REPUBLIC OF ZAMBIA
MINISTRY OF HEALTH

Guidelines for Prevention, Diagnosis, Care and Treatment of Viral Hepatitis Infection

2025

Directorate of Clinical Care and Diagnostic Services

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Acronyms

AFP	Alpha-fetoprotein
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
Anti-HAV	Antibody against hepatitis A virus
Anti-HBc	Antibody against hepatitis B core antigen
Anti-HCV	Antibody against hepatitis C virus
Anti-HDV	Antibody against hepatitis D virus
Anti-HEV	Antibody against hepatitis E virus
APRI	Aspartate aminotransferase to Platelet Ratio Index
AST	Aspartate aminotransferase
CHB	Chronic HBV infection
DAA	Direct-acting antiviral
DNA	Deoxyribonucleic acid
ETV	Entecavir
FIB-4	Fibrosis-4 score
GGT	Gamma-glutamyl transferase
HAV	Hepatitis A virus
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
HEV	Hepatitis E virus
HepB_BD	Hepatitis B birth-dose vaccination in newborns
HIV	Human immunodeficiency virus
Ig	Immunoglobulin
LFTs	Liver function tests
MASLD	Metabolic dysfunction associated steatotic liver disease
MOH	Ministry of Health
NAT	Nucleic acid testing
RDT	Rapid diagnostic tests
RNA	Ribonucleic acid
SVR	Sustained virological response
TB	Tuberculosis
TDF	Tenofovir disoproxil fumarate
ULN	Upper limit of normal
WHO	World Health Organization

Foreword



Viral hepatitis remains a major public health challenge in Zambia, contributing significantly to liver-related morbidity and mortality. Among the various forms, hepatitis B continues to pose a particularly pressing concern due to its silent progression and long-term consequences if left undiagnosed or inadequately managed.

These guidelines represent a collaborative and evidence-based effort to equip healthcare providers across the country with the knowledge, tools, and practical strategies necessary to identify, manage, and support individuals affected by viral hepatitis, especially hepatitis B. They are designed to promote the adoption of standardized practices, enhance clinical decision-making, and improve patient outcomes at every level of the healthcare system in Zambia.

In line with national health priorities and the World Health Organization's goal of eliminating viral hepatitis as a public health threat by 2030, this document emphasizes the importance of early diagnosis, comprehensive care, vaccination, and integration of hepatitis services into existing health programs. Special attention has been given to strengthening surveillance systems, ensuring access to quality treatment, and expanding preventive measures.

Equally important is the need to raise public awareness and reduce stigma associated with hepatitis. A well-informed community is a critical partner in disease prevention and health promotion. By combining clinical excellence with public engagement, we can create an enabling environment for early detection, treatment adherence, and long-term disease control.

The success of this initiative depends on the commitment and collaboration of all stakeholders, clinicians, public health professionals, policymakers, and community advocates. We invite all programme managers to utilize these guidelines as a practical resource in their daily practice and to join the broader effort toward the elimination of viral hepatitis as a public health threat.

Together, through shared responsibility and coordinated action, we can move decisively toward a future free of viral hepatitis.



Hon. Dr. Elijah Julaki Muchima, PHD, MP
Minister of Health

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We also acknowledge the valuable technical input and review provided by collaborating government departments and professional bodies, as well as the support of cooperating partners and implementing organisations, who ensured alignment with global evidence and national priorities.

Above all, we commend the leadership within the Ministry of Health and the unwavering commitment of all stakeholders, whose efforts will be critical to translating these guidelines into improved prevention, earlier diagnosis, and enhanced care for the people of Zambia.



Dr Kennedy Lishimpi
Permanent Secretary– Technical Services

Glossary of Terms

Natural history of hepatitis B virus infection

Acute HBV infection	New-onset hepatitis B infection that may or may not be icteric or symptomatic. Diagnosis is based on detection of hepatitis B surface antigen (HBsAg) and IgM antibodies to hepatitis B core antigen (anti-HBc). Recovery is accompanied by clearance of HBsAg, with seroconversion to anti-HBs (anti-bodies to hepatitis B surface antigen), usually within six months
Chronic HBV infection	Defined as persistence of HBsAg for six months or more after acute infection with HBV. Throughout the guidelines, chronic hepatitis B (CHB) is used to indicate chronic HBV infection
Immune-tolerant phase	High replicative phase of infection in the early stage of CHB among people infected at birth or in early childhood. No evidence of liver inflammation (normal liver)
Immune-active phase	Phase of hepatitis B e antigen (HBeAg)-positive disease characterized by fluctuating aminotransferases and high HBV DNA concentrations. May result in seroconversion from HBeAg to antibody to hepatitis B e antigen (anti-HBe)
Inactive phase (or immune-control phase)	Low replicative phase of CHB characterized by HBeAg negativity, anti-HBe positivity, normal alanine aminotransferase (ALT) and HBV DNA concentration below 2000 IU/mL
HBeAg seroconversion	Loss of HBeAg and seroconversion to anti-HBe
HBeAg-negative CHB (Immune-escape phase)	HBeAg-negative but anti-HBe-positive disease with varying levels of HBV replication and liver injury
HBsAg seroconversion	Loss of HBsAg and development of anti-HBs
HBeAg reversion	Reappearance of HBeAg among people who were previously HBeAg negative and usually associated with increased HBV replication
Cirrhosis	An advanced stage of liver disease characterized by extensive hepatic fibrosis, nodularity of the liver, alteration of liver architecture and disrupted hepatic circulation
Decompensated cirrhosis	Clinical complications of cirrhosis become manifest, including jaundice, ascites, spontaneous bacterial peritonitis, oesophageal varices and bleeding, hepatic encephalopathy, sepsis, and renal failure
Hepatocellular carcinoma	Primary cancer of the liver arising in hepatocytes

Serological markers of HBV

Hepatitis B surface antigen	HBV envelope protein and excess coat particles detectable in the blood in acute and CHB infection
Hepatitis B core antigen	HBV core protein, coated with HBsAg and therefore not found free in serum
Hepatitis B e antigen	Viral protein found in the high replicative phase of hepatitis B. HBeAg is usually a marker of high levels of replication with wild- type virus but is not essential for viral replication
Hepatitis B surface anti-body	Antibody to HBsAg that develops in response to HBV vaccination and during recovery from acute hepatitis B, denoting past infection and immunity

Anti-HBe	Antibody to HBeAg detected among people with lower levels of HBV replication but also in HBeAg-negative disease (HBV that does not express HBeAg)
Hepatitis B core antibody (total anti-HBc)	Antibody to hepatitis B core (capsid) protein. Total anti-HBc antibodies are not neutralizing antibodies and are a marker of both exposure and prior infection.
IgM anti-HBc	Subclass of anti-HBc. Detected by sensitive assays during acute hepatitis B and a flare or reactivation of chronic HBV
Occult HBV infection	People who have cleared hepatitis B surface antigen: they are HBsAg negative but HBV DNA positive, although at very low levels (invariably <200 IU/mL); most are also total anti-HBc positive

Hepatitis D infection

HBV and HDV coinfection	Infection simultaneously with HBV and hepatitis D virus (HDV). People with coinfection have increased risk of severe acute hepatitis and acute liver failure. Recovery is usually complete and chronic infection rare
HDV superinfection	When a person with an established CHB infection becomes infected with HDV. Superinfection frequently leads to chronic hepatitis D and increased risk of rapid progression to cirrhosis and development of hepatocellular carcinoma (HCC).
Total anti-HDV	Total antibodies (IgM and IgG) to hepatitis D virus occurring only among people who are HBsAg positive. Detection of anti-HDV antibodies indicates exposure to hepatitis D virus
HDV RNA	HDV RNA can be detected and quantified in serum or plasma. Testing for the presence of HDV RNA confirms active viraemic infection and differentiates it from past cleared infection

Tests for assessing and monitoring hepatitis B infection

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)	Intracellular enzymes that reflect liver cell injury since they are released after cell injury or death
HBV DNA	HBV DNA that can be detected and quantified in serum or plasma. HBV DNA correlates with levels of circulating viral particles. HBV DNA is measured as IU/mL or copies/mL. 1 IU/mL ~ 5.3 copies/mL, and so values given as copies/mL can be converted to IU/mL by dividing by a factor of 5 (10 000 copies/mL = 2000 IU/mL; 100 000 copies/mL = 20 000 IU/mL; 1 million copies/mL = 200 000 IU/mL). All HBV DNA values in the recommendations in these guidelines are reported in IU/mL. An undetectable viral load is an HBV DNA level below the level of sensitivity of the laboratory assay. For sensitive polymerase chain reaction assays, this is generally a concentration below 15 IU/mL.
Alpha-fetoprotein (AFP)	A host cellular protein. High levels can occur among people with hepatocellular carcinoma
Persistently abnormal or normal ALT level	ALT levels fluctuate among people with CHB and require longitudinal monitoring to determine the trend. The upper limits for normal ALT have been defined as below 30 U/L for men and boys and 19 U/L for women and girls, although local laboratory normal ranges should be applied. Persistently normal or abnormal may be defined as two ALT values below or above the

	upper limit of normal (ULN) at unspecified intervals during a 6- to 12-month period. ALT levels fluctuate with CHB and require longitudinal monitoring to determine the trend. In adolescents, treatment of those with HBV DNA >2000 IU/mL and ALT > ULN should be based on at least two elevated ALT >ULN over a 6- to 12-month period

Assessment of liver fibrosis by non-invasive tests

Aspartate aminotransferase (AST)-to-platelet ratio index (APRI)	A simple index for estimating hepatic fibrosis based on a formula derived from AST and platelet concentrations The formula for calculating the APRI is: APRI = (AST/ULN) Í 100)/ platelet count (109 /L). An online calculator can be found at: http://www.hepatitisc.uw.edu/page/clinical-calculators/apri
Fibrosis-4 score (FIB-4)	An index for estimating hepatic fibrosis based on a calculation derived from AST, ALT and platelet concentrations, and age. The formula for calculating FIB-4 is: FIB-4 = (age (years) Í AST (IU/L))/(platelet count (109 /L Í [ALT (IU/L)(1/2)]). An online calculator is available at: http://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4
Transient elastography	A technique to measure liver stiffness (as a surrogate for fibrosis) based on the propagation of a shear wave through the liver

Measures of performance of diagnostic tests

Clinical or diagnostic sensitivity of a test	The ability of a test to correctly identify those with the infection or disease (true positives/true positives + false negatives)
Clinical or diagnostic specificity of a test	The ability of a test to correctly identify those without the infection or disease (true negatives/true negatives + false positives)
Positive predictive value	The probability that when a person's test result is positive, they truly have the infection or disease (true positives/true positives + false positives)
Negative predictive value	The probability that when a person's test result is negative, they truly do not have the infection or disease (true negatives/true negatives + false negatives). Predictive values (negative and positive) are influenced by the prevalence of the disease in the population
Analytical sensitivity or limit of detection	The lowest concentration of measurement that can be consistently detected in 95% of specimens tested under routine laboratory conditions. It defines the analytical sensitivity in contrast to the clinical or diagnostic sensitivity

Measures of hepatitis B treatment response

Hepatitis B treatment response	Undetectable HBV DNA in the blood at a defined time point after treatment ends
Hepatitis B treatment failure (primary non-response)	In settings where HBV DNA testing is available: Primary antiviral nonresponse is defined as <1 log10 IU/mL decrease of serum HBV DNA after three months of initiating therapy. Many with high level of baseline HBV DNA will be positive after one year of therapy but have a decline in HBV DNA and would not be classified as non-response. In settings where HBV DNA testing is not available: treatment failure and drug resistance may be suspected based on the following features: receiving antiviral drugs with a low barrier to resistance together with documented or suspected poor adherence; and laboratory measures such as an increase in serum aminotransferases and/or evidence of progressive liver disease. Note: elevated ALT tends to occur late and is a relatively poor predictive marker of resistance. Confirmation of antiviral drug failure can be established by sequencing the HBV DNA polymerase and identifying specific genetic markers of antiviral drug resistance.

Diagnostic testing for hepatitis

Serological assays	Assays that detect the presence of either antigens or antibodies, typically in serum or plasma but also in capillary or venous whole blood and dried blood spot samples. These include rapid diagnostic tests (RDTs) and laboratory-based immunoassays, such as enzyme immunoassays, chemiluminescence immunoassays and electro- chemiluminescence immunoassays
Rapid diagnostic test	Immunoassays that detect antibodies or antigens and can give a result in less than 30 minutes. Most RDTs can be performed with capillary whole blood collected by finger-stick sampling
Enzyme immunoassay	Laboratory-based serological immunoassays that detect antibodies, antigens or a combination of both
Nucleic acid testing (NAT)	A molecular technology, such as polymerase chain reaction or nucleic acid sequence-based amplification, that can detect very small quantities of viral nucleic acid (RNA or DNA), either qualitatively or quantitatively
Point-of-care testing	Conducted at the site at which clinical care is being provided, with the results being returned to the person being tested or caregiver on the same day as sample collection and test to enable clinical decisions to be made in a timely manner

Approach to the Patient with Viral Hepatitis

Classification and Clinical Course of Hepatitis

Hepatitis may present in either an acute or chronic form, distinguished by the duration and nature of hepatic injury. Acute hepatitis is characterized by a rapid onset of hepatocellular damage, typically secondary to hepatotropic viral infections such as hepatitis A virus (HAV), hepatitis E virus (HEV), hepatitis B virus (HBV), and hepatitis C virus (HCV). Clinically, it progresses through three phases: a prodromal (pre-icteric) phase marked by nonspecific symptoms such as anorexia, malaise, nausea, and fever; an icteric phase featuring jaundice, tender hepatomegaly, and cholestatic symptoms; and a convalescent phase during which clinical and biochemical recovery occurs. While the majority of cases resolve spontaneously, a minority, particularly pregnant women with HEV, may progress to acute liver failure, characterized by coagulopathy and hepatic encephalopathy in the absence of pre-existing liver disease.

Chronic hepatitis is defined by persistent hepatic inflammation lasting longer than six months and is most commonly associated with HBV, HCV, and HDV infections. Ongoing hepatocellular injury leads to progressive fibrosis, eventually culminating in cirrhosis (Stage F4). In the compensated stage, liver function remains preserved; however, with progression to decompensated cirrhosis, clinical manifestations such as ascites, jaundice, variceal bleeding, and hepatic encephalopathy become evident. Chronic hepatitis often follows a subclinical course, with diagnosis frequently made during evaluation for unrelated conditions or through targeted screening programs.

