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	-	kPa >11–14
Significant fibrosis (METAVIR ≥F2)	0.5	1.5	(low) 1.45 (high) 3.25	kPa 8.5–7<

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:

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)	(2>) 34>	(3–2) 51–34	(3<) 51<
(Albumin (g/dL	3.5<	3.5–2.8	2.8>
Prothrombin time prolongation (seconds) or INR	or <1.7 4>	or 1.7–2.3 6–4	or >2.3 6<

Child–Pugh Class A: 5-6 points

Child–Pugh Class B: 7-9 points

Child–Pugh Class C: 10-15 points

Annexure 2: summary guidance for the Model Treatment Center (MTC) for some special situations

The MTC will have cases that are complicated or have special needs, and will be referred from the treatment centers. Some of these include patients with suspected treatment failure, patients where TAF is indicated, patients with malignancy etc. Hence, some information that could be used by the MTC is summarized below. However, with growing evidence and newer established modalities, the MTC will be expected to provide the approved management modalities.

Response to treatment

Responses can be divided into virological, serological, biochemical, and histological. All responses can be estimated at several time points during and after therapy. The definitions of virologicalresponses vary according to the timing (on or after therapy) and type of therapy.

Virological responses:

(1) NA therapy

Virological response during NA is defined as undetectableHBV DNA by a sensitive polymerase chain reaction (PCR) assay with a limit of detection of 20 IU/ml. Primary nonresponseis defined by a less than one log10 decrease of serum HBV DNA after 3 months of therapy. Partial virologicalresponse is defined as a decrease in HBV DNA of morethan 1 log10 IU/ml but detectable HBV DNA after at least12 months of therapy in compliant patients. Virologicalbreakthrough is defined as a confirmed increase in HBVDNA level of more than 1 log10 IU/ml compared to the nadir(lowest value) HBV DNA level on-therapy; it may precede abiochemical breakthrough, characterized by an increase inALT levels.HBVresistance to NA(s) is characterised by selectionof HBV variants with amino acid substitutions that conferreduced susceptibility to the administered NA(s).

However the program advocates the HBV DNA monitoring on a yearly basis. However, as and when the clinician feels a justifiable need the same may be recommended more than once in a year with appropriate documentation and signature of the nodal officer at the MTC.

In patients who discontinue NA, sustained off-therapyvirological response could be defined as serum HBV DNA levels <2,000 IU/ml for at least 12 months after the endof therapy.

(2) PegIFN-alfa therapy

Virological response is defined as serum HBV DNA levels <2,000 IU/ml. It is usually evaluated at 6 months and atthe end of therapy.

Sustained off-therapy virological response is defined as serum HBV DNA levels <2,000 IU/ml for at least12 months after the end of therapy.

Serologic Response

Serological responses for HBeAg are HBeAg loss and HBeAgseroconversion, i.e., HBeAg loss and development of anti-HBe(only for HBeAg-positive patients).

Serological responses for HBsAg are HBsAg loss and HBsAgseroconversion,i.e., HBsAg loss and development of anti-HBs (for allpatients).

Biochemical Response

Biochemical response is defined as a normalization of ALTlevels based on the traditional ULN (<40 IU/L).

Since ALT activityoften fluctuates over time, a minimum follow-up of at least1 year post-treatment with ALT determinations at least every3 months is required to confirm sustained off-treatment biochemicalresponse. It should be noted that the rates of sustainedoff-treatment biochemical responses may sometimes be difficultto evaluate, as transient ALT elevations before long-term biochemicalremission may occur in some CHB patients within thefirst year after treatment discontinuation. In such cases, additionalclose ALT follow-up of at least 2 years after ALT elevationseems to be reasonable in order to confirm sustained offtherapybiochemical remission.

Histological response

Histological response is defined as a decrease in necroinflammatory activity (by P2 points in histologic activity index orIshak's system) without worsening in fibrosis compared to pretreatment histological findings.

