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VIRAL
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Hepatitis B diagnosis and management

PROTOCOL

INTERSECTION DOCUMENT

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MEDECINS SANS FRONTIERES

CONTENT

ABBREVIATIONS

3TC: lamivudine
AASLD: American association for the study of liver diseases
ALP: alkaline phosphatase
ALT: alanine aminotransferase
ANC: antenatal care
APRI: aspartate aminotransferase-to-platelet ratio index
AST: aspartate aminotransferase
anti-HBc: hepatitis B core antibody
anti-HBe: antibody to hepatitis B e antigen
anti-HBs: antibody to hepatitis B surface antigen
CHB: chronic hepatitis B
CrCl: creatinine clearance
CSW: commercial sex worker
CTP: Child-Turcotte-Pugh (score)
CT: computed tomography
EASL: European association for the study of the liver
EMR: electronic medical records
EPI: expanded program on immunization
EPTB: extrapulmonary tuberculosis
ESLD: end of stage liver disease
ETV: entecavir
GAVI: Alliance The Vaccine Alliance (formerly the Global Alliance for Vaccines and Immunization)
GGT: gamma glutamyl transpeptidase
HBcAg: hepatitis B core antigen
HBeAg: hepatitis B e antigen
HBsAg: hepatitis B surface antigen
HBV: hepatitis B virus
HCC: hepatocellular carcinoma
HCV: hepatitis C virus
HDV: hepatitis D virus
INR: international normalized ratio
IPD: inpatient department
LMICs: low- and middle-income countries
MDRTB: multi drug resistant tuberculosis
MSM: men who have sex with men
NCD: non-communicable diseases
OPD: outpatient department
OR: operational research
PHC: primary health care

PMTCT: prevention of mother to child transmission
PSEC: patient support, education and counselling
PT: prothrombin time
PWUD: people who use drugs
RDT: rapid diagnostic test
STI: sexually transmitted infection
TAF: tenofovir alafenamide
TDF: tenofovir (disoproxil)
ULN: upper limit of normal
US: ultrasound
VL: viral load
WHO: World Health Organization

1. INTRODUCTION

1.1. Generalities and epidemiology

Hepatitis B infection is caused by the hepatitis B virus (HBV), a DNA virus that infects the liver, causing hepatocellular necrosis and inflammation. HBV infection can be either acute or chronic, and the associated illness ranges in severity from asymptomatic to symptomatic. Chronic hepatitis B (CHB) is defined as persistence of hepatitis B surface antigen (HBsAg) for six months or more.

Worldwide, there are an estimated 257 million chronically infected persons, particularly in low- and middle-income countries (LMICs), and among them, 900.000 people die every year. The major complications of CHB are cirrhosis and hepatocellular carcinoma (HCC). HBV is the second most important known human carcinogen, after tobacco. Between 20% and 30% of those who become chronically infected will develop these complications [1].

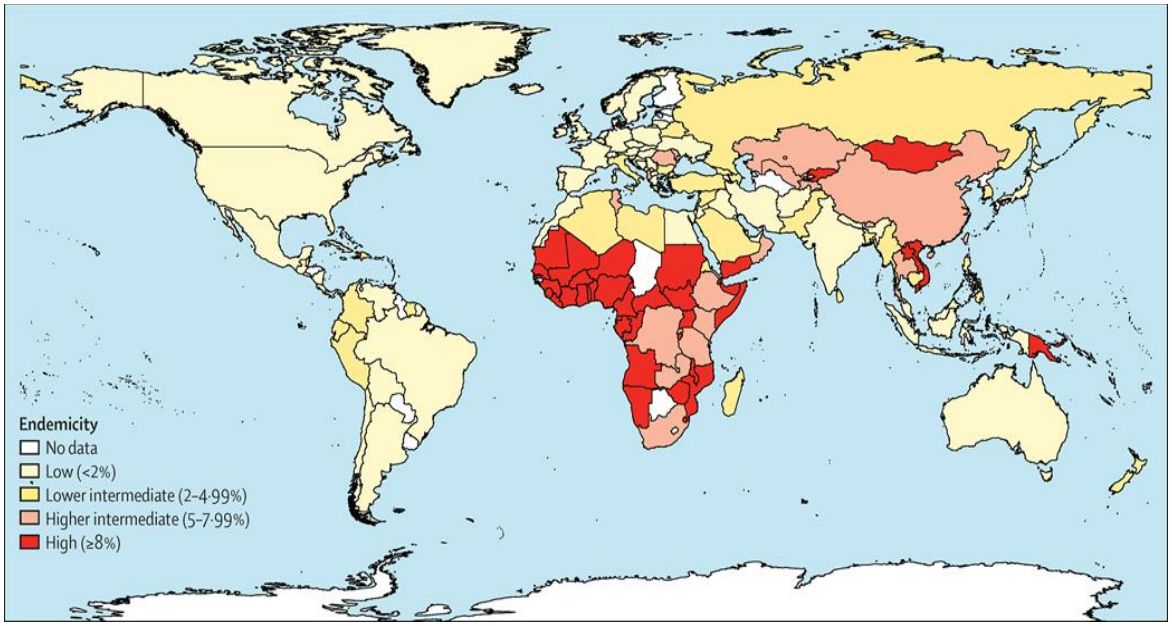


Figure 1: Global HBsAg endemicity (1957-2013) [2]

1.2. Transmission

HBV is transmitted by percutaneous or permucosal exposure to:

- Infected blood or fluids containing blood
- Other body fluids: semen, vaginal secretions

HBV is not spread through sneezing, coughing, kissing although the virus can be found in saliva. HBV can survive outside the body for at least 7 days.

HBV transmission [3-5]:

- Vertical transmission: from mother to child, mainly perinatal transmission; in utero or through breastfeeding transmission is rare.

- Horizontal transmission, including household, intrafamily and especially child to child, is also important. At least 50% of infections in children cannot be accounted for by mother-to-infant transmission and, in many endemic regions, prior to the introduction of neonatal vaccination, the prevalence peaked in children 7–14 years of age.
- In the adult population, mainly by injecting drug use, sexual activities, then inadequate sterilization of medical equipment and sharing of personal items (razors, toothbrushes…).

1.3. Prevention

1.3.1. Vaccination

Vaccination is an important means of preventing infection. Although vaccination is progressively being rolled out, coverage is far less than 100%. In 2015, global coverage with the three doses of hepatitis B vaccine in infancy reached 84%. However, there are regional differences in coverage. The African, Eastern Mediterranean and European regions remain below the global average. Furthermore, national and subnational data often suggest that vaccination coverage varies between and within countries. Coverage with the initial birth dose vaccination is still low at 39% [1].

