A Clinical Guide to the Treatment of Viral Hepatitis

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Edited by

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PREFACE

Viral hepatitides are global health care concerns. Almost every part of the world is affected by acute and/or chronic hepatitis. While hepatitis A to hepatitis E all cause liver disease, their modes of transmission, severity of the illness, geographical distribution and prevention methods differ. Hepatitis B and C, and to a certain extent hepatitis E, lead to chronic disease in hundreds of millions of people culminating in liver cirrhosis, liver cancer, and other viral hepatitis-related deaths. The World Health Organization (WHO) reports that 354 million people worldwide live with chronic hepatitis B or C, and for the majority, testing and treatment remain beyond reach.

Hepatitis A virus is common in low- and middle-income countries, owing to reduced access to clean and reliable water sources and higher risk of contaminated food. Effective vaccination against hepatitis A and pre- or post-exposure prophylactic measures are also available. Although most HAV infections are mild and patients recover spontaneously, it can rarely cause severe and life threatening liver damage.

Hepatitis B infection, which can cause both acute and chronic liver disease, can be prevented by safe and effective vaccination. Vaccination against hepatitis B also prevents the emergence of hepatitis D, which needs hepatitis B to cause virus-related liver infection. Injectable interferons have been used after the mid-1980s for chronic hepatitis B treatment. The nucleoside/nucleotide analogs that conferred significant effect against human immunodeficiency virus (HIV) infection were noted to have similar efficacy against HBV DNA as well. This resulted in a paradigm shift to oral antiviral therapy in the treatment of chronic hepatitis B. Oral antiviral treatment with its few side-effects and good tolerability has enabled the treatment of many patients who could not be treated by interferons. The use of oral antiviral drugs has also reduced the incidence of liver cancer and improved survival of patients with chronic hepatitis B infection.

Hepatitis C (HCV) can lead to both acute and chronic liver infection. While some patients with acute hepatitis C may recover spontaneously, most patients infected with HCV protract a chronic course. For many years and

decades, untreated chronic HCV carried the risk of developing complications, including cirrhosis or liver cancer. No effective vaccination against HCV is available. However, the invention of hepatitis C drugs is a story of success. Directly acting antiviral drugs (DAA) treat and even cure more than 95% of patients with chronic HCV infection and reduce the risk of cirrhosis and liver cancer. Access to antivirals, on the other hand, is a global problem.

Hepatitis D virus (HDV) affects nearly 5% of people with chronic hepatitis B virus (HBV) infection. HDV and HBV infection occurs in individuals either simultaneously known as co-infection, or HDV infection occurs super-infection, that is in patients previously infected with HBV. The number of patients with HDV is decreasing, most probably due to the increasing availability of HBV vaccination and established treatment programs. However, HDV infection seems to be the most severe form of chronic viral hepatitis causing more rapid progression towards liver cancer and liver-related death.

The WHO estimate that there are 20 million Hepatitis E Virus (HEV) infections worldwide every year leading to an estimated 3.3 million patients being symptomatic due to HEV. The disease is most common in East and South Asia. HEV is transmitted via the fecal-oral route, mainly via contaminated water. Acute HEV infection may be challenging in certain groups and may confer a chronic disease course.

The management of acute and chronic viral hepatitis is essential in modern day clinical medicine. We have asked authors with great experience in the field of viral hepatitis treatment to write the following chapters. Considering recent advances in the area, the authors presented an up-to-date review in the management of viral hepatitis. A summary of clinical pharmacology of the drugs used in the treatment of viral hepatitides has been included. We hope you enjoy the book and find it insightful in providing the best to your patients.

We are grateful to Mr. Ryan Holem for editing the chapters.

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CHAPTER 1

TREATMENT OF ACUTE HEPATITIS A

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Introduction

Hepatotropic viruses are the major etiologies of acute and chronic hepatic diseases all over the world. Hepatitis A virus (HAV) infection represents one of the most common etiologies of acute hepatitis. HAV infection is currently a health care problem especially in low- and middle-income countries with poor sanitary conditions. In 2015, there were 114 million infections (GBD) and WHO estimated that in 2016, 7,134 persons died from hepatitis A (1).

The virus

It is a single-stranded, icosahedral, non-enveloped RNA virus in the family Picornaviridae. It lacks a lipid envelope allowing resistance to bile lysis. The virus can survive on human hands, and also for long periods of time in fresh and saltwater and in soil (2). HAV has one serotype and six genotypes. Genotypes I, II, and III infect humans while genotypes IV, V, and VI are seen in simians (3). Genotypes I, II, and III are divided into subtypes A and B. IA is the etiology most commonly seen in human infections.