Use of TAF in Chronic Hepatitis B

Minimal rates of renal function decline have been reported during long-term therapy with ETV and TDF, but the nephrotoxic potential is higher for TDF. Cases of Fanconisyndromeassociated with TDF therapy and rescued after a switch to ETVhave been reported. In addition, studies using sensitive markers of glomerular and tubular kidney function and of bone mineral density have also reported chronic tubular damage and decline ofeGFR and bone mineral density in TDF treated patients.

Therefore, it seems appropriate for now to monitor all CHBpatients treated with TDF therapy for adverse renal effects withserum creatinine (eGFR). Moreover, CHB patients at high renal risk undergoing any NA therapy should be monitored with serum creatinine (eGFR) levels. Thefrequency of renal monitoring can be every 3 months during the first year and every 6 months thereafter, if no deterioration.

Closer renal monitoring is required in patients who developcreatinine clearance <60 ml/min or serum phosphate levels<2 mg/dl.

In CHB patients with deteriorating renal function or low eGFR (<60mL/min/1.73 M2), albuminuria and/or osteopenia/osteoporosis, chronic steroid use, particularly in older age (>60 years)should also be considered when choosing NA therapy. In such subgroups of CHB patients, entecavir represent suitable choice. TAF should be used in patients with previous exposure to nucleoside analogues, such as, lamuvidine or telbuvidine..

Entecavir dose in renal impairment

Usual daily dose (0.5 mg)

- CrCl ≥50 mL/min: No dosage adjustment required
- CrCl 30-49 mL/min: Reduce to 0.5 mg q48hr
- CrCl 10-29 mL/min: Reduce to 0.5 mg q72hr
- CrCl<10 mL/min, hemodialysis, or CAPD: Reduce to 0.5 mg q7days

Use of pegylated interferon

The Nuceotide Analogues are the mainstay of the treatment under the National Program. The two with high genetic barrier to resistance, namely tenofovir and entecavir are recommended.

PegIFNa can be considered as an initial treatment option for patients with mild to moderate HBeAgpositiveor negative CHB.The standard duration of PegIFNa therapy is 48 weeks. The extension of the duration of PegIFNatherapy beyond week 48 may be beneficial in selected HBeAgnegativeCHB patients.

Only patients with mild to moderate CHB with compensated cirrhosis but no portal hypertension should be considered for PegIFNa therapy.

HBeAg loss with HBV DNA <2,000 IU/ml at 6 months post-treatment was achieved in ~23% in a meta-analysis of three large trials. In initiallyHBeAg-positive CHB patients with sustained virologicalresponses, HBsAg loss rates increase after the end of PegIFNa therapy. HBsAgloss is uncommon during PegIFNa therapy in HBeAgnegativeCHB patients, however the rate of HBsAg loss progressivelyincreases after PegIFNa discontinuation, from 3% at month 6% to9% at year 3 to 12% at year 5.

All CHB patients treated with PegIFNa should be followed with periodical assessments of at least completeblood count, ALT, TSH, serum HBV DNA and HBsAg levels. HBeAg-positive CHB patients treated with PegIFNashould be also followed with periodical assessments of

HBeAg and anti-HBe.CHB patients with virological response after PegIFNatherapy should remain under long-term follow-up because of the risk of relapse.

However, the since the selection of patient is critical to the successful outcome to therapy with Peg IFN, it is recommended that this drug should not be used at any site other than MTC that has the required expertise. Also, the selection of eligible patients for Peg IFN should be done on case to case basis by a committee of three experts and one program person from the SVMHU/NVMHU. These committees shall be constituted by the program as it evolves.