Who should receive the vaccine?

- All infants (including low birth weight and premature infants) should receive their first dose of the hepatitis B vaccine as soon as possible after birth and within 24 hours, which can reduce transmission up to 85-90%.
- Although effectiveness declines progressively in the days after birth, after 7 days, a late dose can still be effective in preventing horizontal transmission and therefore remains beneficial at any time up to the time when all doses are provided following the expanded program on immunization (EPI) schedule.
- Other groups benefitting from vaccination include: health care workers, family members of infected patients, people living with HIV (PLHIV), men who have sex with men (MSM), sex workers (SW), people who use drugs (PWUDs).

1.3.2. Prevention of mother to child transmission (PMTCT):

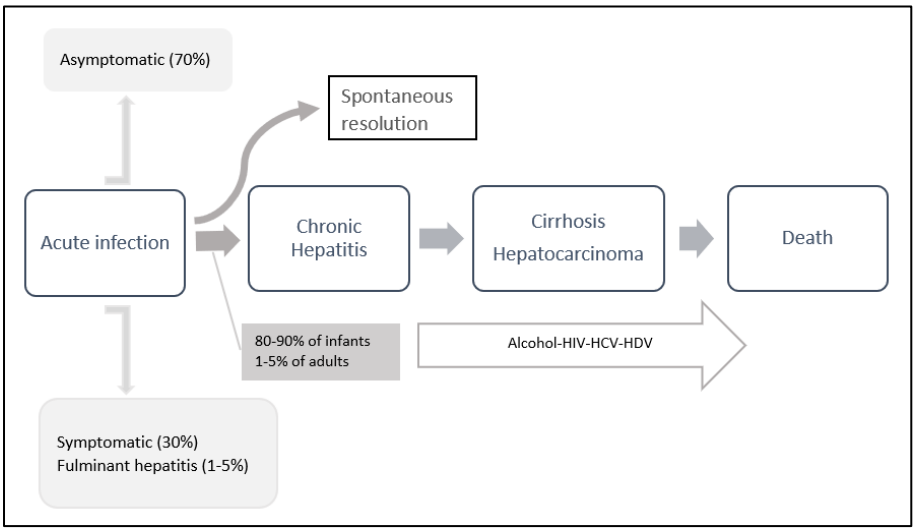
Mother-to-child transmission (MTCT) rates vary significantly according to the mother's hepatitis B e antigen (HBeAg) status (70%–90% transmission rate for HBeAg-positive mothers vs. 10%–40% for HBeAg-negative mothers). Hepatitis B vaccination administered immediately after birth (within 24 hours), followed by additional doses of vaccine according to the immunization schedule, prevents transmission in approximately 95% of cases [6]. However, a recent review of the published literature from 1975 to 2011 demonstrated that immunoprophylaxis fails to prevent HBV transmission in 8%–30% of children born to highly viremic mothers. High viremia, as HBeAg positivity, remains a strong predictor of MTCT [7].

There is a growing body of literature to support both the safety and efficacy of antiviral therapy initiated in late pregnancy for reduction of MTCT among women in the highest risk for immunoprophylaxis failure (those with high HBV DNA levels). The European association for the study of the liver (EASL) and American

association for the study of liver diseases (AASLD) guidelines recommend antiviral prophylaxis with tenofovir (TDF) in all pregnant women with high HBV DNA levels (>200,000 IU/ml) starting at week 24–28 of gestation continuing for up to 12 weeks after delivery. With discontinuation of treatment, women should be monitored for ALT flares every 3 months for 6 months [8-10].

Breastfeeding is not contraindicated in HBsAg-positive untreated women or on TDF-based treatment or prophylaxis. C-section is not indicated owing to insufficient data to support its benefit.

1.4. Natural history



In most cases (95%), acute HBV infection in adult leads to a full recovery with development of immunity. The risk of developing a chronic HBV infection is inversely related to age. Infection at an early age is more likely to become chronic: 80-90% of infants infected during their first year of life develop chronic HBV infection as opposed to 30-50% of children infected before the age of 6 years and 1-5% of adults. Positive HIV status also increases the risk of progression to chronic infection. Chronic infection carries a 15-25% risk of premature death from cirrhosis and hepatocellular carcinoma, with faster progression of liver disease among coinfected HIV+ HBV cases [3-5].

2. WHO TO SCREEN FOR HBV

A serological assay (generally, rapid diagnostic tests (RDT)) will be used to detect Hepatitis B surface antigen (HBsAg) for diagnosis of HBV infection. In case of acute hepatitis symptoms, it is recommended to repeat the same test 6 months later to confirm chronic infection.

Minimum essential	Best practice
Blood bank HIV patients HCV patients	TB patients Key populations: prisoners, PWUD, MSM and SW HIV patients at baseline

Pregnant women at ANC MDR TB patients Patients with symptoms of end stage liver disease (ESLD) complications Adults and adolescents with a clinical suspicion of acute viral hepatitis	Family members or sexual contacts of HBsAg(+) patients Cases of accidental blood exposure and sexual violence (baseline and follow-up)

3. DIAGNOSTICS OF HBV INFECTION AND LIVER STAGE

The following diagnostics and monitoring tools will be provided according to capacity and ambitions:

Minimum Essential	Best practice to assess the liver fibrosis and if HBV is active	Optional for better liver assessment
HBsAg test HIV test*	AST or ALT Platelets Creatinine HCV RDT HBV viral load[1] AgHBe /antiHBe[2]	Bilirubin Albumin INR GGT ALP Prothrombin time (PT) Abdominal ultrasound Fibroscan

*Required to avoid putting a patient with HIV on monotherapy with TDF.

Note: Laboratory facilities to test for creatinine, liver enzymes, platelets, etc. are helpful, but absence of this capacity should not prevent clinically advanced liver disease patients from receiving treatment. Similarly, ultrasound examination to exclude a hepatocellular carcinoma (CHC) (particularly when the image can be sent for telemedicine) is helpful but is not a pre-requisite for treatment.

4. WHO TO TREAT

4.1. Chronic HBV infection with compensated or decompensated cirrhosis:

- Clinical signs of decompensated cirrhosis such as ascites, encephalopathy, and evidence of oesophageal bleeding (hematemesis, haematochezia or melena) or jaundice. *A clinical*

[1] Soon available in geneXpert platform

[2] There is currently no reliable RDT for HBeAg or antiHBe. As such, access to lab based ELISA tests will be limited and only done in reliable validated external labs

presentation of decompensated cirrhosis is itself an indication to initiate chronic treatment and does not require any further lab confirmation.