Infection occurs mainly through fecal-oral transmission via contaminated water, direct contact (household contacts, daycare centers, residential facilities, etc.), and rarely through sexual contact, IV drug use, and blood transfusions (4,5). There is no evidence of maternal-fetal transmission. It can remain infectious even after being exposed to detergents and acids. However it is inactivated by formalin, chlorine and higher temperatures (>85 °C) (6).

After entering the host through the oropharynx or intestine, it reaches the bloodstream. It has an affinity to hepatocytes and gastrointestinal epithelial cells where it replicates. Virions are released from the hepatocytes into blood and bile. Hepatocyte damage takes place through non-specific natural killer cells and virus-specific CD8+ T lymphocytes. The virus itself does not cause cytotoxicity. Rather, a clinical syndrome of acute hepatitis is associated with a host's immune response.

Epidemiology

HAV infection is seen worldwide and according to the prevalence, global epidemiology can be divided in to 4 primary locations:

High prevalence in sub-Saharan Africa, India, Pakistan, and Afghanistan;

Intermediate prevalence in Middle and South America, Northern Africa, the Middle East, Turkey, Iran, Kazakhstan, and Mongolia;

Low prevalence in Eastern Europe, Russia, China, and Oceania; and

Very low prevalence in Western Europe, Scandinavia, North America, and Australia (6).

The incidence is closely correlated with the socioeconomic status and access to safe food and drinking water. Vaccination of children and individuals at risk has been shown to significantly reduce the hepatitis seroprevalence. In high prevalence countries/regions, typically the infection occurs in early life and people remain asymptomatic or with mild symptoms (7). In low prevalence countries, the virus generally affects individuals later in life and has moderate to severe signs and symptoms as well as higher rates of morbidity and mortality (6).

Clinical Presentation

HAV is a systemic disease with varying signs and symptoms in different age groups. It is mild or even asymptomatic in the childhood period and is a self-limited disease. The patients are infectious 2 weeks before the development of symptoms and remain infectious 1 week after. Patients remain no longer infectious 2 months after symptoms begin. The incubation period is 2 to 8 weeks (4 weeks average), during which time viral excretion is the highest in feces (5, 6).

In children younger than 4 years, jaundice is seen in only 7% and the symptoms are reported in only one third in children younger than 6 years old (8). However these children may shed the virus up to 6 months.

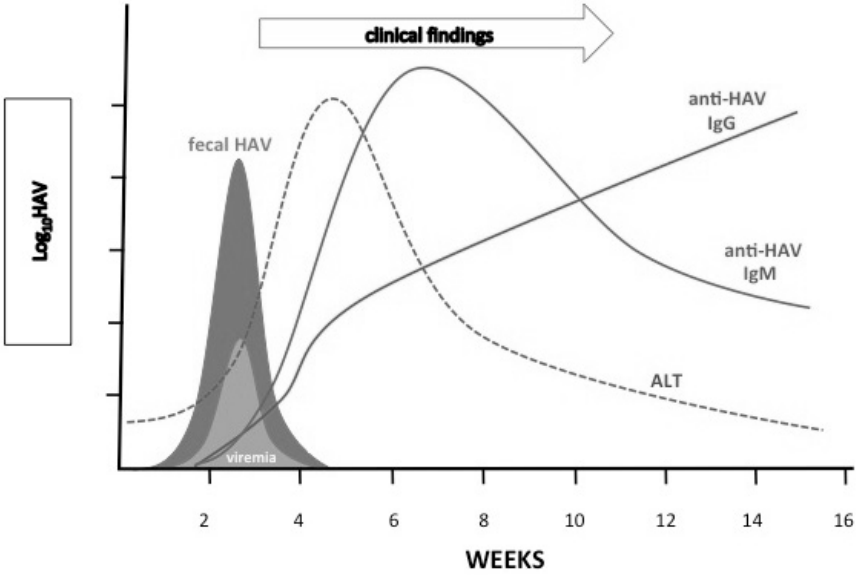
In adults, the majority of patients can present with the following signs and symptoms: nausea, vomiting, anorexia, fever, abdominal pain, jaundice, and pruritus.

Older adults present with gastrointestinal and flu-like prodromal symptoms lasting around 1 week. Then several weeks of jaundice appears (in 70% of adults) followed by a convalescent period lasting for weeks (Figure 1) (9). The clinical illness period lasts up to 8 weeks in the majority of adults. Patients usually complain of fever, anorexia, tiredness, joint pain, headache, nausea, vomiting, pruritus, abdominal pain, dark urine, and pale colored stools. Acute HAV infection during pregnancy may cause preterm labor (6,10,11).