Monitoring patients for HCC, with a family history of HBV related HCC

Chronic HBV infection leads to an increased risk of death from liver cirrhosis and/or liver cancer. In resource-limited and high HBV-burden settings, persons are often diagnosed with HBV only when they present for the first time with HCC. While the majority of these (80–90%) have cirrhosis at the time of diagnosis of HCC, it may sometimes occur without the presence of cirrhosis; this is especially true for HCC due to HBV. A further major challenge with HCC is that it is rapidly progressive, and may be asymptomatic until it presents clinically at an advanced stage. Treatment options for advanced HCC are limited and overall survival is extremely poor. The prognosis of HCC is affected by the size and number of tumours, and the underlying liver function, and is improved if treatment can be commenced at an early stage of the disease, when the tumour is small. Surveillance is therefore required to detect HCC at an early stage (tumour size <3 cm in diameter) and increase the chances of effective treatment. Effective surveillance programmes require a means for implementing such treatment for small HCC in LMICs, recognizing that access to liver transplantation or resection remains limited, even in high-income settings. These treatments would include alcohol injection or radiofrequency ablation of small tumours. Current surveillance tools include ultrasound and/or alpha-fetoprotein (AFP) measurement, but there is no consensus on the best strategy or frequency of monitoring for HCC in persons with CHB, although existing evidence suggests that semi-annual surveillance detects HCC at an earlier stage and improves survival.

Who should be screened for HCC?

Evidence from longitudinal studies shows that the most important risk factors for development of HCC (associated with an approximately four-fold increased risk) are the presence of cirrhosis, HBeAg positivity and a family history of HCC. Global experts opined that the majority of persons (80–90%) also have cirrhosis at the time of diagnosis of HCC and therefore recommended that those with cirrhosis as well as those with a family history of HCC are the most important high-risk groups to target for screening. Although age >40 years is associated with an increased risk of HCC in Asian populations, these experts considered that the optimal age at which surveillance for HCC should commence cannot yet be established with certainty, as the incidence of HCC varies with age according to region, and occurs at a younger mean age in Africans compared to Asians (see http://globocan.iarc.fr/ia/World/ atlas.html, IARC GLOBOCAN). Therefore, no specific age threshold for screening was recommended.

Risk calculators have been developed, which provide an easy-to-use formula to predict the risk of HCC from models that include age, sex, levels of albumin, bilirubin and ALT, HBeAg status, HBV DNA levels and

presence of cirrhosis. These models were derived largely from longitudinal cohort data of Asian patients and have not been extensively validated in non-Asians. The evidence was rated as being of high-to-moderate quality (due to imprecision or limitations in the outcome assessment). More limited data were available in HBV/HIV-coinfected patients, but low CD4+ cell count and longer cumulated time with detectable HIV RNA were associated with an increased risk of developing HCC.

Cumulative incidence of hepatocellular carcinoma (HCC) according to family history of HCC, baseline HBV DNA level and HBeAg status (Ref WHO guidelines, 2015)

	(%) Cumulative incidence	Adjusted HR (95% CI)
NO family history	7.5	Reference
Family history of HCC	15.8	(1.63-3.72) 2.46
NO family history **HBV DNA <10 000 copies/mL**	2.5	Reference
HBeAg positive **Family history of HCC**	40	(22.86-90.63) 45.52
HBeAg positive **No family history**	19.1	(9.31-20.77) 13.91
HBeAg negative **Family history of HCC** **HBV DNA >10 000 copies/mL**	17.6	(4.52-21.37) 9.90
HBeAg negative **No family history** **HBV DNA >10 000 copies/mL**	10.3	(3.02-6.50) 4.43
HBeAg negative **Family history of HCC** **HBV DNA <10 000 copies/mL**	5.4	NS

All data among HBsAg-positive persons with CHB
HR hazard ratio, CI confidence interval