- Clinical signs of cirrhosis and/or laboratory results (if available) with elements suggestive of cirrhosis such as low platelets, low albumin, prolonged PT, high bilirubin.
- High APRI index (using AST and platelets) > 1.5 (see annex 3).
- Signs of advanced liver fibrosis in elastography[3] (F3-F4 > 10 kPa).

Ultrasonographic signs of advanced fibrosis or cirrhosis: coarse echotexture, with mildly increased echogenicity, irregular nodular surface, iso / hypo / hyper echoic nodules, signs of portal hypertension [11]. Ascites can be the first evidence of presence of cirrhosis [12]. For more information, please see MSF Ultrasound Manual for the trained practitioners, 2018, page 172.
This group of patients should be given priority in MSF projects. In addition, treatment is proven to lower mortality in randomized clinical trials in this population [13-16]. However, for these severe patients, other supportive treatments are needed in addition to HBV treatment [17-18].

4.2. Active chronic HBV hepatitis without cirrhosis:

For this subgroup of patients, HBV treatment should be considered especially if follow up of patients with chronic conditions is already implemented in the project. If only ALT is available and can be done several times, it is possible to identify those in need of anti-HBV treatment [8-15]:

- Patients who test HBsAg(+) and who have persistently high ALT or AST **> 2** times the upper limit of normality in at least **2** different blood samples within **3-6** months without any other obvious causes (medications, infections, alcohol) will benefit from treatment as well.
- If HBV viral load available, patients with persistently high transaminases and evidence of high-level HBV replication (HBV DNA >20 000 IU/mL), regardless of HBeAg status, should be treated as well.

5. DIFFERENTIAL DIAGNOSIS

Multiples differential diagnoses should be considered as the symptoms of HBV hepatitis are not specific. This is not an exhaustive list:

Other viral hepatitis: A, C, E	Alcoholic hepatitis
Parasite induced liver diseases (schistosomiasis, malaria…)	Drug/Toxic induced liver injury (paracetamol or TB drugs being the most common)
Tuberculosis	Heart failure
Cholangitis	

[3] A better non-invasive technique for fibrosis assessment is elastography, however access is at best minimal in our project locations

Non-alcoholic steatohepatitis	Other causes of acute / fulminant hepatitis: yellow fever, leptospirosis, sepsis

Differentiating **HBV ascites** from **peritoneal TB** is described in Annex 3.

6. SPECIAL SITUATIONS

The appropriateness of starting treatment should be discussed with your supervisor or Hepatitis referent for the following type of cases:

6.1. Patients with end stage organ failure such as terminal heart, respiratory or renal failure:

- These patients have limited life expectancy and the benefit of treating chronic hepatitis B would be limited.

6.2. Clinical or radiological suspicion of liver cancer:

- Patients with clinical (e.g. fixed and hard abdominal mass on liver palpation and weight loss not due to TB) or sonographic evidence of liver cancer (solid liver mass) would not benefit for treatment; consider palliative care.

6.3. Untreated alcoholism or IV drug use:

- This group of patients requires further evaluation specially to assess adherence to care and psychiatric comorbidities (depression, post-traumatic syndrome, psychosis, etc.). However, if a patient requires treatment, being a drug user or alcoholic should not be a barrier for treatment. These conditions are not a contraindication for treatment and efforts should be made to include patients on psychosocial and harm reduction services as part of the therapy.

6.4. Patients HBsAg (+) on TB treatment with liver toxicity:

- Specific HBV treatment should be considered in this situation, particularly if TB treatment is at risk to be stopped due to liver toxicity. TDF should then be continued at least up to the end of TB treatment; discuss with Hepatitis advisor.

6.5. Coinfection with HCV:

- HBV-HCV coinfection may lead to an increased rate of liver disease progression. HBV therapy should not be denied in this situation; however, HCV is usually the predominant cause of liver disease (viral dominance). Therefore, HCV treatment should be discussed with your supervisor and Hepatitis advisor. Note that during HCV treatment, the general recommendation is that HBV treatment should be given at least up to 12 weeks after the end of HCV treatment to avoid risk of HBV flare among patients with chronic HBV. For cirrhotic patients, HBV treatment should be continued for life [19-21].

6.6. HIV coinfection:

- TDF monotherapy or dual therapy with only TDF/3TC or TDF/FTC should NEVER be used alone for HIV co-infected patients since this will lead to the development of HIV resistance [22].

6.7. Acute fulminant hepatitis:

- Any case of suspected acute fulminant hepatitis should be discussed with Hepatitis referent.

7. TREATMENT REGIMEN

For HIV negative patients, TDF is the drug of choice. Tenofovir alafenamide (TAF) and Entecavir, when available, are alternatives. In the absence of TDF alone, the use of TDF/3TC or TDF/FTC can simplify supply chain implications since it is routinely used in HIV programs in the same formulations. Lamivudine (3TC) has a hepatitis B antiviral effect but it is not used as it can easily develop resistant mutations (within 12 months of treatment).

	Tenofovir (TDF)	**Tenofovir alafenamide (TAF)**	**Entecavir**
Adult **Dosage**	√ 300 mg once daily	√ 10 mg once daily	√ 0.5 mg once daily
Children ≥2 to 12years old and < 30 kg **Dosage**	No	No	√ 10–11 kg: 0.15 mg/day >11-14kg: 0.2mg/day >14-17kg: 0.25mg/day >17-20kg: 0.3mg/day >20-23: 0.35mg/day >23-26kg: 0.4mg/day >26-30kg: 0.45mg/day >30 kg: 0.5 mg/day
Pregnancy/childbearing age women	√ 300 mg once daily	No	No
Risk of emergence of resistance	No	No	+/-
Adverse events	Generally, well tolerated, however headache, gastrointestinal disturbance and fatigue are commonly reported side-effects. Adapt dosage (see Annex 2) from Creatinine clearance < 50ml/min if feasible Renal toxicity is the main adverse event linked to TDF and Entecavir		

Renal failure	For patients with renal failure, interruption of TDF may lead to hepatitis flares if advanced liver disease. If TDF needs to be stopped, 3TC can be continued (while being adjusted to renal clearance). Thus, ideally a small amount of 3TC (without TDF) and/or entecavir[4] should be available in the project for the infrequent cases of severe renal toxicity. Find renal adjustment in Annex 2.