On physical examination, jaundice, abdominal tenderness on palpation, lymphadenopathy (peripheral, and by imaging intraabdominal), bradycardia, hepatomegaly, splenomegaly, and rarely palpable purpura, cardiac rub, and encephalopathy can be noted (12,13).

Laboratory studies show elevations of serum aminotransferases and bilirubin. Clinical and laboratory recovery is seen within 2–3 months in up to 80-85% of patients and within 6 months in almost all patients.

Figure 1. A typical course of acute hepatitis A infection. After an incubation period of 2-4 weeks, clinical findings develop with elevation of ALT. Fecal virus shedding and viremia are present in incubation period. Anti-HAV-IgM appears first in the serum and subsequently anti-HAV-IgG.



Complications

No chronic stage of the disease exists. In addition to signs and symptoms related to liver involvement, there can be extrahepatic manifestations in some patients including arthralgia, glomerulonephritis, leukocytoclastic vasculitis, and others. In 5 to 10 % of patients with acute HAV, cholestatic and relapsing hepatitis can be seen. Rarely, hepatitis A may take a fulminant course or trigger the development of autoimmune hepatitis (14,15). A viral cholecystitis can also be seen during the course (12). Other rare complications include Guillain-Barré syndrome, pure red cell aplasia, autoimmune hemolytic anemia, and acute disseminated encephalomyelitis.

The older the patient at the time of infection, the higher the risk for acute liver failure.

Diagnosis

Acute HAV infection should be considered in patients with sudden onset of prodromal symptoms including nausea, anorexia, fever, fatigue, abdominal pain and jaundice or elevated serum aminotransferase levels. Acute hepatitis A diagnosis is established by the detection of anti-HAV IgM in serum. It is followed by development of anti-HAV IgG. Serum IgM antibodies are detectable at the time of symptom onset, highest during the acute or early convalescent phase of the disease, and remain detectable for three to six months (Figure 1).

Serum IgG antibodies emerge early in the convalescent period of the disease and remain detectable for decades. Development of anti-HAV IgG is associated with recovery and lifelong protective immunity against reinfection (Figure 1). Detection of only anti-HAV IgG in the absence of anti-HAV IgM represents past infection or immunity by vaccination rather than acute infection.

Imaging of the liver is not diagnostic, although it is commonly used to rule out the alternative diagnoses including biliary obstruction. Liver biopsy is generally not indicated in the diagnosis.

Management

Active Immunization

HAV vaccine is mandatory or recommended for many countries except those with high endemicity. The Advisory Committee on Immunization Practices (ACIP) recommends HAV vaccination for all children aged 12–23 months and unvaccinated children and adolescents aged 2–18 years (CDC). It also recommends vaccinating any individual who is at increased risk of infection or at increased risk for severe disease from HAV infection (16,17). (Table 1)

Table 1. Hepatitis A Vaccination Recommendations of The Advisory Committee on Immunization Practices (ACIP). (17).

Children
- All children aged 12–23 months
- Unvaccinated children and adolescents aged 2–18 years

People at increased risk for HAV infection
- International travelers
- Men who have sex with men
- People who use injection or noninjection drugs (all those who use illegal drugs)
- People with occupational risk for exposure
- People who anticipate close personal contact with an international adoptee
- People experiencing homelessness

People at increased risk for severe disease from HAV infection
- People with chronic liver disease
- People with human immunodeficiency virus infection

Other people recommended for vaccination
- Pregnant women at risk for HAV infection or severe outcome from HAV infection
- Any person who requests vaccination

Although no harm has been reported with giving hepatitis A vaccine to infants, the hepatitis A vaccine dose(s) is not recommended to administer prior to 12 months of age due to suboptimal immune response, particularly in infants with passively acquired maternal antibody (18,19). Thus, hepatitis A vaccine dose(s) given at <12 months of age are not considered valid doses. The hepatitis A vaccine series of two doses should be initiated when the child is at least 12 months of age.

Unvaccinated people in an outbreak setting who are at risk for HAV infection or at risk for severe disease from HAV should be vaccinated. Furthermore, people providing services to adults with risk factors for HAV infection should be vaccinated for HAV.

For people who receive blood products for clotting disorders (e.g., hemophilia), hepatitis A vaccination is no longer recommended.

Hepatitis A Vaccine

Two types of HAV vaccines are currently available internationally: Inactive and live-attenuated (Table 2).