Annexure 3 Site Feasibility Checklist

National Viral Hepatitis Control Program			
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	Yes	No
2	Is the In-charge keen on establishing services? Yes No	Yes	No
a	Willing to allocate necessary space Yes No	Yes	No
b	Willing to have nodal person for treatment and lab services Yes No	Yes	No
c	Integrate the functioning and follow the National guidelines and protocols , including recording and reporting Yes No	Yes	No
3	What is the annual OPD of the hospital	Yes	No
4	Is there super-specialty(Gastroenterology/ Hepatology) Yes No	Yes	No
5	(How many cases of acute hepatitis are seen annually (explore last years report	Yes	No
6	(How many cases of hepatitis B and C are seeking care (explore previous reports	Yes	No
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	Yes	No
8	If this is a district hospital, where are patients referred or usually go for complicated cases?	Yes	No
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
10	(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	Yes	No
2	Is there an ICU Yes No	Yes	No
3	Number of rooms	Yes	No
A	Doctors Yes No	Yes	No
B	Pharmacist Yes No	Yes	No
C	Data Entry Operators Yes No	Yes	No
D	Drug Storage & Pharmacist Yes No	Yes	No
E	Lab Technician Yes No	Yes	No
F	Peer supporter Yes No	Yes	No
4	Is institution willing to provide necessary furniture (chairs, tables, Almirahetc) Yes No	Yes	No
5	Will the center have access to internet		

HUMAN RESOURCES		
1	Does the institution have the required capacity to manage chronic hepatitis Cases? Yes No	Yes/No
a	Gastroenterologist/Hepatologist Yes No	Yes/No
b	Physician (Internal Medicine) Yes No	Yes/No
c	Pediatrician Yes No	Yes/No
d	Microbiologist Yes No	Yes/No
e	Pathologist	Yes/No
f	Obstetrician	Yes/No
g	(Others (Mention	Yes/No
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 / Haemogram	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	Yes/No
I	MRI	Yes/No
M	Endoscopy	Yes/No
N	Liver Biopsy	Yes/No
O	Others	Yes/No

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.....

Annexure 4: Hepatitis B Care Register

National Viral Hepatitis Control Program Register for work up of any suspect of Hepatitis B															
1	2	3	4		5	6	7	8		9	10	11		12	13	14
.S. No	Date of 1st visit	hosp. .reg. no	NVHCP ID	Patient's name and address	Age	Sex / M / F TG	Preg-nant ((Y/N If yes, date	Confirmed HBsAg test		Is patient eligible for treatment at time of ? enrolment	Base-line *APRI score	Base-line FIB4	Follow up HBV	Date of eligibility for treatment	Date of initiation of treatment	If the regimen has changed-Date of change and the Reasons for change
								Date	Place							

Annexure 5: Hepatitis B Treatment Register

Month: **Year:**

	1	2	3	4	5	6	7	8	9	10			11			12			13		
S. .N	Date of start of Hep B treatment	Registration Number	Patient's first name and surname	Age	Sex M/F/ TG	Patient's address and contact number	Guardian / Treatment supporter's name and contact number	Prior treatment history	Liver cirrhosis status at registration (no cirrhosis, compensated, (decompensated	HBV VL			APRI score			Platelet count			Regimen started		
								Y ☐		0 M	12 M	24 M	0 M	12 M	24 M	0 M	12 M	24 M			
								N ☐		36 M	48 M	60 M	36 M	48 M	60 M	36 M	48 M	60 M			
								Y ☐		0 M	12 M	24 M	0 M	12 M	24 M	0 M	12 M	24 M			
								N ☐		36 M	48 M	60 M	36 M	48 M	60 M	36 M	48 M	60 M			
								Y ☐		0 M	12 M	24 M	0 M	12 M	24 M	0 M	12 M	24 M			
								N ☐		36 M	48 M	60 M	36 M	48 M	60 M	36 M	48 M	60 M			
								Y ☐		0 M	12 M	24 M	0 M	12 M	24 M	0 M	12 M	24 M			
								N ☐		36 M	48 M	60 M	36 M	48 M	60 M	36 M	48 M	60 M			
								Y ☐		0 M	12 M	24 M	0 M	12 M	24 M	0 M	12 M	24 M			
								N ☐		36 M	48 M	60 M	36 M	48 M	60 M	36 M	48 M	60 M			
								Y ☐		0 M	12 M	24 M	0 M	12 M	24 M	0 M	12 M	24 M			
								N ☐		36 M	48 M	60 M	36 M	48 M	60 M	36 M	48 M	60 M			
								Y ☐		0 M	12 M	24 M	0 M	12 M	24 M	0 M	12 M	24 M			
								N ☐		36 M	48 M	60 M	36 M	48 M	60 M	36 M	48 M	60 M			