Etiology and Transmission of Viral Hepatitis

Hepatitis viruses are classified based on their mode of transmission. Enterically transmitted viruses, HAV and HEV, are spread via the fecal-oral route and predominantly cause self-limiting acute hepatitis. HAV typically affects children, does not result in chronic infection, and is associated with good prognosis. HEV more commonly affects adults and, while usually self-limiting, can cause severe outcome in pregnant women. HEV usually causes acute infection but can cause chronic infection in immunocompromised individuals (Kurma et al., 2014; Hoofnagle et al., 2012; Grewal et al., 2014).

Parenterally transmitted viruses, including HBV, HCV, and HDV, which are transmitted via exposure to infected blood or body fluids. Risk factors include transfusions of unscreened blood products, intravenous drug use, unsafe medical or dental procedures, sexual contact, and perinatal transmission. HBV, a DNA virus capable of integrating into the host genome, carries a high risk of chronicity when acquired perinatally or in early childhood. HDV is a defective RNA virus that requires HBV coinfection for replication and is associated with more severe disease progression.

Pathophysiology of Fibrosis, Cirrhosis, and Portal Hypertension

In chronic liver disease, continuous hepatocellular injury induces fibrogenesis, mediated primarily by hepatic stellate cell activation. Progressive fibrosis disrupts hepatic architecture and vascular integrity, leading to portal hypertension, which manifests clinically as splenomegaly, formation of portosystemic collaterals (e.g., esophageal and gastric varices), and ascites. With the development of cirrhosis, the liver becomes nodular, fibrotic, and functionally impaired. Hepatic synthetic dysfunction results in hypoalbuminemia, contributing to third-spacing of fluids (e.g., ascites and pleural effusions), and coagulopathy due to decreased production of clotting factors. Impaired ammonia metabolism contributes to hepatic encephalopathy. Portal hypertension may also lead to congestive splenomegaly and hypersplenism, resulting in pancytopenia, particularly thrombocytopenia.

Clinical Presentation and Diagnostic Evaluation

The prodromal symptoms of acute viral hepatitis are systemic and quite variable. Constitutional symptoms of anorexia, nausea and vomiting, fatigue, malaise, arthralgias, myalgias, headache, photophobia, pharyngitis, cough, and coryza may precede the onset of jaundice by 1–2 weeks. The nausea, vomiting, and anorexia are frequently associated with alterations in olfaction and taste. A low-grade fever between 38° and 39°C is more often present in hepatitis A and E than in hepatitis B or C, except when hepatitis B is heralded by a serum sickness, like syndrome; rarely, a fever of 39.5°–40°C may accompany the constitutional symptoms. Dark urine and clay-colored stools may be noticed by the patient from 1–5 days before the onset of clinical jaundice.

With the onset of clinical jaundice, the constitutional prodromal symptoms usually diminish, but in some patients, mild weight loss (2.5–5 kg) is common and may continue during the entire icteric phase. The liver becomes enlarged and tender and may be associated with right upper quadrant pain and discomfort. Infrequently, patients present with a cholestatic picture, suggesting extrahepatic biliary obstruction. Splenomegaly and cervical adenopathy are present in 10–20% of patients with acute hepatitis. Rarely, a few spider angiomas appear during the icteric phase and disappear during convalescence. During the recovery phase, constitutional symptoms disappear, but usually some liver enlargement and abnormalities in liver biochemical tests are still evident. The duration of the post icteric phase is variable, ranging from 2–12 weeks, and is usually more prolonged in acute hepatitis B and C. Complete clinical and biochemical recovery is to be expected 1–2 months after all cases of hepatitis A and E and 3–4 months after the onset of jaundice in three-quarters of uncomplicated, self-limited cases of hepatitis B and C (among healthy adults, acute hepatitis B is self-limited in 95–99%, whereas hepatitis C is self-limited in only ~15%). In the remainder, biochemical recovery may be delayed. A substantial proportion of patients with viral hepatitis never become icteric.

Laboratory and Imaging Workup

Liver function tests (LFTs) are essential for assessing hepatocellular and cholestatic injury. Elevated alanine aminotransferase and aspartate aminotransferase suggest hepatocellular injury, with ALT being more specific to the liver. AST elevations may reflect extra-hepatic sources such as skeletal muscle, cardiac muscle, or hemolysis. In most liver diseases, ALT > AST; however, AST predominance is observed in alcohol-related liver disease, Wilson's disease, and cirrhosis. Alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) are markers of biliary tract involvement and cholestasis.

The pattern of enzyme elevation (hepatocellular, cholestatic, or mixed) aids in narrowing the differential diagnosis. Serum bilirubin levels help determine the type of jaundice, unconjugated hyperbilirubinemia typically suggests hemolysis, while conjugated hyperbilirubinemia is more consistent with hepatocellular or obstructive pathology. Assessment of serum albumin and prothrombin time/INR provides insight into the liver's synthetic function. Ultrasound is the first-line imaging modality to evaluate liver morphology, biliary tract pathology, ascites, and signs of portal hypertension such as splenomegaly and dilated portal veins.

Serological and Molecular Testing in Viral Hepatitis

The diagnosis of viral hepatitis is established through serological and molecular testing. For suspected acute hepatitis, anti-HAV IgM and anti-HEV IgM are evaluated. HBsAg and anti-HCV screening identify HBV and HCV infections, respectively. In the early phase of acute HBV infection, IgM anti-HBc is a more sensitive marker than HBsAg alone. For HCV, HCV RNA testing is preferred in the acute phase due to delayed seroconversion.
In chronic hepatitis B, monitoring includes periodic ALT and HBV DNA assessments, along with HBeAg and anti-HBe status. In chronic HCV, AST correlates better with fibrosis progression, while ALT guides ongoing hepatocellular inflammation. Enzyme levels should ideally be assessed in the fasting state, in the morning, as postprandial and exertional elevations may lead to misinterpretation.

Approach to Jaundice and Differential Diagnosis

Jaundice reflects hyperbilirubinemia and can be classified based on the predominant bilirubin fraction. Unconjugated hyperbilirubinemia is typically seen in hemolytic anemias and disorders of bilirubin conjugation, while conjugated hyperbilirubinemia occurs in hepatocellular and obstructive pathologies. In hepatocellular jaundice, there is typically a mixed pattern with a predominance of conjugated bilirubin due to impaired hepatic excretion. Obstructive jaundice, caused by conditions such as choledocholithiasis or malignancy, is marked by cholestatic enzyme elevation (ALP, GGT) and pale stools. Accurate differentiation requires correlation of clinical findings with biochemical patterns and imaging studies.

Epidemiology and Risk Stratification

Epidemiological factors significantly influence disease acquisition and progression. Perinatal transmission poses a high risk for chronic HBV infection, with up to 90% chronicity when infection occurs in neonates. Horizontal transmission in adults more often leads to acute, self-limiting disease. Risk factors for parenteral transmission include blood transfusion (particularly before the implementation of routine screening), intravenous drug use, and unprotected sexual contact. Enterically transmitted hepatitis (HAV and HEV) is more prevalent in areas with poor sanitation, and seasonal peaks may occur during the monsoon and summer. Screening for viral hepatitis is commonly performed during antenatal care, preoperative evaluation, or prior to blood donation. Understanding transmission patterns and risk factors is essential for effective prevention, early diagnosis, and appropriate public health interventions.

Hepatitis B Infection

Overview

Hepatitis B infection is caused by the Hepatitis B virus (HBV), a blood-borne pathogen that can lead to both acute and chronic liver disease. The virus is primarily transmitted through vertical transmission, exposure to infected blood and bodily fluids, through unprotected sex, unsafe injections, blood transfusions, and sharing of contaminated instruments. Acute HBV infection occurs within the first six months of HBV infection. It is often asymptomatic but may present with sudden unexplained fever, jaundice, and abnormally elevated raised ALT, AST levels (~10 times above normal). It is characterized by the presence of hepatitis B surface antigen (HBsAg) and immunoglobulin M (IgM) antibody to the core antigen (IgM anti-HBc). During the initial phase of infection, patients are also seropositive for hepatitis B envelope antigen (HBeAg), which signifies high infectivity. Acute hepatitis B is usually a self-limiting disease with a case fatality rate of 0.5–1%. Chronic HBV infection is defined as the persistence of HBsAg beyond six months of infection. Chronic HBV infection can result in complications such as liver cirrhosis and hepatocellular carcinoma. Signs and symptoms of chronic HBV vary and may not be apparent in all individuals. While some people experience symptoms such as, fatigue, abdominal pain and distension, jaundice (yellowing of the skin and eyes), and dark urine, others may remain asymptomatic for years. This asymptomatic nature calls for regular screening and early detection critical.

Epidemiology and Burden of Infection

According to WHO estimates, approximately 254 million people were living with chronic hepatitis B infection in 2022, with around 1.2 million new cases reported annually. That same year, hepatitis B was responsible for an estimated 1.1 million deaths, primarily due to complications such as cirrhosis and hepatocellular carcinoma. The burden of infection is highest in the WHO Western Pacific Region and the WHO African Region, where 97 million and 65 million people, respectively, are chronically infected.

The Zambia Population-Based HIV Impact Assessment (ZAMPHIA), a household-based national survey, conducted in 2016, indicated that the prevalence of infection with hepatitis B virus (HBV) among adults aged 15 to 59 years is higher among HIV-positive (7.1%) than HIV-negative (5.4%) individuals. Prevalence of HBV is especially high among HIV-positive males ages 15 to 59 years (10.2%). Among children aged 0 to 14 years, HBV infection is more prevalent among those living with HIV (5.2%) than those living without HIV (1.3%).

Transmission

Hepatitis B virus is predominantly transmitted via percutaneous or mucosal exposure to infected blood and bodily fluids, including, semen, vaginal secretions, and menstrual blood. Perinatal transmission accounts for the greatest burden of chronic infection, with 90 95% of neonates progressing to chronicity when infection at birth. Horizontal transmission can occur through medical, surgical, or dental procedures involving contaminated instruments; needlestick injuries; shared or improperly sterilized injection equipment; and practices such as intravenous drug use, tattooing, body piercing, or acupuncture. Sexual transmission is also significant, particularly among unvaccinated individuals with multiple partners.

Natural History

The natural history of CHB is dynamic and complex. The spectrum of illness varies from asymptomatic infection to severe chronic liver disease and HCC. For some people, CHB does not lead to significant liver disease, but others have progressive liver fibrosis, cirrhosis, end-stage liver disease and a markedly increased risk of HCC. Those with cirrhosis have an approximately 20% annual risk of hepatic decompensation, and the risk of developing

hepatitis B–related HCC ranges from <1% to 5%. Untreated people with decompensated cirrhosis have a poor prognosis, with 15–40% survival at five years. The likelihood of chronic hepatitis B virus infection is strongly age dependent. Perinatal (vertical) transmission is associated with approximately 90% progression to chronic infection and only 10% achieving viral clearance. Infections acquired during early childhood result in chronic infection in 20– 50% of cases, with spontaneous resolution occurring in 50– 80% of cases. In contrast, HBV infection acquired in adulthood leads to chronic infection in 5% of cases, with spontaneous resolution occurring in approximately 95% of individuals.

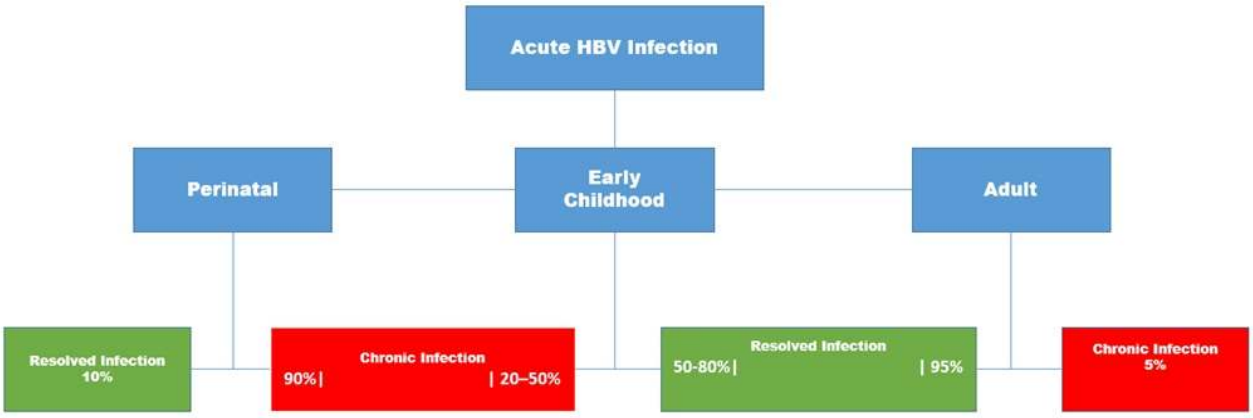


Figure 1: Natural history of chronic hepatitis B

Clinical Presentation

Hepatitis B virus infection presents with a broad clinical spectrum, ranging from asymptomatic carriage to acute illness and chronic liver disease. Symptoms can range from asymptomatic or mild disease to, rarely, fulminant hepatitis. The presence of signs and symptoms varies by age. Most infants and children younger than five years old do not have symptoms. People aged five years and older develop symptoms in 30%– 50% of cases. People younger than 30 years old are less likely to be symptomatic compared with people 30 years and older. Newly infected, immunosuppressed adults generally do not show symptoms. Most people with chronic HBV infection are asymptomatic and have no evidence of liver disease or injury.

In symptomatic acute hepatitis B, the illness typically begins with a prodromal phase marked by non-specific symptoms such as fatigue, malaise, anorexia, nausea, vomiting, low-grade fever, and right upper quadrant discomfort. Some patients may also experience a serum sickness-like syndrome, characterized by fever, rash, and arthralgia, especially in the early stages of infection. This is followed by the icteric phase, during which jaundice becomes apparent, often accompanied by dark urine, pale stools, and hepatomegaly.

A rare but severe manifestation is fulminant hepatitis B, occurring in less than 1% of cases. It involves a rapid onset of liver failure, presenting with deep jaundice, coagulopathy, and hepatic encephalopathy.
Most individuals with chronic HBV infection remain asymptomatic for many years. However, as liver damage progresses, symptoms such as fatigue and right upper quadrant pain may develop, along with signs of advanced liver disease, including ascites, jaundice, hepatic encephalopathy, and variceal bleeding.

In addition to liver-related manifestations, hepatitis B can cause extrahepatic complications. These include polyarteritis nodosa, mixed cryoglobulinemia, a systemic necrotizing vasculitis; glomerulonephritis, particularly membranous and membranoproliferative forms; and a serum sickness-like reaction with rash, fever, and joint pain. In rare cases, HBV infection may also lead to aplastic anemia.