7.1. Treatment interruption:

In patients with cirrhosis, if treatment is abruptly stopped, there is a rare risk of a hepatitis B flare up and acute hepatitis; this is much less frequent in patients without cirrhosis. This risk must be well explained by the clinician or during patient support, education and counselling sessions to ensure adherence and alert to signs/symptoms that require immediate return to the health centre. Re-starting TDF would be indicated for patients who may have interrupted treatment.

7.2. Duration of treatment:

HBV treatment must be life-long for all patients, but especially in cirrhotic patients. The only exceptions to this rule would be pregnant women for PMTCT purpose, TB / MDRTB patients who were started only because of eventual toxicity or patients co-infected with HCV without indication of chronic treatment (see MSF HCV guidelines).

8. PATIENT MONITORING

8.1. Patient with indication for treatment with TDF:

Patients should be clinically evaluated and receive adherence support and evaluation during the first month of therapy. Schedule: M1-M3-M6 and then every 6 to 12 months, mainly to ensure drug refilling, clinical evaluation and adherence support.

Follow up may be done in OPD, at an HIV clinic or at any chronic disease OPD clinic or health care facility. It is important to note that even where creatinine and/or ALT testing is not available, treatment should still be started given the high mortality risk of the disease in severe advanced liver disease patient and the low risk of side effects. Patients should be counselled to come for consultation if signs of hepatitis flare or cirrhosis decompensation occur.

[4] Please, note that when this guideline was written, Entecavir was not part of MSF standard list of medications

Investigations	Clinical	Adherence	HBsAg	HCV	HIV	Creat Cl[5]	AST/ALT	PLT	APRI	HBeAg/ antiHBe[6]	HBV DNA VL	Abdominal US
Baseline	√	√	√	x	√	(x)	(x)	(x)	(x)	(x)	(x)	(x)
M1, M3	√	√										
M6	√	√		x*	x*	(x)	(x)				(x)	
Yearly (basis)	√	√		x*	√	(x)	(x)	(x)	(x)	(If HBeAg(+) at baseline)	(x)	(x)

*to consider every 6 months if risk factors

√: compulsory

(x): if available

If creatinine is not available, it is recommended to monitor urine dipstick for proteinuria. The accuracy of this approach to detect renal toxicity is not clearly demonstrated, but it is an option for settings without creatinine measurement given the low incidence of renal toxicity plus the high efficacy in HBV treatment. Increase in proteinuria is to be considered as a sign of progressive renal damage and TDF is to be stopped if proteinuria 3 +++.

8.2. Patients not requiring treatment

The follow-up of patients with chronic HBV infection but not requiring treatment (i.e. patients without advanced liver fibrosis, AST normal on 2 samples within 3-6 months) will depend on the operational ambitions. The project may decide not to follow these patients at all, as the possibility of the occurrence of an event that would necessitate the start of treatment within the timeframe of the project may be very low. However, the recommendation would be to follow up with these patients on a yearly basis, including lab tests (ALT/AST, HIV testing and HCV testing for high risk at minimum, etc.). The healthcare provider is

[5] To calculate Creatinine Clearance (Cockroft formula): $\frac{140 - \text{age [yrs]} * \text{weight [kg]} (*0.85 \text{ if female})}{\text{Serum creatinine [mg/dl]} * 72}$

[6] There is currently no reliable RDT for HBeAg or antiHBe. As such, access to lab based ELISA tests will be limited and only done in reliable validated external labs

responsible for educating the patient with chronic HBV infection about prevention of onward transmission and harm reduction services as indicated.

8.3. Treatment response:

8.3.1. Clinical markers of treatment response:

It is expected that signs of active liver disease (such as jaundice or abdominal pain) and episodes of cirrhosis decompensation will be controlled with anti-HBV therapy. If cirrhosis develops or signs of active hepatitis (clinical or laboratory e.g. high ALT) persist despite adherence to TDF, another cause of liver disease should be ruled out and it should be checked if the patient is on any drug or traditional medicine with potential for liver toxicity.

Of note, for those with extremely advanced liver disease at the start of treatment, episodes of decompensation may happen even without treatment failure (resistance), reflecting that the start of treatment was likely far too late.

8.3.2. Laboratory markers of treatment response:

- HBV viral load: is the best marker to monitor response to anti-viral treatment, though not usually available in our settings. Response can take longer than 12 months if VL initial is very high (> 8 Log).
- AST and/or ALT: Normalization is to be expected only after at least 6-12 months of anti-HBV therapy.
- If AST and/or ALT increases after a period of normalization, low adherence or drug resistance (if treatment is different than TDF) should be highly suspected, (note: Resistance to TDF is very uncommon, even when used as monotherapy for 5 years).

For other means of monitoring treatment response, see Annex 1.

9. PATIENT SUPPORT, EDUCATION AND COUNSELLING (PSEC):

Similar to HIV and TB treatment, adherence is key for HBV treatment. Adequate patient education and counselling before therapy begins is important to ensure optimal adherence, particularly among those with advanced liver disease. The medical staff and/or PSEC teams from HIV/TB activities may be involved in providing adherence support for HBV cases. In programs without HIV/TB adherence counsellors, adherence support may be provided by one of the nursing staff or by the medical staff providing hepatitis care.

At each visit, it is important for the medical staff member and/or counsellor to evaluate adherence, substance or other medication use, understanding and use of preventive measures, answer to any questions or difficulties the patient has, and to address accordingly. Also, hepatitis support groups are useful to improve coping and compliance with clinical therapies and harm-reducing behaviours. Hence, they can improve quality of life and, potentially, treatment outcomes.

Please, see Annex 4 for more detailed information "Hepatitis B treatment – Key Messages for patient education". Same as for HIV/TB, all healthcare team members are responsible for reinforcing patient education. Knowledge and self-care skills are necessary pre-requisites for maintaining sufficient adherence [23].