Annexure 5: Hepatitis B Treatment Register

Month: **Year:**

	1	2	3	4	5	6	7	8	9	10			11			12			13		
S. .N	Date of start of Hep B treatment	Registration Number	Patient's first name and surname	Age	Sex M/F/ TG	Patient's address and contact number	Guardian / Treatment supporter's name and contact number	Prior treatment history	Liver cirrhosis status at registration (no cirrhosis, compensated, (decompensated	HBV VL			APRI score			Platelet count			Regimen started		
								Y ☐		0 M	12 M	24 M	0 M	12 M	24 M	0 M	12 M	24 M			
								N ☐		36 M	48 M	60 M	36 M	48 M	60 M	36 M	48 M	60 M			
								Y ☐		0 M	12 M	24 M	0 M	12 M	24 M	0 M	12 M	24 M			
								N ☐		36 M	48 M	60 M	36 M	48 M	60 M	36 M	48 M	60 M			
								Y ☐		0 M	12 M	24 M	0 M	12 M	24 M	0 M	12 M	24 M			
								N ☐		36 M	48 M	60 M	36 M	48 M	60 M	36 M	48 M	60 M			

16			18	19																											
If the Regimen has ,been changed			Date and reason for stopping Treatment	Follow up visits: ● **1st row**, write patient outcome: on treatment **(OT)** if patient picked up ART drugs; stopped **(ST)** if ART was stopped by the doctor; missing **(MIS)** if the patient **(**missed the scheduled visit but came back within a week; lost to follow-up **(LFU** if the patient did not come till the end of month; restart **(RS)** if treatment was restarted after an interruption; transferred out **(TR)**; dead **(D); REF: If patient was referred to TC/MTC** (**2nd row:** write compliance to treatment based on pill count (pill taken actually/pills prescribed *100 ●																											
Date of change	*Reason	New Regimen		Week2	M 1	M 2	M 3	M 4	M 5	M 6	M 9	M 12	M 15	M 18	M 21	M 24	M 27	M 30	M 33	M 36	M 39	M 42	M 45	M 48	M 51	M 54	M 57	M 60	M 63	M 66	M 69

Annexure 6: Testing & Treatment Card

Patient Testing & treatment card National Viral Hepatitis Control Program				
Hospital Registration Number				
NVHCP ID				
	……/……/……. Date of starting DAA			
Basic Demographic Information				
Name	Age	Gender	M ☐ F ☐ TG ☐	
/Father's name/Mother's Name Guardian's name				
Address Home & street address State District Village/Town/city Pincode /Post office Contact Number				
Consent for communication: Y ☐ N ☐				
Date of HBsAg testing		Rapid	ELISA	Other
		Result of HBsAg		
Whether sample is being stored	Y ☐ N ☐	Condition of storage	Duration of Storage	
Whether sample is being transported	Y ☐ N ☐	Date of transport	If sample received for viral load in optimum conditions	
Date of HBVDNA testing	Result of HBV DNA			
Is there Cirrhosis at Registration	No ☐ Yes ☐	If yes then ☐ Compensated	Decompensated ☐	
(Criteria for Evaluating cirrhosis (At least one				
Ultrasound			___/_____/___ Date	
Fibroscan	(LSM Value (in kPa)		___/_____/___ Date	
*APRI	Score			
*FIB-4	ALT_____	ALT_____	Platelet Count	Age ___/_____/___ Date
	Score_____ ☐		☐	☐
If decompensated cirrhosis, select basis				
CP Score	Variceal bleed		Ascites	Encephalopathy
Drug Prescribed				
Patient not treated but transferred to higher centre Y ☐ N ☐ Reasons for transfer				
Place			Date	
The centre must do both APRI and FIB 4 scoring*				