Approximately 20% of individuals with chronic hepatitis B develop extrahepatic manifestations, which can significantly affect morbidity, quality of life, and mortality (Mazzaro, 2022; Cacoub, 2022). Awareness and early recognition of these manifestations are essential, as they may warrant the initiation of antiviral therapy to alleviate symptoms and improve clinical outcomes

Diagnosis

Screening for Chronic Hepatitis

According to the World Health Organization, hepatitis B screening is recommended for the general population in regions where the prevalence is 2% or higher. Zambia meets this criterion, with the 2016 Zambia Population-based HIV Impact Assessment estimating a national hepatitis B prevalence of 3.5% among individuals aged 0–59 years.

Despite qualifying for general population screening, Zambia has opted to prioritize targeted screening of high-risk groups to ensure efficient use of resources and maximize public health impact. Identifying hepatitis B virus infection through targeted screening is essential for early diagnosis, timely linkage to care, and the prevention of further transmission. The following populations have been identified as priority groups for HBV screening due to their increased risk of infection, greater potential for transmission, or heightened vulnerability to disease complications:

Table 1: Priority populations for hepatitis B virus testing

Target Group	Specific Populations
Pregnant Women	All pregnant women, preferably during their first antenatal care visit, to enable timely prevention of vertical transmission.
Household and Close Contacts of HBV-Infected Individuals	Sexual partners, Children, siblings, and other household contacts of HBV-positive individuals
Individuals with Clinical Indicators of Liver Disease	Clinical suspicion e.g. (hepatomegaly, elevated liver enzymes, jaundice and other signs of liver disease)
Healthcare Workers and Individuals at Risk Due to Medical Exposure	• Healthcare workers, including those involved in direct patient care, laboratory work, or procedures with risk of exposure to blood and body fluids • Donors of blood, tissues, semen, and organs • Recipients of blood products, stem cell/bone marrow transplants, or organ transplants
Key and High-Risk Populations	Men who have sex with men, Female sex workers, People who inject drugs, Incarcerated individuals, Individuals with multiple sexual partners, Individuals seeking care for sexually transmitted infections
Individuals with Underlying Health Conditions or Immunosuppression	• People living with HIV, Individuals co-infected with HCV, Individuals with chronic kidney disease, including those receiving dialysis • Individuals considered for or undergoing immunosuppressive/ immunomodulatory or chemotherapy. • Individuals with comorbid conditions that may increase susceptibility to HBV infection or worsen disease outcomes, such as diabetes mellitus, sickle cell disease, and tuberculosis.

HBsAg serves as the primary marker for hepatitis B diagnosis as a positive test indicates infection. Additional diagnostic tests are required to determine whether the infection is acute or chronic. The table below summarizes these diagnostic tests and their clinical significance:

Table 2: Hepatitis B serological tests and their significance

Marker	Significance
HBsAg	Active infection (Acute or chronic infection)
HBeAg	Commonly positive in acute hepatitis B. It is associated with high viral load and high infectivity. Persistence implies continued infectious state
HBV DNA	Implies viral replication Found in serum and liver
Anti-HBs	Immunity to HBV; implying previous exposure or vaccination
Anti-HBe	Seroconversion
Anti-HBc	IgM: Acute Infection IgG: Chronic or past infection

Table 3: Interpretation of Hepatitis B serological markers

Marker	Result	Interpretation of Combination
HBsAg Anti-HBc Anti-HBs	Negative Negative Negative	Not infected but susceptible (May need vaccination)
HBsAg Anti-HBc Anti-HBs	Negative Positive Positive	Immune due to natural infection If immunosuppressed, can result in re-activation
HBsAg Anti-HBc Anti-HBs	Negative Negative Positive	Immune due to hepatitis B vaccination
HBsAg Anti-HBc IgM-anti-HBc	Positive Positive Positive	Acutely Infected
HBsAg Anti-HBc IgM-anti-HBc	Positive Positive Negative	Chronically infected
HBsAg Anti-HBc Anti-HBs	Negative Positive Negative	Four possibilities: 1. Resolved infection (most common) 2. False positive anti-HBc, thus susceptible 3. Low level (Occult) chronic infection 4. Resolving acute infection

Adapted from: BCGuidelines.ca 2021 appendix; MMWR 2005; 54 (No. RR-16)

Treatment

Assessment for Treatment Eligibility

Assessment for treatment eligibility in hepatitis B includes assessment of liver disease severity using non-invasive methods such as the APRI score or transient elastography (FibroScan) to evaluate liver fibrosis or cirrhosis. Biochemical and virological markers assessment include measuring of alanine aminotransferase levels and HBV DNA viral load to guide treatment decisions. Medical history and risk factors include screening for coinfections (e.g., HIV, HDV, HCV). Assess for comorbidities such as diabetes and steatotic liver disease. Evaluate for

immunosuppressive conditions, including long-term corticosteroid use or organ transplantation. Identify extrahepatic manifestations (e.g., glomerulonephritis, vasculitis etc). Take note of any family history of liver cirrhosis or hepatocellular carcinoma.

General care for hepatitis B includes lifestyle counselling on reducing or avoiding alcohol consumption, maintaining a healthy diet, and encouraging physical activity. Before starting treatment, patients should receive adherence counselling and assess for risk factors for renal dysfunction. Perform baseline renal function tests, if indicated, before initiating antiviral therapy (e.g., tenofovir). Preventive Interventions involve screening family members, household contacts, and sexual partners for HBsAg, and offering hepatitis B vaccination to those who are uninfected. The figure below outlines an algorithm for the assessment of individuals with chronic hepatitis B infection.

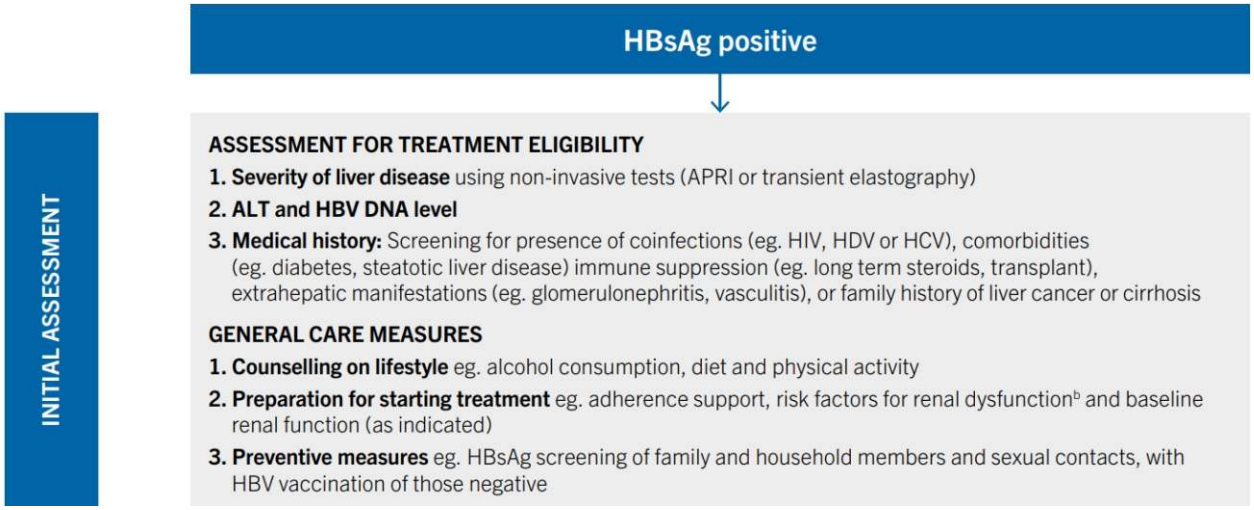


Figure 2: Algorithm for assessment for treatment eligibility of people with chronic hepatitis B infection (Adopted from 2024 WHO Guidelines)

Eligibility for all Adults and Adolescents Aged 12 Years and Above, Including both Pregnant and Non-Pregnant Women and Girls of Reproductive Age

Treatment is recommended for all adults and adolescents aged 12 years and above, including both pregnant and non-pregnant women and girls of reproductive age, who meet one of the four options for treatment eligibility:

1. Treatment is recommended for all who have evidence of significant liver fibrosis or cirrhosis. Evidence of significant fibrosis is defined as stage F2 or higher is based on an APRI score greater than 0.5 or transient elastography value greater than 7 kPa; and evidence of cirrhosis stage F4 is based on clinical criteria (or an APRI score greater than 1 or transient elastography value greater than 12.5 kPa), regardless of HBV DNA or ALT levels.
2. Treatment is recommended for all with HBV DNA >2000 IU/mL and an ALT level above the upper limit of normal (ULN) (30 U/L for men and boys and 19 U/L for women and girls). For adolescents, this should be based on ALT>ULN on at least two occasions in a 6-to 12-month period.
3. Treatment is recommended for all with presence of coinfections (such as HIV, hepatitis D or hepatitis C); family history of liver cancer or cirrhosis; immune suppression (such as long-term steroids, solid organ or stem cell transplant); comorbidities (such as diabetes or metabolic dysfunction, associated steatotic liver disease); or extrahepatic manifestations (such as glomerulonephritis or vasculitis), regardless of the aspartate aminotransferase-to-platelet ratio index or HBV DNA or ALT levels.

4. In the absence of access to an HBV DNA assay: persistently abnormal ALT levels (defined as two ALT values above the ULN at unspecified intervals during a 6- to 12-month period), regardless of APRI score.

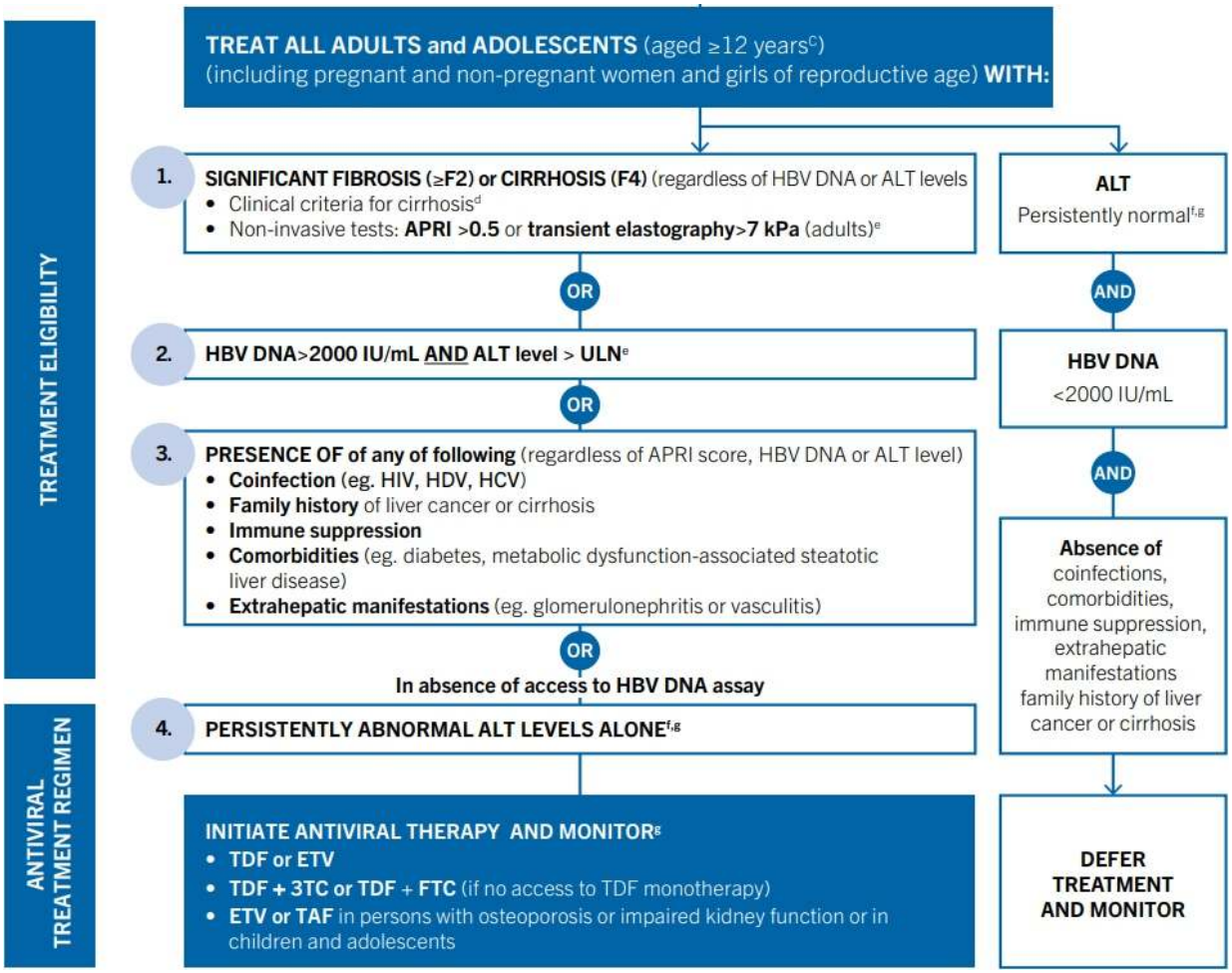


Figure 3: Algorithm for treatment eligibility of all adults and adolescents aged 12 years and above

Key

ALT: alanine aminotransferase, APRI: aspartate aminotransferase-to-platelet ratio index.

a - Defined as the presence of HBsAg for adults and persistence of HBsAg for six months or more for adolescents and children.
b - Age groups: these guidelines use the following definitions for the purpose of implementing treatment recommendations for adolescents and children aged two years and older. An adult is a person aged 18 years or older; an adolescent 12 17 years old inclusive; and a child is 2 11 years old. Countries may have other definitions under national laws.
c - Clinical features of decompensated cirrhosis: portal hypertension (ascites, variceal haemorrhage and hepatic encephalopathy), coagulopathy or liver insufficiency (jaundice). Other clinical features of advanced liver disease and cirrhosis may include: hepatomegaly, splenomegaly, pruritus, fatigue, arthralgia, palmar erythema and oedema.
d - Non-invasive tests including APRI and transient elastography have not yet been validated for children and adolescents.
e - The ULN for ALT have been defined as <30 U/L for men and boys and <19 U/L for women and girls. Persistently normal or abnormal may be defined as two ALT values below or above the ULN at unspecified intervals during a 6- to 12-month period. ALT levels fluctuate with CHB and require longitudinal monitoring to determine the trend.
f - Raised ALT may normalize in pregnancy and is therefore not a good marker for deciding about long-term treatment in pregnancy. Pregnant women should be reassessed after delivery.
g - Before initiation, consider assessing renal function: serum creatinine level, estimated glomerular filtration rate, urine dipsticks for proteinuria and glycosuria and risk factors for renal dysfunction (decompensated cirrhosis, creatinine clearance <50 mL/min, poorly controlled hypertension, proteinuria, uncontrolled diabetes, active glomerulonephritis, concomitant nephrotoxic drugs, solid organ transplantation, older age, BMI <18.5 kg/m2 (or body weight <50 kg), concomitant use of nephrotoxic drugs or a boosted protease inhibitor for HIV). Monitoring should be more frequent for those at higher risk of renal dysfunction.
h - All people with CHB should be monitored regularly for disease activity and progression and detection of HCC and after stopping treatment for evidence of reactivation. More frequent monitoring may be required for those with more advanced liver disease, during the first year of treatment or if adherence is a concern.