Table 2. Hepatitis A virus Vaccines

Vaccine	Age	Antigens	Volume	Route	Schedule
INACTIVATED VACCINES					
Havrix® Adult	>16 yr	1440 ELISA Units HA/20 µg HbsAg	1 ml	IM, into deltoid	0 and 6-12 mo
Havrix® Paediatric	12 mo to 16 yr	720 ELISA Units HA/10µg HBsAg	0.5 ml	IM, >2 yr into deltoid, <2 yr antero-lateral part of the thigh	0 and 6-12 mo
Vaqta® adult	>19 yr	50 U HAV antigen	1 ml	IM, into deltoid	0 and 6-18 mo
Vaqta® pediatric	12 mo to 18 yr	25 U HAV antigen	0.5 ml	IM, >23 mo: into deltoid; <23 mo: antero-lateral part of the thigh	0 and 6-18 mo
Avaxim® adult	>16 yr	160 U HAV antigen	0.5 ml	IM, into deltoid	0 and 6-12 mo
Avaxim® pediatric	12 mo to 15 yr	80 U HAV antigen	0.5 ml	IM, into deltoid	0 and 6-12 mo
LIVE-ATTENUATED VACCINES*					
H2 strain	>1 yr	$10^{6.5}TCID_{50}$ (tissue culture infective dose)	1 ml	Subcutaneous	Single dose
LA-1 strain	>18 mo	$10^{6.5}CCID_{50}$ (cell culture infective dose)	1 ml	Subcutaneous	Single dose

*Live attenuated vaccines are manufactured and used mainly in China and India (BioVac-A) and other countries (MEDVAC-A) including Guatemala, the Philippines, Bangladesh, Nepal, Uzbekistan, and Chile.

Formaldehyde-inactivated hepatitis A vaccines are commonly used in most countries. They are safe and effective. Although a single dose can be effective in healthy individuals, a two-dose schedule is recommended with the second dose being given 6-18 months after the first one. A check for

antibody titer is not recommended. Studies reveal that antibodies after a two-dose series persist for at least 25 years (1).

Combination Vaccines including Hepatitis A Vaccine

HAV vaccines are often combined with HBV or typhoid vaccines (Table 3).

Table 3. Hepatitis A Combination Vaccines

Vaccine	Age	Antigens	Volume	Route	Schedule
Twinrix® Adult	>16 yr	720 ELISA Units HAV/20 µg HBsAg	1 ml	IM, into deltoid	0, 1, and 6 mo or days 0,7,21, and at 12 mo
Twinrix® Paediatric	1 yr to 15 yr	360 ELISA Units HAV/10µg HBsAg	0.5 ml	IM, into deltoid	0, 1, and 6 mo or days 0,7,21, and at 12 mo
Vivaxim®	>16 yr	160 ELISA Units HAV/25 µg *Salmonella typhi* Vi polysaccharide (Ty2 strain)	1 ml	IM, into deltoid	0 and 6-36 mo
Hepatyrix®	>15 years	1440 ELISA Units HAV/25 µg *Salmonella typhi* Vi polysaccharide (Ty2 strain)	1 ml	IM, into deltoid	0 and 6-12 mo

A combination HAV/*Salmonella typhi* Vi polysaccharide (Ty 2 strain) vaccine is effective against HAV and typhoid. A single dose does not provide long-term protection against HAV infection. A booster dose after 6 to 36 months is required for long-term protection. This two-dose schedule provides a protection against HAV for at least 10 years. For typhoid fever,

revaccination (with purified Vi polysaccharide typhoid) should be done every 3 years if the individual is at the risk.

HAV/HBV combination vaccines provide protection against both viruses. If the individual is at risk of both infections and not immunized/exposed to, a combination vaccine can be considered. Instead of two-dose schedule in HAV vaccine, HAV/HBV vaccines need three (0, 1, and 6 month) or four-dose (days 0,7,21, and at 12 month) schedules to provide effective protection against both viruses.

Live attenuated hepatitis A vaccines use cell or tissue cultures of LA-1 or H2 stains. These vaccines are manufactured in China and available in China, India (BioVac-A), and other countries (MEDVAC-A) including Guatemala, the Philippines, Bangladesh, Nepal, Uzbekistan, and Chile. These vaccines have been shown to be safe and highly protective (95%) against HAV infection for > 3 years.

Adverse reactions in both inactivated vaccine and live vaccines are typically either mild systemic reactions or short-lasting local reactions.

For travelers: HAV vaccines should be given for individuals aged ≥1 year traveling to countries or areas with moderate to high risk of HAV infection Since protection is provided 2–4 weeks after first dose by inactivated and live vaccines, travelers should be vaccinated ideally >4 weeks before departure. If this is not possible, considering the long incubation period of hepatitis A (approximately 2–4 weeks), the vaccine should be administered up to the day of departure.