10. IMPLEMENTATION STRATEGIES

Three potential options for implementation of HBV activities:

- For programs in resource limited settings where HBV treatment is still in the first steps of implementation, the ambition is to focus on the patients with more urgent needs, which are those with hepatic cirrhosis due to HBV. Patients suffering from chronic hepatitis are frequently seen in MSF programs when admitted with end stage liver disease. Currently these patients do not receive treatment unless they have HIV.
- In well-established settings/projects, where patients are treated and followed up for middle/long term chronic disease (NCD, HIV, TB, HCV), the ambition goes beyond cirrhotic patients, and includes diagnosis and treatment of patients at risk of developing cirrhosis or hepatocarcinoma in the mid and long term (patients with persistently high AST and/or ALT showing liver inflammation) .
- In setting where MSF is involved in ANC, the ambition is to prevent mother-to-child transmission using the gold standard of early birth HBV immunization regardless of the mother's HBV status. Short term TDF introduction during pregnancy in MSF projects to further decrease the risk of transmission to the baby should be done as a pilot project or as operational research (OR) until further implementation and feasibility data are available.

For monitoring & evaluation (M&E) indicators and resources, please see Annex 7 and 8.

REFERENCES

1) WHO hepatitis global report 2017
2) Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet. 2015 Oct 17;386(10003):1546-55.
3) Mandeville KL, Krabshuis J, Ladep NG, Mulder CJ, Quigley EM, Khan SA. Gastroenterology in developing countries: issues and advances. World J Gastroenterol. 2009 Jun 21;15(23):2839-54.
4) Liaw YF, Chu CM. Hepatitis B virus infection. Lancet. 2009 Feb 14;373(9663):582-92.
5) Carneiro de Moura M, Marinho R. Natural history and clinical manifestations of chronic hepatitis B virus. Enferm Infecc Microbiol Clin. 2008 May;26 Suppl 7:11-8.
6) WHO. Weekly epidemiological record. 16 Feb 2018, No 7, 2018, 93, 61–72. https://www.who.int/immunization/policy/position_papers/hepatitis_b/en/
7) Pan CQ, Duan ZP, Bhamidimarri KR, et al. An algorithm for risk assessment and intervention of mother to child transmission of hepatitis B virus. Clin J Gastroenterol Hepatol 2012; 10:452–9
8) An CQ, Duan Z, Dai E, Zhang S, Han G, Wang Y, et al. Tenofovir to prevent hepatitis B transmission in mothers with high viral load. N Engl J Med 2016;374:2324–2334.
9) Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH. AASLD guidelines for treatment of chronic hepatitis B. Hepatology 2016; 63: 261-83
10) European Association for the Study of the Liver. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. J Hepatol 2017; 67: 370-98
11) MSF Ultrasound Manual for trained practitioners, 2018
12) Runyon BA, American Association for the Study of Liver Diseases Introduction to the revised American Association for the Study of Liver Diseases practice guideline management of adult patients with ascites due to cirrhosis 2012. Hepatology. 2013; 57(4):1651–3.
13) Thursz M, Cooke GS, Hall AJ. Hepatitis B treatment in resource poor settings: time for action. Trop Med Int Health. 2010 Jan;15(1):2-4.
14) Lok AS, McMahon BJ. AASLD PRACTICE GUIDELINES: Chronic hepatitis B: update 2009. Hepatology. 2009 Sep;50(3):661-97.
15) Liaw YF, Leung N, Kao JH, Piratvisuth T, Gane E, Han KH, Guan R, Lau GK, Locarnini S; Chronic Hepatitis B Guideline Working Party of the Asian-Pacific Association for the Study of the Liver. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update. Hepatol Int. 2008 Sep;2(3):263-83.
16) European Association For The Study Of The Liver. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol. 2012 Jul;57(1):167-85.
17) Marcellin P, Gane E, Buti M, Afdhal N, Sievert W, Jacobson IM, Washington MK, Germanidis G, Flaherty JF, Schall RA, Bornstein JD, Kitrinos KM, Subramanian GM, McHutchison JG, Heathcote EJ. Regression of cirrhosis during treatment with Tenofovir Disoproxil fumarate for chronic hepatitisB: a 5-year open-label follow-up study. Lancet. 2013 Feb 9;381(9865):468-75.
18) MSF protocol for management of End Stage Liver disease (ESLD)

19) Ayoub WS, Keeffe EB. Review article: current antiviral therapy of chronic hepatitis B. Aliment Pharmacol Ther. 2011 Nov;34(10):1145-58.
20) Riaz M, Idrees M, Kanwal H, Kabir F. An overview of triple infection with hepatitis B, C and D viruses. Virol J. 2011 Jul 27;8:368.
21) Hughes SA, Wedemeyer H, Harrison PM. Hepatitis delta virus. Lancet. 2011 Jul 2;378(9785):73-85.
22) Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. 1–239. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf
23) 2018 MSF PSEC Guideline for Adults Living with HIV and/or TB

ANNEX 1: Relevant scores

1) APRI index: gives a proxy of the liver fibrosis.

AST-to-platelet ratio index (APRI): this is a non-invasive test using AST and platelet counts to estimate the level of liver fibrosis; the accuracy for co-infected HIV + HBV cases is decreased. The calculation is made as follows:

$$APRI = \frac{\frac{AST\ level}{ULN\ *}}{Platelet\ counts\ (10^9/L)} x100$$

ULN: depending on the Lab norm (if not available take 40UI)

2) Clinical and laboratory markers of cirrhosis prognosis – Child Pugh score:

This score is used in patients with cirrhosis or with an APRI score 1.5 and above to estimate the degree of liver dysfunction and estimate prognosis (survival). The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement.

Table 1. CTP scoring

Measure	1 point	2 points	3 points
Total bilirubin, µmol/L (mg/dL)	<34 (<2)	34-51 (2-3)	>51 (>3)
Serum albumin, g/dL	>3.5	2.8-3.5	<2.8
INR	<1.7	1.70-2.30	> 2.30
Ascites (see below)	None	Mild	Moderate to Severe
Hepatic encephalopathy (see below)	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

CTP interpretation

Points	Class	One year survival	Two years survival
5-6	A: advanced liver disease compensated	100%	85%
7-9	B: advanced liver disease decompensated	81%	57%
10-15	C: advanced liver disease decompensated	45%	35%

Measure: West Haven Criteria of hepatic encephalopathy:

- **Grade I** - Trivial lack of awareness; euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction; altered sleep rhythm

- **Grade II** - Lethargy or apathy; disorientation for time; personality change; inappropriate behaviour; asterixis
- **Grade III** – Somnolence to semi-stupor but responsive to verbal stimuli; confusion; gross disorientation;
- **Grade IV** - Coma (unresponsive to verbal or painful stimuli).