There may also be individual circumstances in which, although individuals may not meet any of the four options for treatment eligibility, there are specific individual concerns regarding infectivity, transmission, associated stigma, the risk of oncogenicity and progressive liver fibrosis and a strong individual motivation to consider treatment, despite the lack of direct evidence. In such cases, a patient-centred approach with discussion between individuals

and their health-care provider will be key in helping them make informed decisions about whether to begin treatment or not. This should consider the uncertainties resulting from lack of direct evidence for treatment benefit and low risk of transmission for those with HBV DNA.

First-line antiviral therapies for CHB (Adults, Adolescents and Children)

Treatment for hepatitis B aims to suppress viral replication, reduce liver inflammation, prevent progression to cirrhosis, hepatic decompensation, liver failure, or hepatocellular carcinoma, and improve survival. The management of hepatitis B virus infection has evolved significantly with the development of antiviral therapies. These drugs play a crucial role in suppressing viral replication, preventing disease progression, and reducing the risk of liver-related complications. The main classes of anti-viral agents against HBV include nucleos(t)ide analogues and interferons, each with distinct mechanisms of action and clinical application. While these drugs significantly reduce HBV levels, their potency, toxicity, and potential for developing resistance varies, highlighting the importance of selecting appropriate agents based on individual patient factors and treatments costs.

Nucleoside analogues with a low barrier to resistance such as lamivudine, adefovir, or telbivudine are prone to developing resistance and are therefore not recommended. For all adults, adolescents, and children aged two years and above who require antiviral treatment, the preferred options are nucleos(t)ide analogues with a high resistance barrier, specifically tenofovir disoproxil fumarate (TDF)/tenofovir alafenamide (TAF) or entecavir (ETV).

In cases where patients have pre-existing osteoporosis or reduced kidney function, ETV or TAF is advised. ETV is suitable for children aged two years and older, while TAF can be used as an alternative in adolescents aged 12 years and weighing 25kg when treatment is necessary. The table below summarizes the first-line antiviral therapies and their properties:

Table 4: First-line antiviral therapies and their properties

Antiviral	Potency Against HBV	Resistance Barrier	Activity Against HIV	Cost	Potential Side effect
Recommended					
Tenofovir disoproxil fumarate	High	High	High	Generally Low, High in some Asian countries	Nephropathy, osteomalacia, lactic acidosis
Tenofovir alafenamide fumarate	High	High	High	High	Lactic acidosis
Entecavir	High	High	weak	low	Lactic acidosis (decompensated cirrhosis only)
Interferons	moderate	Not applicable	moderate	high	Flu-like symptoms, mood disturbances, cytopenia, autoimmune disorders
Not Recommended					
Lamivudine	low	Low	moderate	low	Pancreatitis, lactic acidosis
Adefovir	moderate	Low	low	Moderate to high	Acute renal failure, Fanconi syndrome, lactic acidosis
Telbivudine	Moderate to high	Low	low		Myopathy, peripheral neuropathy, lactic acidosis

Note: Combinations like TDF with lamivudine (3TC) or TDF with emtricitabine (FTC) are suggested as alternative regimens when TDF monotherapy is not accessible.

Table 5: Summary of preferred first line anti-viral regimens for HBV

Population	Preferred first-line regimen	Alternative First-line regimen	Special Circumstances
Adults	TDF ETV	TDF + 3TC TDF + FTC (Where TDF monotherapy is not available)	ETV TAF (For people with established osteoporosis and/or impaired kidney function)
Adolescents	TDF ETV	TDF + 3TC TDF + FTC (Where TDF monotherapy is not available)	
TDF: Tenofovir disoproxil fumarate; ETV: Entecavir; 3TC: Lamivudine; FTC: Emtricitabine; TAF: Tenofovir alafenamide fumarate.			

Adopted from WHO guidelines 2024

Second Line Antiviral Therapies for Managing Treatment Failure

Table 6: Definition of treatment failure according to WHO guidelines 2024

DNA Testing Setting	Treatment failure Definition
In settings with access to HBV DNA testing	Primary treatment failure is defined as the inability of an antiviral medication to reduce HBV DNA levels by more than 1 $\log_{10}$ IU/mL within three months of starting therapy. Secondary treatment failure refers to a rise in HBV DNA levels by more than 1 $\log_{10}$ IU/mL from the lowest point (nadir) after an initial effective response to treatment.
In settings without HBV DNA testing	Treatment failure or drug resistance may be suspected based on certain clinical indicators, such as the use of antivirals with a low resistance barrier, suspected or confirmed poor adherence, rising serum aminotransferase levels, or signs of worsening liver disease.

The likelihood of treatment failure is notably higher in individuals who were previously managed with monotherapy using nucleos(t)ide analogues that have a low genetic barrier to resistance, such as 3TC, adefovir, or telbivudine. These medications were widely used, particularly in high-prevalence regions like Asia and the Pacific leading to a significant rise in 3TC-resistant HBV strains. This problem was further worsened by limited access to effective second-line treatment options at the time. Fortunately, the introduction of potent first-line agents with a high resistance barrier, such as TDF, ETV, and TAF has significantly reduced the prevalence of resistance, making it more manageable in clinical practice. Entecavir shows a very low rate of resistance, except in individuals with prior exposure to 3TC or adefovir.

In Zambia, most patients with chronic HBV infection are initiated on TDF-based regimens, which carry a low risk of treatment failure. To date, there is little definitive evidence of antiviral resistance in individuals with HBV monoinfection who are treated with TDF or TAF.

When to stop treatment with antiviral therapy for hepatitis B after NA therapy
Recommendation for cessation:

In Zambia, it is recommended that antiviral therapy with nucleos(t)ide analogues (NAs) should only be discontinued after consultation with a physician experienced in the treatment of hepatitis B, and only if close monitoring can be guaranteed. Note that, HBsAg levels, HBeAg status, comorbidities, duration of HBV DNA suppression, stage of liver fibrosis in addition to patient understanding and preference should be taken into account;

Indications for cessation of NA therapy

- **HBsAg loss** (patient has been on hepatitis B treatment who then seroconverts from HBsAg positive to HBsAg negative) for a period longer than 12months, in the **ABSENCE** of coexisting risk factors e.g., cirrhosis, co-infections with HIV and /or Hepatitis C, and comorbid conditions such as CKD, Metabolic dysfunction-associated steatotic liver disease (MASLD), malignancy and necroinflammation evidenced by elevated aminotransferases and with undetectable hepatitis B DNA Viral load
- In HBeAg positive chronic hepatitis B patients who seroconvert, (HBeAg positive to Negative with Anti-HBe), with undetectable Hepatitis B viral load and in ABSENCE of hepatic necroinflammation, and fibrosis; e.g., normal aminotransferases, 12 months after stopping therapy in patients where close monitoring is guaranteed

Note; Due to persistence of covalently closed circular DNA (cccDNA) in the liver, sero reversion (reactivation) of hepatitis B after cessation is possible, hence the decision to stop treatment should be carefully considered with expert advice. In Zambia, due to limited and robust follow ups and limited availability of DNA tests, the indication to stop therapy is usually based on **HBsAg loss** and **not** HBeAg/Anti-HBe seroconversion without HBsAg loss.

Who to Treat among Children Aged 2–11 years old

Current evidence is insufficient to support extending the same treatment eligibility criteria used for adults and adolescents to include children with HBV 2–11 years old. However, treatment is generally offered on a case-by-case basis to selected children in this age range who are identified to have the following: cirrhosis or advancing liver fibrosis stage ≥F2, persistent hepatitis flare with HBV DNA >2000 IU/mL, comorbidities that increase the risk of progressive liver disease, or a need for immunosuppressive therapy. Drug of choice for children in this age group is Entecavir.

Drug of Choice and Dosing in Children and Adolescents

Table 7: Drug of choice and dosing in children and adolescents

Drug	Patient Group	Dose
ETV[a]	Weight < 30kg	0.015 mg/kg once daily (maximum 0.5 mg daily)
	Weight ≥30 kg	0.5 mg once daily
TDF[b]	Age ≥12 years (>30kg)	300 mg daily
TAF[c]	Age ≥12 years (weight > 25kg)	25 mg once daily
	In the absence of ETV and ineligible to use TDF or TAF call for expert opinion	

a ETV: approved for children aged two years or older.
b TDF: the EMA has approved TDF for children two years or older with CHB (1) and the FDA for children two years and older weighing at least 10 kg (2).
c TAF: the EMA has approved TAF for children six years and older and weighing more than 25 kg (3) and the FDA for children 12 years and older with compensated liver disease (4).

Management Considerations for Specific Populations

Coinfections

HIV/HBV Co-Infection:

The burden of HIV/HBV coinfection is high in low- and middle-income countries, particularly in South-East Asia and sub-Saharan Africa. In Zambia, the exact burden of viral hepatitis and HIV coinfection remains unknown. However, data from the 2016 Zambia Population-Based HIV Impact Assessment, though somewhat outdated, offer valuable insight into the national disease burden. According to ZAMPHIA, hepatitis B virus prevalence was notably high among HIV-positive males aged 15 to 59 years (10.2%). Among children aged 0 to 14 years, HBV infection was more common in those living with HIV (5.2%) compared to those without HIV (1.3%). (Cheng, Lin and Cheng, 2021) (*Ministry of Health,* 2016).

HIV/hepatitis B coinfection is a significant public health issue, as it remains a leading cause of death among people living with HIV. This makes timely identification and treatment of coinfected individuals a priority. Without treatment, HIV accelerates the natural course of HBV infection, leading to faster progression to cirrhosis and hepatocellular carcinoma, higher liver-related mortality, a greater likelihood of developing chronic HBV after acute infection, an increased risk of reactivation, and a reduced treatment response compared to those without HIV.

Historically, management was complicated by issues such as drug cross-resistance between HIV and HBV therapies, increased liver damage from drug-induced hepatotoxicity, and immune reconstitution inflammatory syndrome (IRIS) upon starting ART, which could trigger ALT elevations or, in rare cases, fulminant hepatitis if the ART regimen did not adequately cover both viruses. Fortunately, the expanded availability of antiretroviral therapy that is also effective against HBV has significantly improved clinical outcomes in recent years (Vinikoor *et al.*, 2016) (Chen *et al.*, 2024) (Cheng, Lin and Cheng, 2021).

People living with HIV are at increased risk of hepatitis B infection. As such, all individuals newly diagnosed with HIV should be screened for HBsAg, anti-HBs, and anti-HBc to identify chronic HBV infection and determine immunity. Those without immunity, particularly individuals from high-risk groups such as people who inject drugs and men who have sex with men should be vaccinated. It is important to also note that vaccine response is often reduced in people with HIV, especially those with low CD4 counts.

Assessing HBsAg status is essential before initiating or changing ART or starting pre-exposure prophylaxis. The preferred nucleoside reverse transcriptase inhibitors (NRTIs) for ART are TDF combined with either 3TC or FTC, as these agents are also active against HBV. All individuals coinfected with HIV and HBV should receive a TDF-based regimen with 3TC or FTC as the NRTI backbone, regardless of disease stage or HBV DNA level.
If changes to ART are necessary due to drug resistance or toxicity, TDF with 3TC or FTC should still be maintained alongside the new antiretrovirals. In cases where TDF is contraindicated, ETV is the recommended alternative for HBV treatment, used alongside a fully suppressive ART regimen. TAF may be considered in specific clinical situations, such as for patients with renal or bone concerns, and may also be suitable for adolescents. Dolutegravir (DTG), in combination with an NRTI backbone, remains the preferred first-line ART regimen for adults, adolescents, and children with HIV, including those coinfected with HBV.

In people coinfected with HIV and HBV, initiating HIV treatment without including TDF in the regimen may occasionally trigger hepatitis B flares due to immune reconstitution. Similarly, sudden discontinuation of TDF can lead to HBV reactivation, hepatic flares, and, in rare cases, liver failure. While the risk of cirrhosis is very low in individuals receiving long-term treatment with TDF in combination with FTC or 3TC, the risk of developing hepatocellular carcinoma remains, though it is significantly reduced. (Cheng, Lin and Cheng, 2021)

HBV/HCV coinfection

HCV and HBV coinfection is relatively common in hepatitis B endemic regions such as Asia, sub-Saharan Africa, and South America, particularly among people who inject drugs, where up to 40% of individuals with HCV may also have HBV. However, there is limited data on the prevalence of HCV/HBV coinfection in Zambia. (Maqsood *et al.*, 2023).

In many coinfected individuals, HCV tends to be the dominant virus and may suppress HBV DNA levels. Similar to HIV/HBV coinfection, individuals with both HCV and HBV are at a significantly increased risk of developing HCC. The HCC associated with coinfection is often more aggressive, infiltrative, and occurs at a younger age compared to the nodular type seen in monoinfection, indicating a more rapid process of liver cancer development. (Awadh *et al.*, 2024).

Treatment is usually required for both viruses. While interferon (IFN) may be effective in some cases, current treatment strategies primarily rely on separate direct-acting antiviral (DAA) regimens for HBV and HCV (See Figure 10 for HCV treatment).

The presence of active or past HBV infection does not prevent the use of HCV DAAs; however, all individuals initiating HCV treatment should be screened for current or past HBV infection and monitored for potential HBV reactivation after therapy. Among those who are HBsAg-positive, there is a moderate risk of reactivation during DAA treatment, and these patients should receive a nucleoside analogue during and following the course of HCV therapy. Regular monitoring, including serum ALT and HBV DNA levels is recommended for all coinfected individuals throughout HCV treatment, (Pisaturo *et al.*, 2019).

Hepatitis D and Hepatitis B Coinfection (HBV/HDV)

Hepatitis D virus (HDV) is highly endemic in parts of Africa, the Middle East, Eastern Europe, and the Amazon Basin. However, data on HDV prevalence in Zambia remain limited. In local studies of HBV monoinfection and HIV-HBV coinfection, the presence of HDV antibodies was rare, with a prevalence of approximately 2 3%. (*WHO*, 2021) (*Ministry of Health*, 2019).