Pre-exposure Prophylaxis (PrEP)

Immune globulin (IG) and/or HAV vaccine can be used for pre-exposure prophylaxis (Table 4). Recently, the prescribing information for immune globulin was updated. Changes include instructions for hepatitis A pre- and postexposure prophylaxis indications. These changes were made due to decreased HAV immunoglobulin G antibody potency, most probably resulting from decreasing prevalence of previous HAV infection among plasma donors, thus declining anti-HAV antibody levels in donor plasma (20).

IG or vaccination (Table 4) should be given to persons traveling to regions that carry high risk for HAV. Vaccination is usually sufficient for those aged 6 months to 40 years. In immunocompromised persons, in those with

chronic liver disease, and in those older than 40 years, immunoglobulin should be co-administered with vaccine. Immune globulin dose is adjusted to the length of stay: 0.1 mL/kg for travel up to 1 month; 0.2 mL/kg for travel up to 2 months, 0.2 mL/kg every 2 months for travel of ≥2 months' duration.

Table 4. Recommendation Before Hepatitis A Exposure

Group	Pre-exposure Prophylaxis	
	Vaccine	Immune globulin *
<6 mo	No	Yes, 0.1-0.2 mL/kg**
6 mo to 40 years	Yes, 1 dose***	No
>40 yr	Yes, 1 dose	Yes, 0.1-0.2 mL/kg
>6 mo, Immunocompromised persons or those with chronic liver disease	Yes, 1 dose	Yes, 0.1-0.2 mL/kg
>6 mo, persons who elect not to receive vaccine or for whom vaccine is contraindicated	No	Yes, 0.1-0.2 mL/kg

* Measles, mumps, and rubella vaccine should not be administered for at least 2 weeks before and 6 mo after administration of immune globulin
** 0.1 mL/kg for travel up to 1 mo; 0.2 mL/kg for travel up to 2 mo, 0.2 mL/kg every 2 mo for travel of ≥2 mo' duration.
***For children aged between 6 mo to 11 mo, this dose should not be counted toward the routine 2-dose series, it should be initiated at age 12 months.

Infants aged <6 months and travelers for whom vaccine is contraindicated or who elect not to receive vaccine should receive immune globulin before travel.

Hepatitis A vaccine should be administered to infants aged 6–11 months traveling to regions where protection against hepatitis A is recommended. This vaccine dose does not count towards the 2-dose series, and the 2-dose hepatitis A vaccine series should then be initiated at age 12 months according to the routine, age-appropriate vaccine schedule (16,17).

Postexposure Prophylaxis for Hepatitis A

Postexposure prophylaxis should be given immediately after the exposure. Hepatitis A vaccine should be administered as soon as possible, within 2

weeks of exposure, to all unvaccinated people aged ≥12 months (Table 5). The efficacy of vaccination or giving prophylaxis later than 2 weeks after exposure is not established.

The vaccine should contain 1440 ELISA units. The combination HepA and HepB vaccine, Twinrix, containing 720 ELISA units of hepatitis A antigen, is not recommended for use as PEP because no data is available for use of Twinrix for PEP.

Infants younger than 12 months should receive IG (at a dose of 0.1 mL/kg) instead of hepatitis A vaccine as soon as possible within 2 weeks of exposure. MMR vaccine should not be administered <6 months after IG administration.

Persons aged ≥12 months who have been exposed to HAV within the past 2 weeks with no previous vaccine series should receive 1 dose of hepatitis A vaccine (Table 5). IG is not needed for those aged 12 months to 40 years in addition to hepatitis A vaccine. Hepatitis A vaccine in combined with IG (0.1 mL/kg) may be administered to persons aged >40 years. If the dose of hepatitis vaccine administered for PEP is the first dose of the person, a second dose should be administered 6 months after the first for long-term immunity; although the second dose is not necessary for PEP.

Table 5. Recommendation after Hepatitis A Exposure

Group	Postexposure Prophylaxis	
	Vaccination	Immune globulin*
<12 mo	No	Yes, 0.1 mL/kg
12 mo-40 yr	Yes, 1 dose	No
>40 yr	Yes, 1 dose	Yes, 0.1 mL/kg**
≥12 mo, immunocompromised persons or those with chronic liver disease	Yes, 1 dose	Yes, 0.1 mL/kg**
≥12 mo, vaccine is contraindicated	No	Yes, 0.1 mL/kg**

* Measles, mumps, and rubella vaccine should not be administered for at least 2 weeks before and 6 mo after administration of immune globulin
**Vaccine and immune globulin should be administered in a different anatomic site

Persons who are immunocompromised or have chronic liver disease and who have been exposed to HAV within the past 2 weeks and did not have a completed hepatitis A vaccination series should receive IG (0.1 mL/kg)

combined with hepatitis A vaccine simultaneously in a different anatomic site after exposure (Table 5). If the dose of the vaccine administered for PEP is the first dose of the person, a second dose should be administered 6 months after the first for long-term immunity, although the second dose is not necessary for PEP.