Measure: Grades of ascites:

- Mild- only visible on ultrasound and CT
- Moderate- detectable with flank bulging and shifting dullness
- Severe- directly visible, confirmed with the fluid wave test

ANNEX 2: Drug dosage adaptation according to renal function

	CrCl ≥ 50ml/min	CrCl 30–49ml/min	CrCl < 30 ml/min
Tenofovir(TDF) (Adults and adolescents >12 years)	One 300 mg tablet/day	One 300 mg tablet every 48 hours	No
Tenofovir Alafenamide 10mg	One tablet 10mg /day	One tablet 10mg/day	No
Entecavir (ETV) (Adults)	0.5 mg tablet/day	0.5 mg every 48 hours	No
Entecavir adults and Decompensated liver disease	1 mg tablet/day	0.5 mg / day OR 1 mg every 48 hours	No
Lamivudine (3TC) (Adults)	100mg/ day if available. If not, use 300 mg OD	100 mg first dose, then 50 mg once daily	15-29ml/min*: 100 mg first dose, then 25 mg once daily ---------- 5-14ml/min* : 35 mg first dose, then 15 mg once daily ---------- <5 ml/min* : 35 mg first dose, then 10 mg once daily

*For end stage renal failure, contact your Hepatitis Advisor.

ANNEX 3: Differentiating HBV ascites from peritoneal TB

There is a high incidence of TB in many MSF project locations; therefore, it is important to first rule out TB as TB treatment is the priority even in HBV patients. Although unusual, it is not impossible for a patient with liver cirrhosis to have TB as well and even peritoneal TB – discuss with HIV/TB/Hepatitis advisor and pay attention to the peritoneal fluid exams.

	Ascites from decompensated HBV liver disease	**TB peritonitis**
Presentation	Ascites : • Voluminous • no pain and no fever (however, they may be present if there is spontaneous bacterial peritonitis) • other signs of chronic liver disease and cirrhosis (see above: telangiectasia, gynecomastia; encephalopathy, history of hematochezia or melena)	Ascites: • less voluminous • abdominal pain and systemic signs of TB (weight loss, fever, night sweats) • signs related to TB elsewhere, particularly pulmonary TB in roughly 1/3 of cases (cough > 2 weeks, with or without sputum, with or without bloody sputum; abnormal chest radiography) • Other signs of EPTB and/or disseminated TB may be present as well, e.g. lymphadenopathy or increased liver/spleen).
Lab	Signs of cirrhosis: • prolonged prothrombin time; low albumin; low platelets, increased direct bilirubin Ascites fluid: Rivalta test positive High serum-ascites albumin gradient (>1.1 g/dL) (with low serum albumin, <2.5g/dL and low protein content in ascites fluid). White blood cells (WBC) not increased (unless there is spontaneous bacterial peritonitis, when neutrophils > 250/mm3 and antibiotic treatment should be prescribed)	Xpert MTB/RIF positive or negative; always check for concomitant pulmonary TB! Ascites fluid: Rivalta test negative low serum-ascites albumin gradient (<1.1g/dL), protein levels may be increased, as well as lymphocytes.Acid fast bacilli (AFB) is frequently negative even with confirmed TB, while Xpert MTB/RIF may have moderate sensitivity to detect true TB (around 30%).

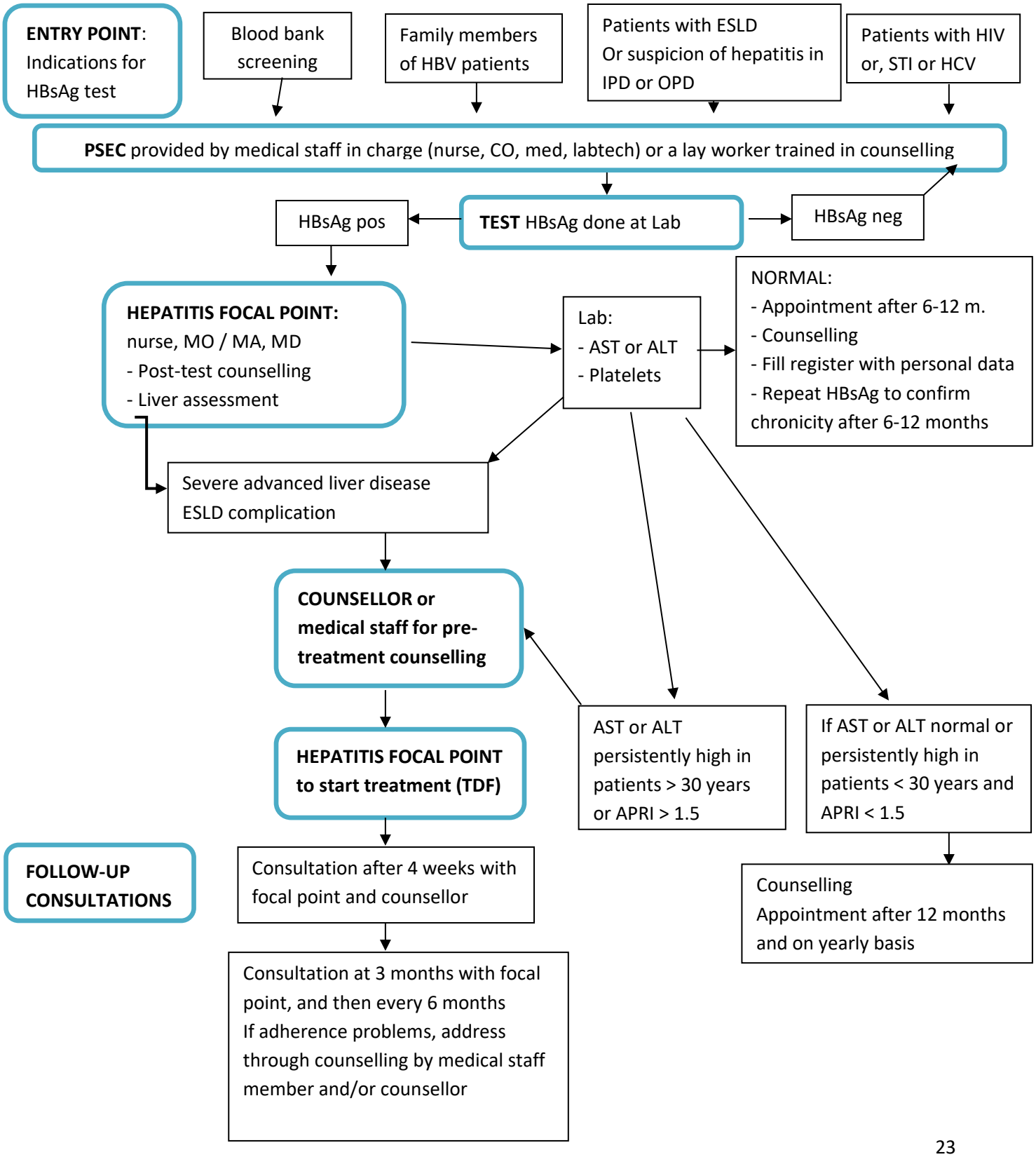
ANNEX 4: HBV Patient Education – Key Messages