HDV is a defective RNA virus that requires the presence of HBV for replication and pathogenicity. It cannot infect or cause disease independently (American Association for the Study of Liver Diseases, 2022); therefore, coinfection with HBV is essential for HDV-related disease to occur. Two types of HDV/HBV coinfection are recognized. The first is simultaneous coinfection, which occurs when HBV and HDV infect a person at the same time. This form is often self-limiting but may cause severe acute hepatitis. The second is superinfection, which occurs when HDV infects a person already chronically infected with HBV. This form is typically more severe and frequently progresses to chronic HDV infection (Coffie et al., 2017). The clinical impact of HBV/HDV coinfection is significant. It accelerates the progression to cirrhosis and hepatocellular carcinoma and is associated with more severe liver disease compared to HBV monoinfection. Chronic HBV infection develops in up to 90% of individuals with HDV superinfection (Brunetto et al., 2023).

According to the 2024 World Health Organization guidelines, serological testing for anti-HDV antibodies is recommended for all individuals with chronic hepatitis B infection (HBsAg-positive) to ensure timely diagnosis and linkage to appropriate care. In settings with limited laboratory capacity, testing should be prioritized for high-risk groups. These include individuals originating from HDV-endemic regions; those with advanced liver disease, those receiving HBV treatment, or individuals with clinical features suggestive of HDV infection, such as low HBV DNA levels with elevated ALT; as well as key populations at increased risk, including people living with HIV or HCV, haemodialysis patients, people who inject drugs, sex workers, and men who have sex with men.

If anti-HDV is positive, HDV RNA testing is required to confirm active infection. With regards treatment, nucleos(t)ide analogues used for HBV (e.g., TDF, ETV) do not suppress HDV replication. However, HBV vaccination is an effective strategy for preventing HDV infection, as HDV cannot propagate without HBV. (Brunetto *et al.*, 2023) (*WHO*, 2024)(See the specific section on Hepatitis D treatment for detailed management guidelines)

HBV/Tuberculosis Coinfection

People living in regions where both tuberculosis and hepatitis B virus (HBV) are endemic, such as sub-Saharan Africa and parts of Asia are at increased risk of coinfection. (*WHO, 2021*). High-risk groups include people who inject drugs and individuals in prisons (Dolan *et al.*, 2016). Importantly, individuals coinfected with HBV face a significantly higher risk, three- to six-fold, of developing drug-induced liver injury due to the hepatotoxic effects of anti-TB medications such as isoniazid, rifampicin, and pyrazinamide (Chou *et al.*, 2022) (Chen *et al.*, 2018). This underscores the need for increased clinical vigilance, routine screening, and liver function monitoring during TB treatment.

Comorbidities such as Diabetes and Steatotic Liver Disease

According to the World Health Organization, while the exact impact of hepatitis B infection on liver inflammation and fibrosis progression in individuals with metabolic dysfunction associated steatotic liver disease (MASLD) is not fully understood, available evidence suggests that treatment and appropriate management of hepatic steatosis should be considered. Diabetes is also recognized as a potential risk factor for the development of hepatocellular carcinoma. Although these risk factors are not yet fully defined, WHO recommends initiating antiviral therapy for hepatitis B if MASLD is believed to contribute significantly to liver inflammation or fibrosis in a person with chronic hepatitis B. It is also important to note that tenofovir, a commonly used antiviral, may increase serum lipid levels. *(WHO*, 2024) (Lin *et al.*, 2024) (Zhou *et al.*, 2025).

Decompensated Cirrhosis and Advanced Liver Disease

Decompensated chronic liver disease is a deterioration of liver function associated with the liver related complications such as, ascites, hepatitis encephalopathy, variceal bleeding and jaundice. Decompensation is an important event in chronic liver disease as prognosis significantly worsens with increased mortality and morbidity. Liver cirrhosis is a terminal consequence of chronic liver disease associated with functional and histological changes in the liver. Treatment with NAs is indicated in patients with decompensated CLD and cirrhosis, as it leads to significant clinical improvement as well as reduced the risk of hepatocellular carcinoma. NAs should be started in all decompensated chronic liver disease patients and those with cirrhosis regardless of, ALT level HBV DNA level, HBeAg status, to decrease risk of worsening liver-related complications.

All NAs are reasonable as initial treatment in hepatitis B but special consideration must be made in patients with hypophosphatemia, osteopenia/osteoporosis, renal insufficiency or risk factors for TDF-related nephrotoxicity as well as those at risk of lactic acidosis such as those with a Child Pugh Score of C. Interferon, however, should not be used as treatment in decompensated CLD.

Immunomodulatory and immunosuppressive therapy such as high dose IgG, rituximab, high dose corticosteroids and plasmapheresis are usually (alongside antiviral therapy) indicated to treat major renal (membranous nephropathy, membranoproliferative glomerulonephritis and polyarteritis nodosa), neurological and haematological manifestations or refractory cases (Mazzaro 2022)

Reactivation

Persistence of covalently closed circular DNA in the liver makes reactivation of hepatitis B possible. Hepatitis B Virus reactivation (HBVr) refers to a sudden increase in DNA replications in HBsAg positive individuals with an inactive profile (HBeAg negative chronic infection) or HBsAg-negative individuals with resolved hepatitis B (HBsAg-negative, anti-HBc-positive). It is thought to be typically due to natural or iatrogenic loss of immune control (Hoofnagle 2009). Reactivation is defined by either reappearance of HBV DNA (>100IU/ml) or HBsAg (HBsAg seroreversion) in individuals with previously undetectable levels, or by at least a10-fold increase in HBV DNA levels from baseline. It is potentially a life-threatening complication of chemotherapy or immunosuppressive therapies. Therefore, NA prophylaxis is recommended in high-risk patients undergoing above therapies.

Treatment for HCC in HBV

All patients with HBV require to be started on treatment as it ensures viral control, improves liver function, and potentially improves survival outcomes. According to EASL, HBsAg-positive patients with HCC should always receive long-term antiviral therapy. HBsAg-negative/anti-HBc-positive patients with HCC should receive NA prophylaxis based on the type of HCC treatment, particularly if transarterial chemoembolization (TACE), radiotherapy, or combination therapies are used.

Monitoring

Regardless of the criteria guiding the initiation of treatment, WHO recommends that all individuals starting treatment should undergo annual monitoring involving HBV DNA, ALT and APRI score assessments, with continuous support to ensure adherence. Individuals who have not yet initiated treatment should also undergo close monitoring.

Monitoring CHB Patients Not Yet on Treatment

During the first year of infection; ALT every 3 months, DNA every 6 months where feasible to determine phase of infection, monitor for fluctuations and possibility of reaction (EASL 2025). Studies assessing the risk of disease progression, including HCC, in individuals with low HBV DNA levels (<20,000IU/m L) have shown ALT to be an important key predictor of disease progression (Papatheodoridis GV 2008). Although spontaneous sero clearance of HBsAg is unlikely, annual HBsAg monitoring is recommended.

Monitoring of People Receiving HBV Treatment

The following are recommended in those receiving treatment;

- Non- invasive tests such as APRI or transient elastography (FibroScan)
- ALT every 3 months especially during first year, and annually for DNA after baseline
- At each visit, there is need to monitor treatment adherence

Monitoring the safety of nucleoside analogues (adopted from WHO 2024 guidelines)

The aim of monitoring people receiving treatment is to evaluate the effectiveness of treatment response, treatment adherence, adverse effects of treatment, progression of liver disease and development of HCC. HBV DNA testing is important for monitoring treatment response, even when HBV DNA measurement was not part of initial assessment for treatment eligibility. Very rarely it can indicate the potential for ending treatment. If antiviral therapy

is discontinued, liver function should be monitored closely, since severe acute exacerbations of hepatitis have been reported, and antiviral therapy may need to be resumed.

Among people who do not meet the criteria for antiviral therapy or want to defer therapy, the aim of monitoring in people not on antiviral therapy is to identify an early change in clinical status (levels of HBV DNA or serum ALT or increasing APRI or transient elastography score) that indicates a risk of progressive liver disease and need for antiviral therapy, before advanced hepatic fibrosis or cirrhosis develops.

Surveillance for Hepatocellular Carcinoma among People with CHB

As shown in figure 4 on surveillance and monitoring of treatment response, It is important to do abdominal ultrasound every 6 months to look for HCC. Additionally, alpha feto protein (AFP) may be done every 6 months. It is not a reliable marker as some variants of HCC such as fibrolamellar may not secrete AFP. HCC surveillance should be continued in at-risk patients irrespective of effective antiviral therapy or HBsAg loss (EASL guidelines 2025)

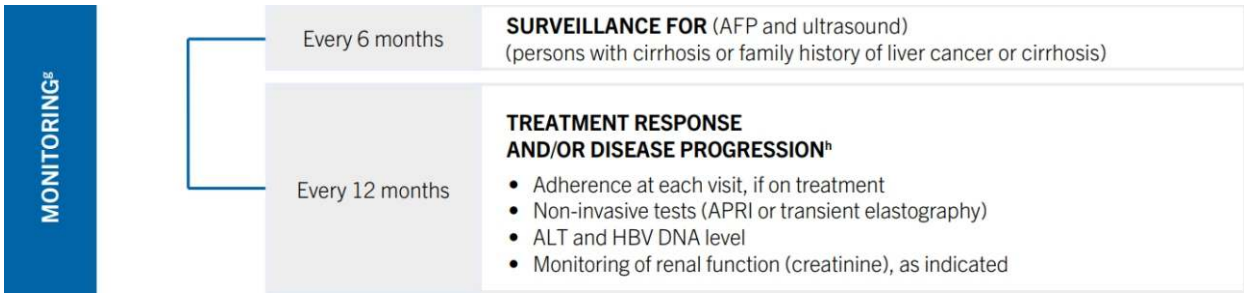


Figure 4: Surveillance and monitoring of treatment response (Adapted from WHO guidelines 2024)

Prevention of Vertical Transmission

Key prevention strategies for vertical transmission of HBV include early maternal screening during pregnancy to guide treatment and vaccination, with repeat testing for at-risk mothers. Non-immune pregnant women should receive the HBV vaccine. HBsAg-positive women with high viral loads may require antiviral therapy from 28 weeks gestation. At birth, all infants of HBsAg-positive mothers must receive both the HBV vaccine and HepB immunoglobulin (HBIG) within 12 hours if available. Completion of the full vaccine series and post-vaccination testing at 9–12 months ensures protection and guides further management for non-responders.

HBsAg Testing in Pregnant Women and Adolescent Girls

All pregnant women should be tested for HBsAg at their first antenatal visit or as early as possible, as part of triple testing for HIV, syphilis and HBsAg toward triple elimination initiative. Early detection of HBV infection is essential to guide appropriate clinical management.

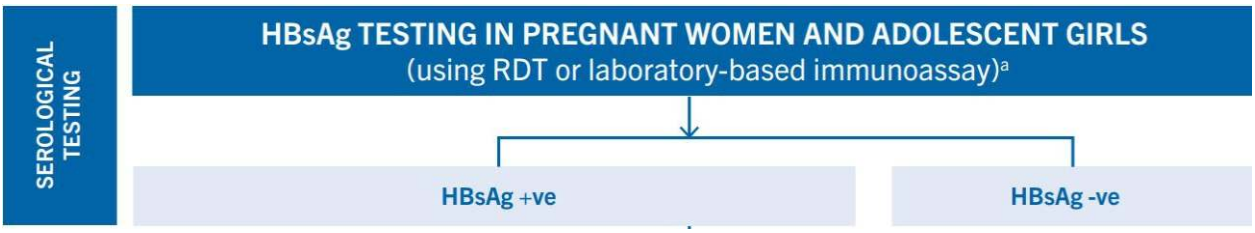


Figure 5: HBs testing in pregnant women and adolescent girls

If HBsAg is positive, further evaluation, including HBV DNA levels and HBeAg status, should be conducted to determine the need for antiviral therapy during pregnancy and to plan appropriate postpartum care. For HBsAg-negative women with ongoing risk factors for HBV infection (e.g., infected partner, household exposure, high-risk behaviors), repeat serological testing should be conducted at the time of delivery to ensure timely detection and management.

Eligibility for Long-Term Treatment in Pregnant Women and Adolescent Girls for Their Own Health

All pregnant women should be assessed first for eligibility for long-term treatment for their own health and then for antiviral prophylaxis to prevent mother-to-child transmission. Long-term treatment for their own health is recommended for those with:

1. Treatment is recommended for all who have evidence of significant liver fibrosis or cirrhosis. Evidence of significant fibrosis is defined as stage F2 or higher is based on an APRI score greater than 0.5 or transient elastography value greater than 7 kPa; and evidence of cirrhosis stage F4 is based on clinical criteria (or an APRI score greater than 1 or transient elastography value greater than 12.5 kPa), regardless of HBV DNA or ALT levels.
2. Treatment is recommended for all with HBV DNA >2000 IU/mL and an ALT level above the upper limit of normal (ULN) (30 U/L for men and boys and 19 U/L for women and girls). For adolescents, this should be based on ALT>ULN on at least two occasions in a 6- to 12-month period.
3. Treatment is recommended for all with presence of coinfections (such as HIV, hepatitis D or hepatitis C); family history of liver cancer or cirrhosis; immune suppression (such as long-term steroids, solid organ or stem cell transplant); comorbidities (such as diabetes or metabolic dysfunction, associated steatotic liver disease); or extrahepatic manifestations (such as glomerulonephritis or vasculitis), regardless of the APRI score or HBV DNA or ALT levels.
4. In the absence of access to an HBV DNA assay: persistently abnormal ALT levels (defined as two ALT values above the ULN at unspecified intervals during a 6- to 12-month period), regardless of APRI score.