Persons for whom vaccine is contraindicated, IG is administered in a dose of 0.1 mL/kg, instead of the vaccine as soon as possible within 2 weeks of exposure.

MMR and varicella vaccines should not be administered for 6 months following IG administration.

Specific Treatment

Hepatitis A infection is a self-limited disease. No specific antiviral therapy is available and the therapy includes supportive care. Hydration, antipyretics and antiemetics are provided for symptomatic cases. Drugs that are potentially hepatotoxic should be avoided and those metabolized by the liver should be used with caution.

Extrahepatic manifestations should be screened. Hemodialysis may be needed for the patients with renal disfunction.

Pruritus may be a disturbing symptom especially during the prolonged cholestasis and use of ursodeoxycholic acid or cholestyramine may be considered (21).

In prolonged cholestasis of acute HAV infection, corticosteroid use has been reported in a few studies (22,23). However use of corticosteroid may prolong the existence of HAV RNA in the liver up to 12 months and delay the natural immune control of the virus (24).

For hepatitis A-associated acute liver failure, intensive, multidisciplinary care and approach and recognition of poor prognostic factors are needed. These patients require aggressive supportive therapy and should be transferred to a center capable of performing liver transplantation.

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CHAPTER 2

TREATMENT OF HEPATITIS B INFECTIONS

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1. Introduction

Chronic hepatitis B virus (HBV) infection is a significant public health concern. The World Health Organisation (WHO) estimates that in 2015, 257 million people were living with chronic HBV infection which is defined as hepatitis B surface antigen positivity for more than 6 months. Hepatitis B prevalence is highest in the Western Pacific and African regions where approximately 6% of the adult population is infected. The overall prevalence is 3.5%. In 2016, of the more than 250 million people living with HBV infection, 27 million (10.5%) were aware of their infection and 4.5 million (16.7% of those diagnosed) were under antiviral treatment (1).

The course of the disease and rate of complications depend on the host, the viral kinetics, and environmental factors. The natural course of chronic HBV infection consists of four characteristic phases: HBeAg positive chronic infection (formerly known as immune tolerant), HBeAg positive chronic hepatitis, HBeAg negative chronic infection (formerly known as inactive carrier), and HBeAg negative chronic hepatitis. There is also a fifth phase with negative HBsAg which is called occult chronic hepatitis B (CHB). The natural course of CHB is a dynamic process in which the duration of phases is variable and not all patients go through all phases (2).

Chronic hepatitis B (CHB) is one of the main causes of cirrhosis and hepatocellular carcinoma (HCC). In 2015 alone, an estimated 887,000 CHB-related deaths occurred, revealing the disease burden caused by

CHB. Increasing public awareness, preventing transmission, and scaling up screening, care and treatment are the main strategies to control the disease burden (1).

2. Goals of Treatment

The primary goal of CHB treatment is to prevent cirrhosis and HCC through suppression of HBV DNA to undetectable levels. Treatment is also important for preventing transmission and reversing fibrosis by supression of viral replication. Prevention of recurrent or new HCC in patients even after they have developed HCC might be another goal. Additional goals are treatment of extrahepatic manifestations, preventing mother to infant transmission (MTIT), and acute exacerbations (2,3).

The primary endpoints of treatment are: suppression of HBV DNA defined as virological response, loss of HBeAg defined as serological response, and ALT normalisation defined as biochemical response. The definition of virological response differs according to whether interferon or nucleoside analogues are given. For interferon treatment, response is defined as HBV DNA level <2000 IU/ml at 6 months, at end of treatment and 6 and 12 months after the completion of therapy; while for nucleoside analogues, undetectable HBV DNA levels are accepted as response. Reversal of fibrosis and even cirrhosis is another goal with long-term treatment. Histological response is defined as a decrease in necrosis and inflammation score by ≥2 points with no worsening of fibrosis (4).