Date of visit	Hemoglobin	Platelet count	ALT	AST	S.Bilirubin ((T/D/I	S.Albumin	INR	HBV DNA	Other ((USG	Remarks
Follow up visits										

S.No	Visit No.	Date of visit	Any new complaints or side-effects	Any other medications	Any remarks	Next Follow up Date	Signature of Doctor	Signature of pharmacist	Patients signature/ Thumb impression
Outcome of treatment									
On Treatment									
Loss to follow up									
Death									
Missed									
Interruption									
Restart									

Monthly Report

S.No	National Viral Hepatitis Control Program monthly report-Hepatitis B	
1	Name of Centre	
2	Code No.	
3	Name of District	
4	Name of State	
5	Name of Site-Incharge	
6	Report for the period	
7	**Total Number of patients found positive for Hepatitis B registering in Care**	
7.1	Total number of patients screened for HBsAg in that month	
7.2	Total Number of patients found positive for HBsAg in that month	
7.3	Total number of patients found eligible for treatment of Hepatitis B in that month	
8	**Initiation of Treatment for Hepatitis B**	
8.1	Total number of patients eligible for treatment for Hepatitis B put on treatment in that month	
8.2	Total number of patients ever started on treatment for Hepatitis B at the starting of the month	
9	**Treatment Outcomes for Hepatitis B**	
9.1	Total number of patients put on treatment for Hepatitis B continuing treatment as recorded through follow up visits in that month	
10	**Regimen status**	
10.1	Cumulative number of Hepatitis B patients onRegimen 1 at the end of the month	
10.2	Cumulative number of Hepatitis B patients on Regimen 2 at the end of the month	
10.3	Cumulative number of Hepatitis B patients on Regimen 3 at the end of the month	
11	**Treatment Outcome**	
11.1	"Cumulative number of patients who "transferred out	
11.2	"Cumulative number of patients who "transferred in	
11.3	The number of all patients whose treatment status in this month is “stopped treatment” due to medical reasons	
11.4	(Cumulative Number of patients who are lost to follow-up (LFU	
11.5	The number of patients who missed their doses in this month	
11.6	Total number of patients Referred to Higher center for further management	

Drug Stock								
Generic Drug name	Opening Stock	Stock Received during month	Add expiry date	Consumption during the month	Expiry during the month	Stock on last day of the month	Amt required for 3 months based on existing stock	Issues comment

Was there a stock out in this month Reasons for the stock out Yes ☐ No ☐

Signature of the nodal officer

Annexure 7: Patient's Referral Register

National Viral Hepatitis Control Program patient's referral register			
S.No.		Hospital Reg No	
Date		NVHCP Unique Id	
State	District	Block/CHC	PHC/Sub-centre
Name & Address		Age	Sex
Brief History of illness		Phone/Mobile	
Tested for		Suspected for	
Reasons for referral			
Referred by Signature Mobile No Designation		Referred to Signature Mobile No Designation	

Annexure 8: drug stock register

Dte.	Opening Stock	Stock Received				Stock transferred out	Stock dispensed (consumpt-(ion	Stock /expired discard-ed	Balance stock	Rem-ark
		Qty. (No of tablets)	Batch No.	Expiry Dte	Manu-facturing Date					

Annexure 9 :drug dispensation register

S.No.	Patient name	Patient registration No.	No. of tablets dispensed			Patient's signature
			Regimen 1	Regimen 2	Regimen 3	

Annexure 10: supervisory checklist

Supervisory checklist for treatment site National Viral Hepatitis Control Program		
S.No.	**Head**	**Response**
1	Name of the State/ District/ City/ town:	
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 healthcare facility for treatment	
5	Date of Supervisory Visit	
6	Members of the Visiting Team	
	i.	
	ii.	
	iii.	
7	Complete postal address of the Hospital with Pin Code	
8	Contact details of the Nodal person (mobile and email)	
9	Number of human resource available with designation under the program	S.No. Name Designation I II III IV
10	Number of human resource trained with Designation under the program	S.No. Name Trained (Y) I II III IV
11	How many cases have been identified for Viral hepatitis in the FY A B C E	
12	How many cases were treated/managed for viral hepatitis in the FY A B C E	
13	Is the record being maintained as per the NVHCP guidelines	
A	Patient treatmentCard	Y/N If no then why?
C	Stock for drugs	Y/N If no then why?