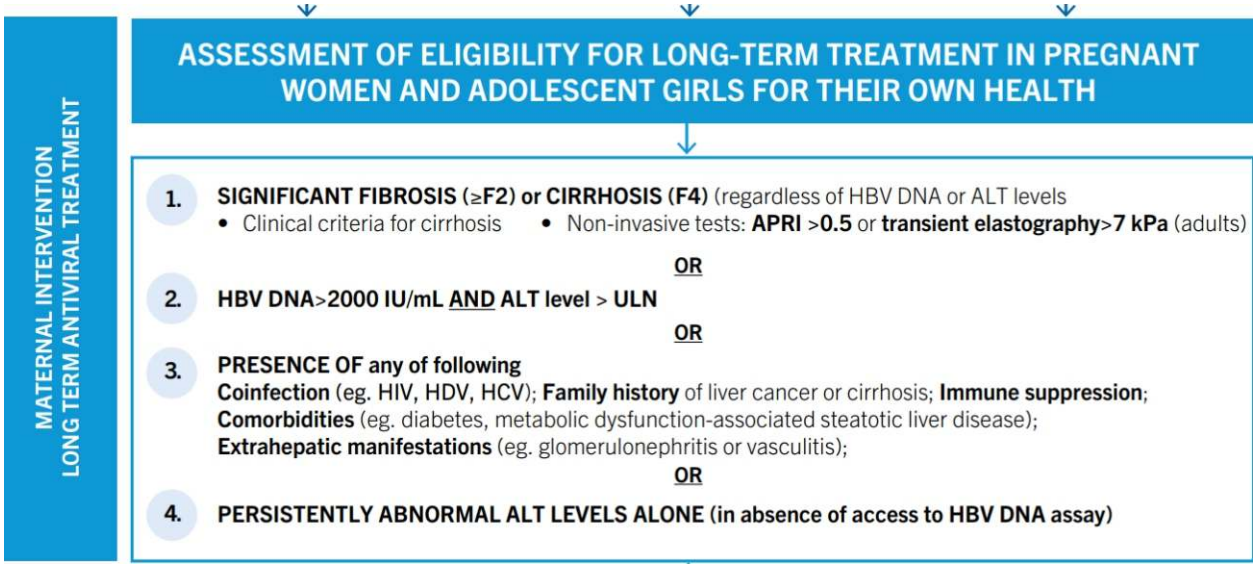


Figure 6: Eligibility for long-term treatment in pregnant women and adolescent girls for their own health (adapted from WHO guidelines 2024)

Eligibility for Antiviral Prophylaxis Among Pregnant Women and Adolescent Girls who do not Meet Treatment Eligibility Criteria

TDF antiviral prophylaxis (from at least the second trimester of pregnancy until at least delivery or completion of the infant HBV vaccination series) is recommended for the following:

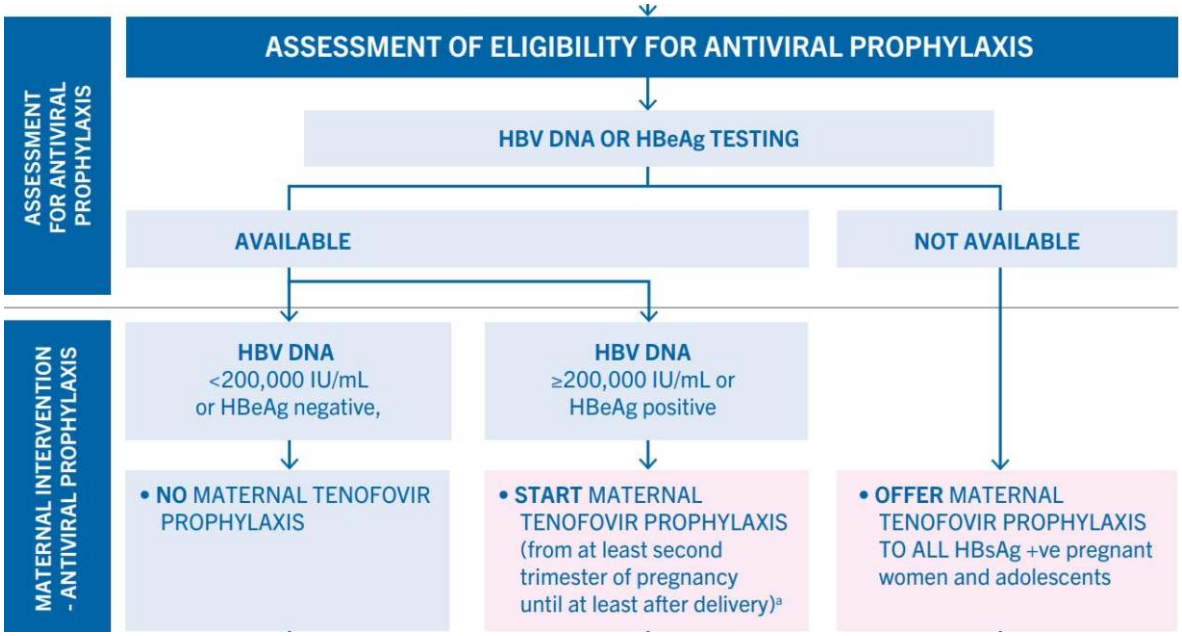


Figure 7: Assessment for antiviral prophylaxis in pregnant women and adolescent girls with CHB (Adapted from WHO guidelines 2024)

In settings where HBV DNA or HBeAg testing is available, prophylaxis with TDF is recommended for all HBsAg-positive pregnant women with HBV DNA ≥200 000 IU/mL or positive HBeAg (preferably from the second trimester of pregnancy until six weeks after delivery (coinciding with the first Under 5 clinic visit), to prevent the vertical transmission of HBV.

1. In settings where neither HBV DNA nor HBeAg testing is available, prophylaxis with tenofovir disoproxil fumarate for all HBsAg-positive pregnant women may be considered (preferably from the second trimester of pregnancy until six weeks after delivery (coinciding with the first Under 5 clinic visit, to prevent vertical transmission of HBV.

HIV-coinfected pregnant women who are taking an ART regimen containing tenofovir disoproxil fumarate are fully treated and do not need any additional HBV treatment. Any change to second line ART should include TDF for Hep B treatment. Mothers have a potential risk of exacerbation or postpartum flare after antiviral therapy ends, and therefore need to be monitored carefully after the discontinuation of TDF. For women who test positive for HBsAg during labour and for the first time, every effort should be made to give the Hepatitis B Birth Dose vaccine and HBIG to the baby within 12- 24 hours of delivery.

Infant Immunization

Infants born to mothers with hepatitis B virus infection with a high viral replication rate are at highest risk for perinatal transmission. This mode of transmission is associated with a greater than 90% likelihood of developing chronic HBV infection, which significantly increases the risk of serious liver complications such as cirrhosis and hepatocellular carcinoma, the most common type of primary liver cancer. Because perinatal or early postnatal transmission is the most important source of chronic HBV infection, a timely birth dose followed by two or three additional doses is the most effective and cost-efficient vertical transmission preventive measure.

All infants (including low birth weight and premature infants) should receive their Hepatitis B Birth Dose vaccine (HepB BD), a monovalent vaccine, as soon as possible after birth, ideally within 24 hours. A dose of 0.5ml I.M. given soon after birth or within 24 hours of birth on the thigh is recommended. The birth dose should be followed by childhood pentavalent vaccines as per national immunization schedule. High coverage of the timely hepatitis B birth dose and completion of the infant hepatitis B vaccine series are the most important interventions for reducing vertical transmission of HBV as well as early childhood transmission.

Vaccination against HBV During Pregnancy

Pregnant women who at risk of acquiring HBV need to be vaccinated as well. Vaccination against HBV during pregnancy is safe and effective. Following the vaccination, maternal antibodies are passively transferred across the placenta to newborns, although without the active vaccination at birth, its titres rapidly wane over time. Pregnant women can be considered HBV-immune when anti-HBs levels are higher than 10 mIU/mL.

Viral Hepatitis A Infection

Overview

Hepatitis A is an inflammation of the liver caused by the hepatitis A virus. The virus is primarily spread when an uninfected (and unvaccinated) person ingests food or water that is contaminated with the faeces of an infected person. An infected person excretes hepatitis A virus in the faeces. The disease is closely associated with unsafe water or food, inadequate sanitation, poor personal hygiene, and oral-anal sex. Unlike hepatitis B and C, hepatitis A does not cause chronic liver disease, but it can cause mild to severe symptoms and rarely fulminant hepatitis (acute liver failure), which is often fatal. Hepatitis A occurs sporadically and in epidemics worldwide, with a tendency for cyclic recurrences. Epidemics related to contaminated food or water can erupt explosively. They can also be prolonged, affecting communities for months through person-to-person transmission. Hepatitis A viruses persist in the environment and can withstand food production processes routinely used to inactivate or control bacterial pathogens.

Epidemiology and Burden of Infection

HAV is an RNA Virus typically transmitted through the faecal-oral route. An infected person excretes hepatitis A virus in the faeces. The disease is closely linked to environmental and socio-economic conditions such as unsafe drinking water, poor personal hygiene, inadequate sewage disposal, and poor food safety practices. It is also associated with certain sexual practices, particularly oral-anal sex. Unlike hepatitis B and C, hepatitis A does not cause chronic liver disease, but it can cause mild to severe symptoms and rarely fulminant hepatitis (acute liver failure), with mortality rate of about 0.5 %.

The global burden of hepatitis A remains significant, particularly in low- and middle-income countries. According to WHO estimates, approximately 100 million HAV infections occur annually, with around 1.5 million symptomatic cases and up to 30,000 deaths. There are estimated to be 100 million HAV infections and 1.5 million symptomatic cases annually worldwide, and these are responsible for 15,000 to 30,000 deaths per year (WHO 2019). Children are most frequently affected, and although many experience asymptomatic infection, they contribute substantially to viral transmission. Outbreaks of HAV do occur. Others may experience several relapses during the course of a year.

Transmission

The hepatitis A virus is transmitted primarily by the faecal-oral route; that is when an uninfected person ingests food or water that has been contaminated with the faeces of an infected person. In families, this may happen though dirty hands (poor personal hygiene) when an infected person prepares food for family members. Waterborne outbreaks, though infrequent, are usually associated with sewage-contaminated or inadequately treated water. The virus can also be transmitted through close physical contact (such as oral-anal sex) with an infectious person, although casual contact among people does not spread the virus.

Natural History

Hepatitis A has an incubation period of about 4 weeks between the time of exposure and onset of symptoms. Its replication is limited to the liver, but the virus is present in the liver, bile, stools, and blood during the late incubation period and acute preicteric/presymptomatic phase of illness. Despite slightly longer persistence of virus in the liver, fecal shedding, viremia, and infectivity diminish rapidly once jaundice becomes apparent. The virus is excreted in stool during the first few weeks of infection, before the onset of symptoms.

Antibodies to HAV (anti-HAV) can be detected during acute illness when serum aminotransferase activity is elevated and fecal HAV shedding is still occurring. This early antibody response is predominantly of the IgM class and persists for several (~3) months, rarely for 6 12 months. During convalescence, however, anti-HAV of the IgG class becomes the predominant antibody. Therefore, the diagnosis of hepatitis A is made during acute illness by demonstrating anti-HAV of the IgM class. After acute illness, anti-HAV of the IgG class remains detectable indefinitely, and patients with serum anti-HAV are immune to reinfection. Neutralizing antibody activity parallels the appearance of anti-HAV, and the IgG anti-HAV present in immune globulin accounts for the protection it affords against HAV infection.

Clinical Presentation

The acute presentation of hepatitis A is no different from other types of hepatitis. The infection may be asymptomatic or may present mild to severe symptoms which may include fever, malaise, loss of appetite, diarrhea, nausea, abdominal discomfort, dark coloured urine and jaundice. Patients may experience cholestatic hepatitis, marked by the development of an elevated ALP level, in contrast to the classic picture of elevated aminotransferase levels. Infected children under six years of age do not usually experience noticeable symptoms, and only 10% develop jaundice.

Diagnosis

The specific diagnosis of acute HAV infection can be made by detection of HAV- specific immunoglobulin M (IgM) antibodies in blood. Presence of hepatitis A immunoglobulins of IgG type (IgG) imply past exposure and not acute infection. Other tests that can be done include reverse transcriptase polymerase chain reaction (RT- PCR) to detect the hepatitis A virus RNA.

Treatment

There is no specific antiviral treatment for hepatitis A. Management is primarily supportive, focusing on relieving symptoms, maintaining adequate hydration and nutrition, and avoiding hepatotoxic drugs. Specific complications, if they arise, should be managed appropriately based on clinical presentation. In rare cases of fulminant hepatic failure, liver transplantation may be considered. Recovery from symptoms may be slow and may range from weeks to months.

Prevention

Prevention of hepatitis A primarily relies on improved sanitation, safe water and food practices, immunization, and the avoidance of high-risk behaviors such as oral-anal sexual contact. Among these, immunization, food and water safety, and effective sanitation remain the most impactful strategies for controlling transmission. Reducing the spread of HAV requires access to safe drinking water, proper sewage disposal, and consistent personal hygiene practices, particularly regular handwashing with clean water.

Vaccination is highly effective and forms the cornerstone of prevention. Nearly 100% of people develop protective levels of antibodies to the virus within one month after injection of a single dose of vaccine. Even after exposure to the virus, a single dose of the vaccine within two weeks of contact with the virus has protective effects. However, for long-term protection, manufacturers recommend a two-dose schedule, with the second dose given six months after the first, providing immunity lasting at least five to eight years.

Hepatitis E Infection

Overview

Hepatitis E virus (HEV) is an RNA virus, which causes epidemics of largely water-borne. It causes acute hepatitis with an incubation period ranging from 14 to 60 days (average 5– 6 weeks). It is transmitted via the fecal-oral route, similar to hepatitis A, spread by fecally contaminated water in endemic areas or through the consumption of uncooked or undercooked food. The infection is usually self-limiting and resolves within 2– 6 weeks. Outbreaks can be epidemic often associated with rainy seasons, floods, and overcrowded conditions. HEV has many similarities with HAV. The virus is detectable in stool, bile, and liver during the late incubation phase. The course of infection has two phases, the prodromal phase, and the icteric phase. The overall case fatality rate is ~4%, although pregnant women and liver transplant recipients may be at substantially higher risk. To contain the disease prevention is key, relying on clean drinking water, good sanitation, and proper personal hygiene. A successful recombinant hepatitis E vaccine exists but not readily available in many African countries.

Epidemiology and Burden of Infection

Hepatitis E has worldwide distribution, but predominating factors include tropical climates, inadequate sanitation, and poor personal hygiene. Water supply contamination with human feces is a frequent source of epidemics. Infection can occur as outbreaks or as sporadic cases. Outbreaks are associated with rainy seasons, floods, and overcrowding. The overall case fatality rate in sub-Saharan Africa is 1-2% in general population and about 20% in pregnant women (Husein et al, 2020). A study by Jacobs et al, 2014 among people in Lusaka observed high levels of Hepatitis E Virus (HEV) antibodies suggesting substantial transmission may be occurring.

Transmission

Hepatitis E virus is transmitted primarily via the faeco-oral route and is spread by contaminated water within endemic areas or through the consumption of uncooked or undercooked meat. Though food-borne infections are increasingly being identified, vertical transmission from infected pregnant women can occur. The virus reaches the liver, presumably via the portal vein, and replicates in the cytoplasm of hepatocytes. While man is the natural host, it seems very likely that animals serve as a reservoir, with several claims of infection in domestic sheep and swine.

Natural History

The incubation period following exposure to HEV ranges from 2 to 10 weeks, with an average of 5 to 6 weeks. The infected persons excrete the virus beginning from a few days before to 3– 4 weeks after onset of the disease. After exposure, viral RNA can be detected just before the onset of clinical symptoms in both blood and stool samples. HEV RNA does not persist for long, becoming undetectable in blood about 3 weeks after the onset of symptoms. HEV RNA in stool can be detected in the pre-icteric phase, and then declines, disappearing by the peak of ALT. The virus is shed in stool for a further 2 weeks. The window of detectable RNA is, therefore, narrow, and if patients present late in their illness, an undetectable HEV RNA result does not exclude recent infection. The anti-HEV IgM usually starts rising 4 weeks after infection and remains detectable for 2 months after the onset of illness. Anti-HEV IgM in serum can be identified at onset of symptoms, detectable for 2 weeks to 3 months. Anti-HEV IgG increases promptly after IgM, persisting for up to several years in 50% of patients.