With novel treatment options, new endpoints for CHB treatment are introduced. Complete cure is eradication of HBV DNA including intrahepatic cccDNA and integrated HBV DNA. Functional cure is undetectable HBsAg and HBV DNA in serum with or without seroconversion to hepatitis B surface antibody, resolution of residual liver injury, and a decrease in risk of HCC. Partial cure is detectable HBsAg but persistently undetectable HBV DNA in serum after completion of finite course of treatment. With these improvements, functional cure might be the optimal endpoint in CHB treatment (5).

3. Treatment Indications

The indications for CHB treatment are mainly based on serum HBV DNA levels, serum ALT levels, and severity of liver disease. Patient's age, risk of transmission, family history of cirrhosis and HCC, extrahepatic manifestations,

HCV/HDV/HIV co-infections, pregnancy, and immunosuppressive treatment are other factors that should be taken into account while making treatment decisions (2,6,7).

The ALT upper limits of normal (ULN) are 35 U/L for men and 25 U/L for women according to 2018 AASLD guidelines. EASL, APASL and WHO guidelines consider 40 U/L as ULN of ALT for both genders. The EASL guidelines use HBV DNA cut-off of 2,000 IU/mL regardless of HBeAg status while the AASLD and APASL guidelines suggest cut-off of 20,000 IU/mL for HBeAg-positive and 2,000 IU/mL for HBeAg-negative patients (8).

An abdominal ultrasound is recommended for all patients. A liver biopsy or a non-invasive test should be performed to determine severity of liver disease in cases where biochemical markers are inconclusive. The results of transient elastography may be confounded by severe inflammation associated with high ALT levels. Patients with chronic HBV infection can be considered to have severe fibrosis if either with normal ALT and liver stiffness >9 kPa, or with elevated ALT but below 5x ULN and liver stiffness >12 kPa (9,10).

Antiviral treatment indications according to EASL 2017 guidelines are as follows (2):

- HBV DNA> 2000 IU/ml and ALT> ULN and/or at least moderate liver necroinflammation or fibrosis regardless of HBeAg status.
- Compensated or decompensated cirrhosis regardless of HBV DNA and ALT levels.
- HBV DNA> 20,000 IU/ml and ALT> 2x ULN regardless of the degree of fibrosis

EASL recommends treatment to patients with family members diagnosed with cirrhosis or HCC even if they do not fullfill the above criteria.

AASLD recommends treatment to patients with immune active disease which is defined as elevated ALT >2xULN or evidence of significant histologic disease with elevated HBV DNA above 2,000 IU/mL in HBeAg negative or above 20,000 IU/mL HBeAg positive patients. Additionally, treatment is recommended in those who do not meet this criteria but are: older than >40 years which is associated with significant histological disease, have family history of cirrhosis or HCC, previous treatment

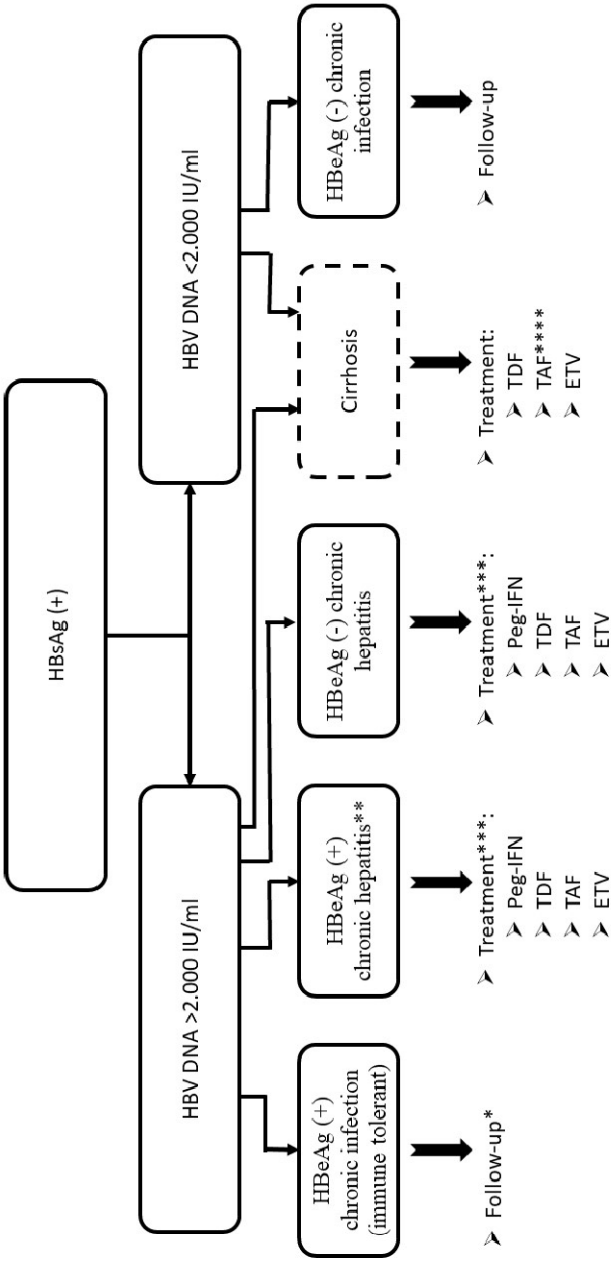
history, presence of extrahepatic manifestations or presence of cirrhosis (11).