How to use the messages	• Assess patient baseline understanding and ask what they would like to know; • Respond to key gaps of importance to self-management and prevention of further transmission and to what patient wants to know; • Try to adapt messages to health literacy level of patient.
What is Hepatitis B virus (HBV)?	- Hepatitis means inflammation of the liver; the inflammation can be acute or chronic. - The main function of the liver is to remove all toxic substances from the body. - There are many causes of hepatitis, for example but not limited to: several different viruses, alcohol, exposure to various recreational drugs or prescription medication. - One virus that causes hepatitis is called the **Hepatitis B virus (HBV).** - The Hepatitis B virus is transmitted from human to human (see below).
What happens if someone gets infected by Hepatitis B?	- HBV will cause a short-term **acute infection**, with or without symptoms. - In most patients infected by HBV, the immune system will be able to clear the virus or keep it under control without treatment. - Any individual's capacity to clear the virus depends on the age when HBV infection occurs. The earlier it occurs in childhood, the higher is the risk of becoming chronically infected. - Few patients will develop a long-term infection called **chronic hepatitis B.** - Many people with **chronic Hepatitis B** (CHB) remain well but can still pass on the virus to others. - Some people with CHB will develop serious liver problems that may require treatment. - The younger a person is when infected with HBV, the higher is the chance that they develop CHB later in life**.**
How is HBV transmitted?	- A person can become infected with HBV if in direct contact with the blood or bodily fluids (i.e. vaginal secretions or semen) of someone living with HBV. - HBV is mainly passed on by unprotected sexual contact, sharing needles/razors and from mother to child during childbirth (but not by kissing nor breastfeeding)
What are the symptoms?	- In the acute phase, less than half of HBV cases will have symptoms. They include nausea, vomiting, stomach pain, fever and jaundice (the skin may look yellow). - People with CHB may have jaundice, fatigue, bleeding, abdominal tenderness and discomfort.
How can Hepatitis B be prevented?	- By Hepatitis B vaccination for people who are not yet infected. - By using condoms consistently and correctly during sexual activity. - By single use syringes needles or razors, and avoidance of sharing toothbrushes or any sharp objects. - By using clean and safe medical and dental equipment and procedures.

How is hepatitis B diagnosed?	- A rapid test is done to check for Hepatitis B infection. If the rapid test is positive, that means the virus is present. However, the test cannot tell the difference between recent and chronic infection. If there are no symptoms of liver disease, the doctor/nurse will ask to repeat the test in 6 months. If there are already symptoms or complications of liver disease, the doctor/nurse may propose to start treatment. The doctor may also order additional blood tests to measure the health of the liver and to monitor the amount of virus in the blood. - This information will help to determine if the liver is swollen (inflamed), how well it is working, and if treatment is needed.
Who needs HBV treatment?	- All patients who also have HIV - Patients with symptomatic HBV infection (e.g. jaundice, fatigue, bleeding, abdominal tenderness and discomfort) or if blood tests indicate liver inflammation or advanced disease.
What is the treatment for Active Chronic Hepatitis B?	- A combination of one (Tenofovir) or two anti-retroviral medications (either Tenofovir/Lamivudine or Tenofovir/Emtricitabine) usually combined in one pill per day. - Entecavir will be used for children or in case of contraindication to Tenofovir. For patients co-infected with HIV the treatment may be the same as for HIV if patients have TDF and 3TC or FTC as part of their HIV regimen. - Treatment is lifelong.
What to do if treatment is not needed?	- The partners and children of people living with HBV infection need to be screened. Those who are not infected must receive three doses of hepatitis B vaccine. - To keep the liver healthy, people with HBV should avoid the consumption of alcohol as much as possible, as it makes hepatitis worse. - Using recreational drugs and some traditional remedies is also a heavy burden for the liver as it has to remove more toxins. The best thing would be to avoid all recreational drugs and discuss any medicine or traditional remedy with a doctor. - The best thing to keep the liver healthy is to maintain a healthy body weight and to have a well-balanced diet. - The people living with HBV infection will need to practice prevention methods (as specified above). - People living with HBV infection will have to go for check-ups including blood tests every 6-12 months.
What to do when on treatment?	- All the steps mentioned above are also crucial for people on treatment for CHB - It is very important to take the pills every day; to decrease the risk of severe liver damage and avoid stopping treatment without consulting your doctor. - In general terms, the HBV treatment is for life long. - In the case of interruption of HBV treatment, there is a risk for the disease to be reactivated which may lead to severe liver damage that can be life threatening if not treated (mainly patients with very advanced liver disease)

	- The treatment has minor side effects like feeling fatigue, headache and nausea that may be similar to symptoms of hepatitis, but usually last only for a couple of weeks at the beginning of treatment. - The treatment can have an influence on renal function (another organ involved in filtration) so kidney function should be monitored through a blood test. If side effects persist, treatment should not be interrupted without medical advice.

ANNEX 5: Example of flow for hepatitis B patients



ANNEX 6: Hepatitis B indicators

Minimum set of indicators:

Data element or indicator	Target	Data element	Numerator	Denominator	Reporting
Health facility					
Proportion of the HBsAg positive results amongst all RDT performed	N/A		Number of HBsAg tests positive	Total number of HBsAg tests performed in the project	Monthly
Hep B program (cascade):			Numerator	Denominator	
Number of patients with chronic hepatitis B** eligible for treatment	N/A	Number of patients with chronic hepatitis B** enrolled into cohort who are eligible for treatment			Quarterly
Number of patients who start chronic hepatitis B treatment during the period	N/A	Number of patients who start chronic hepatitis B treatment during the period			Quarterly
Hep B outcomes					
Hepatitis B: patients on treatment under care at the end of the period (%)	>90%		Number of patients with chronic hepatitis B under chronic treatment who are active by the end of the period	Number of patients who ever started chronic hepatitis B treatment	Quarterly
Hepatitis B: lost to follow up rate (%) by the end of the period	<10%		Number of patients with chronic hepatitis B who defaulted during the period	Number of patients with chronic hepatitis B enrolled in the program	Quarterly
Hepatitis B: mortality rate by the end of the period	<5%		Number of patients with chronic hepatitis B who died during the period	Number of patients with chronic hepatitis B enrolled in the program	Quarterly