Clinical Presentation

Infected patients may have a range of presentations, from asymptomatic to mild hepatitis to fulminant hepatic failure. In nonendemic (autochthonous) type of acute hepatitis E infection, the majority of patients have subclinical manifestations and mild symptoms, especially in women and young persons. The course of infection has the prodromal phase (often of short duration) and the icteric phase. Pre-icteric phase, lasting 1– 10 days (average 3– 4 days) with GI symptoms (epigastric pain, nausea and vomiting). Icteric-phase symptoms may last days to several weeks and begin abruptly with jaundice, dark urine and clay-coloured stools. Two-thirds of patients also report arthralgia. The liver may become enlarged and tender, and mild right upper quadrant pain can occur. In areas with high disease endemicity, symptomatic infection is most common in young adults aged 15 to 40 years. In these areas, although infection does occur in children, they often have either no symptoms or only a mild illness without jaundice that goes undiagnosed. In rare cases, acute hepatitis E can be severe, and results in fulminant hepatitis; these patients are at risk of death. Pregnant women with hepatitis E, particularly those in the second or third trimester, are at increased risk of fulminant hepatic failure, fetal loss and mortality. Up to 20– 25% of pregnant women can die if they get hepatitis E in third trimester (Nan et al., 2014; Smith et al., 2014).

Cases of chronic hepatitis E infection are rare, and have been reported in immunosuppressed people, particularly organ transplant recipients on immunosuppressive drugs, with genotype 3 or 4 HEV infection (Zhongren et al., 2022). An uncomplicated infection lasts 12– 15 days with complete recovery within 1 month. Superinfection in chronic liver disease causes severe liver decompensation, a protracted course, and high morbidity and mortality.

Diagnosis

Cases of hepatitis E are not clinically distinguishable from other types of acute viral hepatitis or potentially other infectious disease that cause jaundice. Because many patients with HEV infection are asymptomatic, the diagnosis of HEV infection relies on a high index of clinical suspicion. Definitive diagnosis of hepatitis E infection is based on detection of specific anti-HEV immunoglobulin M (IgM) antibodies in serum in early acute infection or IgG anti-HEV after about three months. Additional tests include reverse transcriptase polymerase chain reaction (RT-PCR) to detect the hepatitis E virus RNA in blood and/or stool. This assay requires specialized laboratory facilities. However, diagnosis can often be strongly suspected in appropriate epidemiologic settings, for example when several cases occur in localities in known disease-endemic areas, in settings with risk of water contamination when the disease is more severe in pregnant women or if hepatitis A has been excluded. Other laboratory findings include elevated serum concentrations of bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST).

Treatment

There is no specific treatment capable of altering the course of acute hepatitis E. As the disease is usually self-limiting, hospitalization is generally not required. It is important to avoid unnecessary medications that can adversely affect liver function, for example acetaminophen (paracetamol). However, hospitalization, is required for people with fulminant hepatitis, and should also be considered symptomatic pregnant women. Immunosuppressed people with chronic hepatitis E benefit from specific treatment using ribavirin. Ribavirin monotherapy is typically administered for 3– 6 months, continuing until HEV RNA is undetectable in stool on two occasions one month apart (Kamar et al., 2010, 2012).

Prevention

Hepatitis E virus infection control and prevention strategies focus primarily on improving hygiene conditions in endemic areas and identifying contaminated sources. Enhancing sanitation, ensuring access to clean drinking water, and implementing effective sewage disposal systems are essential measures to reduce transmission. Key preventive measures include maintaining the safety and quality of public water supplies and practicing good personal hygiene. Regular handwashing with safe water, especially before handling or preparing food, significantly lowers the risk of infection. The safe preparation of food is also critical; particular care should be taken when washing raw fruits and vegetables, and the use of boiled or treated water is advised when washing produce or preparing food in uncertain sanitary conditions. While boiling water is considered effective against HEV, the efficacy of chlorination remains unclear. Immunocompromised individuals and those with chronic liver disease require additional precautions. They should avoid undercooked meat entirely, as HEV can be transmitted through consumption of infected animal products. It is recommended that meat, particularly pork, be cooked thoroughly to an internal temperature of at least 71°C for a minimum of 20 minutes. While an effective hepatitis E vaccine has been developed and licensed in some countries, it is not yet widely available or WHO-prequalified for global use.

Viral Hepatitis C Infection

Overview

Hepatitis C infection is a viral infection of the liver caused by Hepatitis C virus, an RNA virus transmitted through contact with infected blood and blood products. HCV can cause both acute (less commonly) and chronic disease. Recently acquired HCV infections are usually asymptomatic and rarely lead to symptomatic acute HCV. Transmission can happen through unsafe injections and procedures in health care, unscreened blood transfusions, sharing of needles and syringes among people who inject drugs and sexual practices that lead to exposure to blood. Acute HCV infections are usually asymptomatic, and most do not lead to a life-threatening disease (Racheal Westbook et al. 2014). Approximately 30% (15– 45%) of infected persons spontaneously clear the virus within 6 months of infection without treatment, with a median time to clearance of 16.5 weeks. Spontaneous clearance is more likely to occur in women, genotype 1 infection, and in people with clinical evidence of acute hepatitis, but is less likely to occur in people with HIV. The remaining 70% (55– 85%) of persons will develop chronic HCV infection. Of those with chronic HCV infection, the risk of cirrhosis ranges from 15% to 30% within 20 years (Racheal Westbook et al. 2014). Patients with HCV-related cirrhosis may develop HCC, which is in contrast to HBV, in which patients without cirrhosis can also develop hepatocellular carcinoma. Importantly, individuals that have cleared their HCV infection (spontaneously or through HCV treatment) are not immune to the virus, and those with ongoing risk and exposure can get reinfected. HIV infection accelerate HCV progression and hence HCV/HIV-coinfected people should be treated on a priority basis. Symptoms can include fever, fatigue, loss of appetite, nausea, vomiting, abdominal pain, dark urine, and jaundice. Early detection and successful virus clearance reduces HCV-related long-term morbidities and mortality. There is no vaccine for hepatitis C.

Epidemiology and Burden of Infection

Hepatitis C virus significantly contributes to disease burden and high mortality associated with chronic hepatitis C and its complications such as cirrhosis and hepatocellular carcinoma. According to the World Health Organization (WHO, 2025), HCV is responsible for approximately 290,000 deaths worldwide each year. In Zambia, the true burden of hepatitis C remains unknown. However, previous estimates suggest a prevalence of approximately 0.7% to 1% among blood donors (unpublished data). HCV burden has been documented to be disproportionally high in people who inject drugs, people in prisons and men who have sex with men, particularly in men who have sex with men living with HIV.

Transmission

Hepatitis C virus is a bloodborne virus transmitted primarily through parenteral exposure to infected blood and blood products. The highest rates of infection are observed among people who inject drugs, men who have sex with men, and individuals in prison settings. The most common modes of transmission include the reuse or inadequate sterilization of medical equipment, particularly syringes and needles in healthcare settings, the transfusion of unscreened blood and blood products, and injecting drug use through the sharing of injection equipment. Less commonly, HCV can be passed from an infected mother to her baby during childbirth, and through sexual practices that involve exposure to blood, especially among individuals with multiple sexual partners and men who have sex with men. Hepatitis C is not spread through breast milk, food, water, or casual contact such as hugging, kissing, or sharing food or drinks with an infected person.

Natural History

After HCV exposure, the virus typically causes an acute infection, which is mostly asymptomatic. Approximately 30% (15–45%) of infected persons spontaneously clear the virus within 6 months of infection without treatment, with a median time to clearance of 16.5 weeks. Spontaneous clearance is more likely to occur in women, genotype 1 infection, and in people with clinical evidence of acute hepatitis, but is less likely to occur in people with HIV. The remaining 70% (55–85%) of persons will develop chronic HCV infection. Of those with chronic HCV infection, the risk of cirrhosis ranges from 15% to 30% within 20 years (Racheal Westbook et al. 2014). Patients with HCV-related cirrhosis may develop HCC, which is in contrast to HBV, in which patients without cirrhosis can also develop hepatocellular carcinoma. Importantly, individuals that have cleared their HCV infection (spontaneously or through HCV treatment) are not immune to the virus, and those with ongoing risk and exposure can get reinfected (Racheal Westbook et al. 2014).

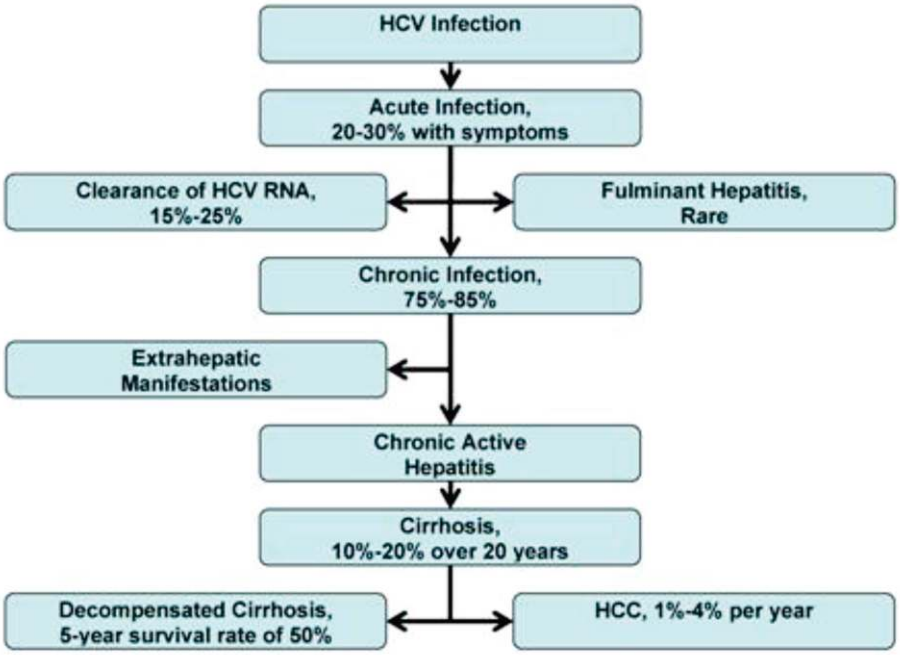


Figure 8: Natural History of hepatitis C infection (Racheal Westbook et al. 2014 (https://doi.org/10.1016/j.jhep.2014.07.012))

Following the acute phase, anti-HCV antibodies typically remain positive for life, regardless of whether the infection resolves or persists. However, only individuals with ongoing (persistent) infection will be HCV RNA positive, indicating active viremia. Thus, the presence of HCV RNA distinguishes active infection from resolved cases. Among the various factors influencing the natural history of HCV, the presence or absence of cirrhosis is the most critical. It determines the choice of antiviral therapy, duration of treatment, risk of relapse, and the need for long-term follow-up after successful viral eradication.

Clinical Presentation

Symptomatic acute hepatitis C infection is uncommon. In most cases, individuals do not experience any symptoms during the initial weeks following infection. When symptoms do occur, they typically appear between two weeks and six months after exposure. These symptoms can include fever, extreme fatigue, loss of appetite, nausea and

vomiting, abdominal pain, dark urine, pale stools, joint pain, and jaundice. Because early symptoms are often mild, non-specific, or absent altogether, many cases of acute HCV go undiagnosed.

Those with chronic infection may present with extra-hepatic manifestations which include cryoglobulinemia, lymphoproliferative disorders, renal diseases, thyroid disorders, skin disorders among others. HCV can lead to the development of liver cirrhosis and hepatocellular carcinoma. Liver fibrosis is a result of ongoing liver injury and the healing process. Hence, liver fibrosis progresses as a continuum from no fibrosis, mild, moderate and severe fibrosis to frank cirrhosis. The most important key determinant in the natural history of HCV is the presence or absence of cirrhosis because it determines the drug of choice, duration of treatment, risk of relapse following treatment, and need for regular follow up after successful virus eradication. Acute fulminant hepatitis infection is rare among hepatitis C infected patients.

Diagnosis

The diagnosis of Hepatitis C Virus infection involves a series of stepwise investigations, beginning with initial screening and followed by confirmatory testing, genotyping, liver disease staging, and the assessment of potential co-infections and complications. Accurate diagnosis is crucial for effective disease management, treatment planning, and prevention of long-term liver damage. The initial screening involves the anti-HCV antibody test, a serological assay that detects antibodies produced in response to the virus, indicating that an individual has been exposed to HCV at some point in their life. In settings with low HCV prevalence, HCV antibody-positives are likely to be false positives. A negative anti-HCV antibody test generally indicates that the individual has never been exposed to the virus. However, it is important to consider the window period. A positive anti-HCV antibody test result must be followed by confirmatory testing, typically an HCV RNA (viral load) or cAg test, to determine whether the virus is still present and actively replicating in the body. A positive HCV RNA or cAg test confirms that the individual has an active, ongoing HCV infection. Conversely, a negative HCV RNA or cAg test result in someone with a positive antibody test suggests either spontaneous viral clearance or successful prior treatment. Once active infection is confirmed, HCV genotyping is performed, as treatment regimens, duration, and response rates vary depending on the specific viral strain.