14	Has there been stock out of the drugs in the last three months?	Y/N	
15	If Yes, then when and why?		
16	How many patients diagnosed with Hepatitis B put on each regimen in that FY and the previous FY	Current FY	Previous FY
	Regimen I		
	Regimen II		
17	How many patients put on treatment have successfully completed treatment	Current FY	Previous FY
	Regimen I		
	Regimen II		
18	Are the sanctioned positions under the NVHCP for the treatment site filled	?Y/N	If No then why
	Positions	?Y/N	If No then why
	A	?Y/N	If No then why
	B	?Y/N	If No then why
	C	?Y/N	If No then why
	D		
S.No.	Key Issues Identified	Follow up Action recommended	
	Name of the supervisory visit officer	Signature	
1			
2			
3			
4			

REFERENCES

1. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. WHO 2015
2. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd ed. WHO, 2016
3. Guidelines for the screening care and treatment of persons with chronic hepatitis C infection. Updated version, April 2016, WHO
4. WHO Global Disease estimates 2016; WHO 2016
5. Central Bureau of Health Intelligence, Ministry of Health and Family Welfare. National Health Profile. New Delhi : s.n., 2016.
6. Cost-effectiveness of Hepatitis C Treatment using generic direct-acting antivirals available in India. Aggarwal, R, et al., et al. s.l. : PLOS One, 2017, Vol. 12. e0176503.
7. Prevalence of Hepatitis A virus, Hepatitis B virus, Hepatitis C virus, Hepatitis D virus and Hepatitis E virus as causes of acute viral hepatitis in north India: A Hospital based study. Jain, Prakash P, et al., et al. 2013, Indian Journal of Medical Microbiology, Vol. 31, pp. 261-5.
8. WHO guidelines on hepatitis B and C testing, WHO, Feb 2017
9. World Health Organization media centre. Hepatitis A fact sheet in world health organization media centre. [Online] 2016. http://www.who.int/mediacentre/.Harrison's Principles of Internal Medicine, 19th edition
10. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents; Downloaded from https://aidsinfo.nih.gov/guidelines on 6/27/2018
11. Colin JF, Cazals-Hatem D, Loriot MA, Martinot-Peignoux M, Pham BN, Auperin A, et al. Influence of human immunodeficiency virus infection on chronic hepatitis B in homosexual men. Hepatology. 1999;29(4):1306–10.133
12. Konopnicki D, Mocroft A, de Wit S, Antunes F, Ledergerber B, Katlama C, et al. Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. AIDS. 2005;19(6):593–601.
13. Thio CL, Seaberg EC, Skolasky R Jr, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). Lancet 2002;360:1921-1926.
14. Thio CL. Hepatitis B and human immunodeficiency virus co-infection. Hepatology. 2009;49(5 Suppl):S138–45.
15. Santantonio T, Fasano M,Current concepts on management of chronic hepatitis B. http//dx.doi.org/10.5772/54759: Karen C. Carroll, Stephen A. Morse, Timothy Meitzner, Steve Miller: Jawetz, Melnick, and Adelberg's Medical Microbiology, 27th Edition, Mc-Graw Hill Education.
16. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection , European Association for the Study of the Liver, Journal of Hepatology 2017 vol. 67 j 370–398
17. National guidelines for Diagnosis and management of Viral hepatitis, 2018. NVHCP, MoH& FW
18. National laboratory testing guidelines for viral hepatitis, 2018, NVHCP, MoH& FW
19. Operational guidelines for the National Viral Hepatitis Control Program, 2018. MoH& FW
20. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection, 2015

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