Extended set of indicators (including minimum set of indicators):

Data element or indicator	Target	Data element	Numerator	Denominator	Reporting
Health facility					
Proportion of the HBsAg positive results amongst all RDT performed	N/A		Number of HBsAg tests positive	Total number of HBV tests performed in the project	Monthly
Proportion of hospitalisations due to complications of chronic hepatitis B among total of hospitalizations	N/A		Number of hospitalisations due to complications of chronic hepatitis B	Number of hospitalizations	Monthly
Proportion of patients who died due to complications of chronic hepatitis B among total hospitalization due to complications of chronic hepatitis B	N/A		Number of patients who dies due to complications of chronic hepatitis B	Number of hospitalisations due to complications of chronic hepatitis B	Monthly
Proportion of new-borns in MSF supported maternity vaccinated for Hep B at birth (first 24 hours)	>95%		Number of new-borns vaccinated for Hep B at birth (first 24 hours)	Total number of new-borns in MSF supported maternity	Monthly
Hep B program (cascade):			Numerator	Denominator	
Total number of patients enrolled in the Hepatitis B program		Patients with HBsAg positive enrolled in the program (carriers/ chronic hepatitis)			Quarterly
Number of patients with chronic hepatitis B** eligible for treatment	N/A	Number of patients with chronic hepatitis B** enrolled into cohort who are eligible for treatment			Quarterly
Proportion of patients with chronic hepatitis eligible for treatment among total patients enrolled with hepatitis B	<20%		Patients with active chronic hepatitis B**	Patients with HBsAg*	Quarterly
Number of patients who start chronic hepatitis B treatment during the period	N/A	Number of patients who start chronic hepatitis B treatment during the period			Quarterly

Proportion of patients eligible for treatment who start chronic treatment during the period	>90%		Number of patients who start chronic hepatitis B treatment during the period	Number of patients with chronic B hepatitis**enrolled into cohort who are eligible for treatment	Quarterly
Hep B outcomes					
Hepatitis B: patients on treatment under care at the end of the period (%)	>90%		Number of patients with chronic hepatitis B under chronic treatment who are active by the end of the period	Number of patients who ever started chronic hepatitis B treatment	Quarterly
Hepatitis B: lost to follow up rate (%) by the end of the period	<10%		Number of patients with chronic hepatitis B who defaulted during the period	Number of patients with chronic hepatitis B enrolled in the program	Quarterly
Hepatitis B: mortality rate by the end of the period	<5%		Number of patients with chronic hepatitis B who died during the period	Number of patients with chronic hepatitis B enrolled in the program	Quarterly
Hepatitis B: virological suppression among patients on treatment	>90%		Number of hepatitis B patients on treatment with virological suppression	Number of hepatitis B patients with available viral load	Quarterly

* HBsAg positive = asymptomatic carriers or chronic hepatitis B

**Active chronic hepatitis B: persistent hepatic cytolysis (AST or ALT >2 times the upper limit of normality or evidence of ESLD (clinical, APRI, US, elastography)

ANNEX 7: Example of clinical form baseline & treatment (WHO model)

Appendix 1. WHO template for a chronic hepatitis B and C patient management card

Identification:

Unique identifier |_|_|_|_|_|_|_|_|_|_|

District: _____ | Health unit: _____ | District clinician/team: _____

Name: _____ | First name: _____ | Patient clinic number: _____

Sex: |_|Female |_| Male|_| Other | Date of birth: ___ / ___ / ___ | Nationality: _____

Address: _____ | District: _____ | Telephone: _____

Infection status on enrolment:

Enrolment date: ___ / ___ / ___

HBsAg: |_|Positive|_| Negative |_| Not done | HBV DNA (IU/mL): |_____|Value|_| Negative |_| Not done | HBeAg: |_|Positive|_| Negative |_| Not done

Date of first diagnosis of HBV infection: ___ / ___ / ___ | HDV RNA (IU/mL): |_|Positive|_| Negative |_| Not done | Anti-HDV: |_|Positive|_| Negative |_| Not done

Anti-HCV: |_|Positive|_| Negative |_| Not done | HCV RNA (IU/mL): |_|Value|_| Negative |_| Not done | HCV core Ag: |_|Positive|_| Negative |_| Not done

Date of first diagnosis of HCV infection: ___ / ___ / ___ | HCV genotype: |_|

Anti-HIV: |_|Positive|_| Negative |_| Not done | HIV treatment regimen: _____ | Date HIV treatment started: _____

Latest HIV viral load (copies/mL): _____|_| Not done | CD4 count: _____ x 10^9/L |_| Not done

Tuberculosis: |_|Active|_| On treatment|_| No

Injection drug use: |_|Active (last 12 months) |_| Past history |_| No | Daily alcohol consumption: _____ | Metabolic syndrome: _____

Staging:

Staging date: ___ / ___ / ___

ALT: ____ IU/mL AST: ____ IU/mL PLT: ____ /mm^3 | Clinical diagnosis of cirrhosis: |_|Yes|_| No | If yes, Child–Pugh score: _____

APRI score: ___ |_| Not done FIB4: _____ |_| Not done | Transient elastography (kPa): _____ |_| Not done | Liver biopsy stage (F): _____ |_| Not done

Bilirubin: Total_____µmol/L and Direct: _____µmol/L | Ultrasound scan: _____ | Prothrombin time/INR: _____

Hepatitis B treatment:

Past experience with treatment: |_|Yes|_| No | Past treatment regimen: _____

HBV treatment regimen started (medicine): _____ | Date stated: ___ / ___ / ___ | Date stopped: ___ / ___ / ___

First annual viral response assessment

Date tested: ___ / ___ / ___ | HBV DNA(IU/mL: |_|Positive|_| Negative |_| Not done | ALT: ____ IU/mL

Hepatitis C treatment:

Past experience with treatment: |_|Yes|_| No | Past treatment: _____

HCV treatment regimen started: _____ | Date stated: ___ / ___ / ___ | Date completed: ___ / ___ / ___

Sustained viral response assessment post treatment (usually at SVR12, i.e. 12 weeks after the completion of treatment)

Date tested: ___ / ___ / ___ | HCV RNA: |_|Positive|_| Negative |_| Not done