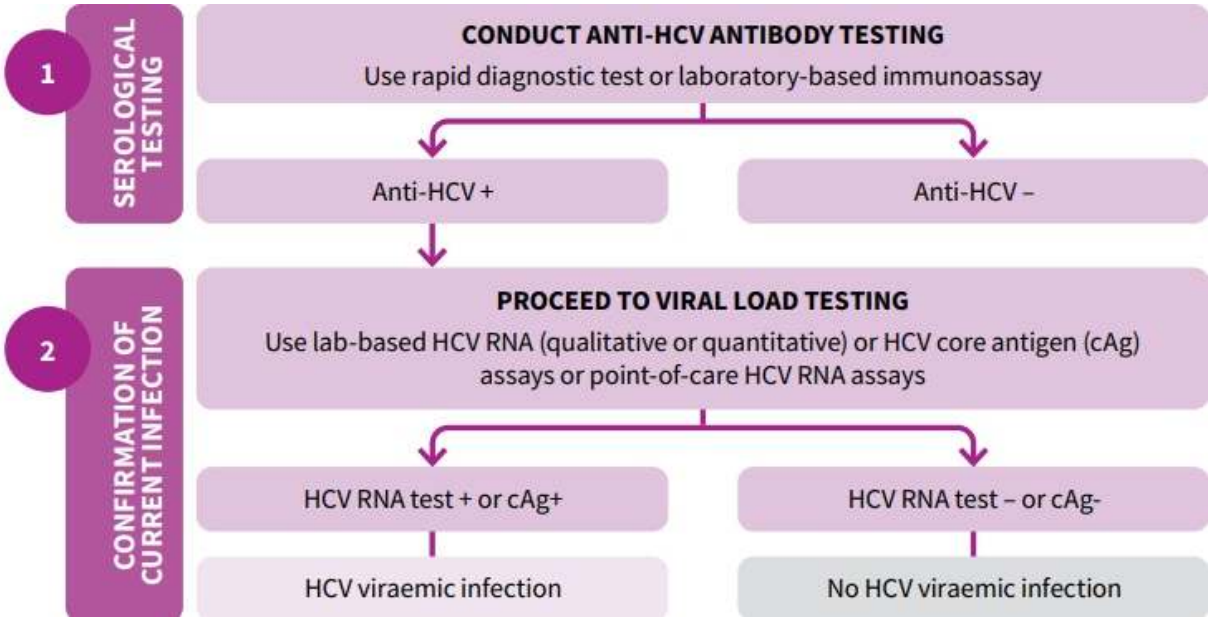


Figure 9: Summary algorithm on HCV testing (Adapted from 2023 WHO Policy Brief: New recommendation on hepatitis C virus testing and treatment for people at ongoing risk of infection)

Liver function tests (LFTs), including ALT, AST, bilirubin, and albumin, provide a basic assessment of liver health. In affected patients, ALT and AST levels may rise to 10 times the upper limit of normal (ULN), though the elevation is generally less pronounced than in acute hepatitis caused by hepatitis A, B, or E viruses. To estimate fibrosis, non-invasive tools like FibroScan, APRI, and FIB-4 are commonly used as alternatives to liver biopsy. Individuals with HCV should also be screened for HIV and HBV, as co-infections can accelerate liver disease progression and affect treatment outcomes. Imaging studies are essential for assessing liver complications, particularly in patients with chronic or advanced disease. Among these, liver ultrasound is commonly used to evaluate liver structure and detect signs of cirrhosis, portal hypertension, or hepatic tumors.
WHO recommends offering testing for HCV to all adults in settings where prevalence of HCV antibodies in the general population is over 2%, and focused testing in all settings for most affected populations, which usually includes the key populations.

Treatment

The primary goal of treating hepatitis C virus infection is to achieve a sustained virologic response (SVR), defined as the virus becoming undetectable in the blood 12 weeks or more after completing therapy. Achieving SVR is considered equivalent to a cure and significantly reduces the risk of liver damage and related complications. Several factors influence the choice of treatment regimen, including the patient's HCV genotype, the presence or absence of cirrhosis, previous treatment history, and any coexisting medical conditions such as HIV infection or kidney disease. While many DAA regimens are effective against all genotypes (pangenotypic), some treatments are tailored to specific genotypes. WHO currently recommends HCV therapy with pan-genotypic direct-acting antivirals for all persons with chronic infection over the age of 12 years and irrespective of disease stage. DAAs can cure most persons with chronic HCV infection, and treatment duration is short (usually 8 to 24 weeks), depending on the absence or presence of cirrhosis. Treatment should be started as shown in the algorithm below:

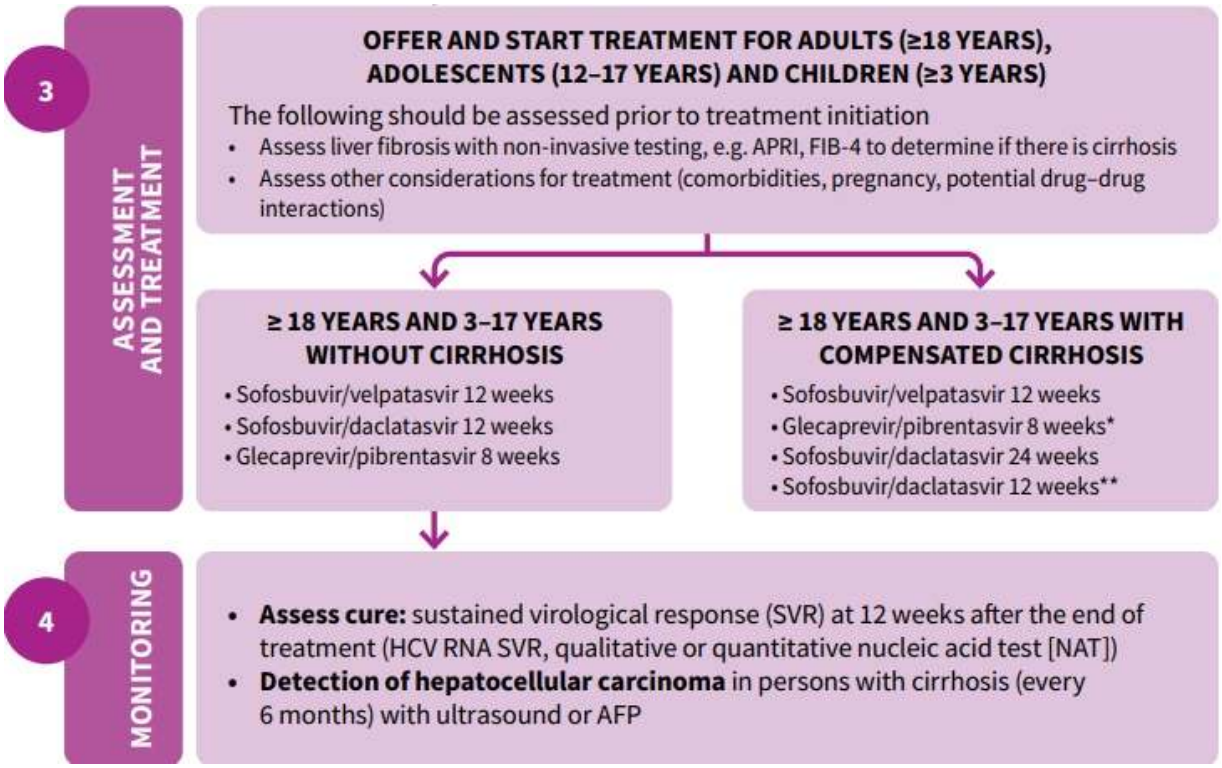


Figure 10: Summary algorithm on HCV treatment (Adapted from 2023 WHO Policy Brief: New recommendation on hepatitis C virus testing and treatment for people at ongoing risk of infection)

* Persons who failed prior therapy with interferon, ribavirin, and/or sofosbuvir with HCV genotype 1, 2, 4–6 with cirrhosis should be treated for 12 weeks, and with HCV genotype 3 with or without cirrhosis should be treated for 16 weeks.
** May be considered in countries where genotype distribution is known, and genotype 3 prevalence is <5%.

Prevention

Currently there is no approved vaccine available for hepatitis C infection. Prevention focuses on safe medical practices, harm reduction, screening, and early treatment to limit transmission.

Viral Hepatitis D Infection

Overview

Hepatitis D is an RNA virus which requires hepatitis B virus for its replication. Hepatitis D infection cannot occur in the absence of HBV. HDV–HBV co-infection is considered the most severe form of chronic viral hepatitis due to more rapid progression towards hepatocellular carcinoma and liver-related death. Vaccination against hepatitis B can prevent HDV infection. HDV has recently been classified as carcinogenic to humans (class I) by the World Health Organization International Agency for Research on Cancer monograph programme, just like hepatitis B and C.

Epidemiology and Burden of Infection

Hepatitis D virus affects nearly 5% of people globally who have a chronic infection with hepatitis B virus and that HDV co-infection could explain about 1 in 5 cases of liver disease and liver cancer in people with HBV infection (WHO 2020 (https://apps.who.int/iris/handle/10665/333453).

Transmission

HDV is blood borne and transmitted in the same way as HBV. Transmission may occur through contact with infected human blood or other bodily fluids. It may also be transmitted through sexual intercourse, or rarely from vertical transmission. HDV can also spread within families in endemic areas. Chronic HBV carriers are at risk of infection with HDV. People who are not immune to HBV (either by natural disease or immunization with the hepatitis B vaccine) are at risk of infection with HBV, which puts them at risk of HDV infection. Those who are more likely to have HBV and HDV co-infection include indigenous people, people who inject drugs and people with hepatitis C virus or HIV infection.

Natural History

Hepatitis D virus infection presents in two forms: coinfection and superinfection. In coinfection, HDV and hepatitis B virus (HBV) are acquired simultaneously, typically causing acute hepatitis that is often self-limiting and rarely progresses to chronic infection. In superinfection, HDV infects an individual already chronically infected with HBV, and this form more commonly leads to chronic HDV infection, with a higher risk of severe liver disease, including rapid progression to cirrhosis and hepatic decompensation and significantly increases the risk of liver failure and hepatocellular carcinoma.

Clinical Presentation

Simultaneous infection with HBV and HDV can lead to mild-to-severe hepatitis with signs and symptoms of indistinguishable from those of other types of acute viral hepatitis infections. These features typically appear 3– 7 weeks after initial infection and include fever, fatigue, loss of appetite, nausea, vomiting, dark urine, pale-coloured stools, jaundice and even fulminant hepatitis. However, recovery is usually complete, development of fulminant hepatitis is infrequent, and progression to chronic hepatitis D is rare (less than 5% of acute hepatitis).
In a superinfection, HDV can infect a person already chronically infected with HBV. The superinfection of HDV on chronic hepatitis B accelerates progression to a more severe disease in all ages and in 70–90% of persons. HDV superinfection markedly accelerates progression to cirrhosis when compared with HBV mono-infected persons. Patients with HDV induced cirrhosis are at an increased risk of hepatocellular carcinoma; however, the mechanism

in which HDV causes more severe hepatitis and a faster progression of fibrosis than HBV alone remains unclear (WHO 2020 ; https://apps.who.int/iris/handle/10665/333453)

Diagnosis

Testing for HDV is indicated in all patients who are HBsAg-positive, especially those with unexplained liver disease progression, high ALT levels, or poor response to HBV treatment. Diagnosing chronic HDV requires serology to demonstrate exposure (past or current infection) and molecular methods to demonstrate the presence of HDV RNA and active infection. Serological testing for HDV involves detection of anti-HDV antibodies (IgG and/or IgM). A positive anti-HDV result indicates current or past exposure to the virus but does not differentiate between active and resolved infection. Detection of HDV RNA confirms active HDV infection. However, HDV diagnostics are not widely available, especially in low- and middle-income countries, and there is only little standardization for HDV RNA assays, which are essential to detect active, viremic infection and for monitoring response to antiviral therapy.

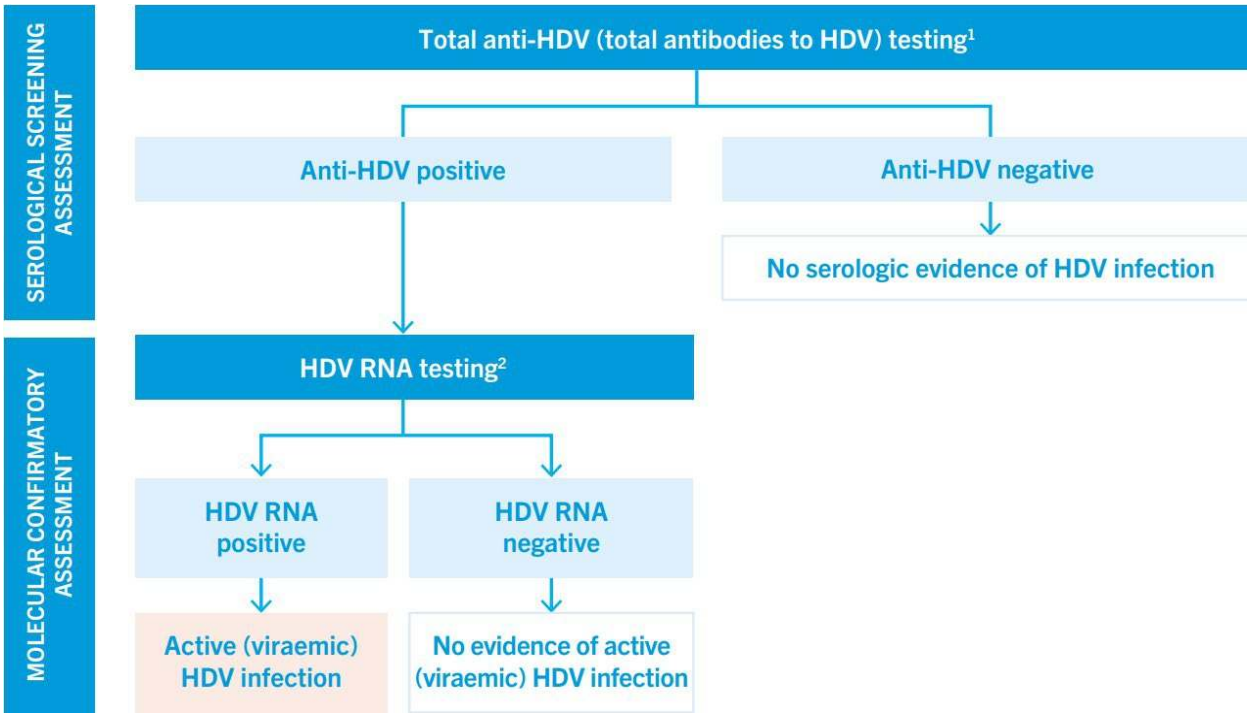


Figure 11: Testing strategy for diagnosing HDV infection among individuals who are HBsAg positive Adapted from WHO 2024 Guidelines

Treatment *(Adapted from WHO Treatment Guidelines)*

Until recently, pegylated interferon α (PEG-IFNα) had been the only treatment option for chronic HDV. However, its use has been limited by poor treatment outcomes, side-effects and contraindications. Only about 20 30% of those treated with PEG-IFNα achieve complete virological response under treatment, and relapse is frequent. The HDV treatment landscape is now rapidly evolving, with some novel agents showing favorable results. In 2023, Bulevirtide, an entry inhibitor that is given once daily through subcutaneous injection, received approval for treatment of chronic HDV by the European Medicines Agency (EMA) among adults with compensated liver disease. Several multi-centre studies continue to evaluate best treatment dosage, treatment duration and possible combination with PEG-IFNα. Nucleoside analogues used for hepatitis B treatment have shown no direct benefit in controlling HDV although they are generally used for managing the chronic HBV infection.

Prevention

Prevention services of hepatitis D should focus on reducing HBV transmission through hepatitis B immunization, including timely birth dose, additional antiviral prophylaxis for eligible pregnant women, blood safety, safe injection practices in health-care settings and harm reduction services with clean needles and syringes. Hepatitis B immunization does not provide protection against HDV for those already infected with HBV.

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