Recent studies suggest that quantitative HBsAg might be used for disease staging and in the decision to treat in CHB (12). One study suggests that antiviral treatment can be given to patients with quantitative HBsAg > 20,000 IU/ml and HBV DNA levels between 2,000 and 20,000 IU/ml without further evaluation with liver biopsy (13).

While the HBeAg-positive patients with chronic infection (immunotolerant phase) are not routinely given treatment, EASL guidelines recommend consideration of treatment in those >30 years of age while the AASLD guidelines recommend treatment in those >40 years if there is histological evidence of significant liver disease and APASL guidelines suggest histological evaluation in those >35 years of age (2,6,7,11). Immunotolerant patients who are pregnant or immunosuppressed can be treated with antivirals even if above criteria is not fullfilled as details are given in respective parts below.

Healthcare workers (HCWs) with CHB performing exposure-prone procedures should be regularly tested for HBV DNA levels every 6 months (8,14). Those HCWs with high serum HBV DNA should be treated with nucleos(t)ide analogues (NA) to reduce transmission risk. The HBV DNA cut-off to treat in HCWs is >200 IU/ml according to EASL and >1000 IU/ml according to CDC and APASL.

Figure-1 (next page): Treatment indications for CHB (*treatment might be considered in advanced age, pregnancy, immunosuppression, or in health care workers, **certain guidelines suggest treatment if HBV DNA >20.000 IU/ml, ***treat in patients with high ALT and/or fibrosis, ****TAF is not recommended in advanced cirrhosis), Peg-IFN: pegylated interferon, TDF: tenofovir disoproxil fumarate, TAF: tenofovir alafenamide, ETV: entecavir.


HBsAg (+)
HBV DNA >2.000 IU/ml
HBV DNA <2.000 IU/ml
HBeAg (+) chronic infection (immune tolerant)
HBeAg (+) chronic hepatitis**
HBeAg (-) chronic hepatitis
Cirrhosis
HBeAg (-) chronic infection
Follow-up*
Treatment***:
Peg-IFN
TDF
TAF
ETV
Treatment***:
Peg-IFN
TDF
TAF
ETV
Treatment:
TDF
TAF****
ETV
Follow-up

4. Monitoring the patients during treatment

All patients receiving IFN or NA should be monitored regularly for the safety and efficacy of treatment. Baseline values of renal and liver function tests, complete blood count, and HBV DNA level should be obtained.

During NA therapy, liver function tests should be performed every 3–4 months during the first year and every six months thereafter (2). Serum ALT elevations can occur during the natural course of the infection. Self-limiting ALT flares are usually associated with a reduction in HBV DNA level, HBeAg loss, and rarely HBsAg loss. On the other hand, ALT flares can be associated with progressive liver injury (15).

HBeAg and anti-HBe in HBeAg-positive patients monitored every 3 months (6). HBsAg should be tested at 12-month intervals in patients with HBeAg seroconversion. Serum HBV DNA should be determined every 3–4 months during the first year and every 6–12 months thereafter (2). APASL recommends follow-up of HBV DNA every 3-6 months if a drug with low genetic barrier (lamivudine, adefovir, telbivudine) is used.

Renal function and bone profile should be monitored at least every 3 months if TDF or ADV is used. In patients at risk of renal failure; creatinin clearence, serum phosphate, urine glucose, and protein should be tested (6).

For patients under interferon treatment, complete blood count and serum ALT levels should be assessed every month and thyroid function tests every 3 months. Serum HBV DNA and HBsAg levels in all CHB patients and HBeAg and anti-HBe in HBeAg-positive CHB patients should be checked at 3, 6, and 12 months of pegylated interferon alpha (PegIFNa) treatment and at 6 and 12 months posttreatment (2).

5. Treatment options

Current treatment options for CHB can be categorized into two groups: NA and interferon (IFN). EASL recommends long-term administration of a potent NA with high genetic barrier to resistance. Entecavir and tenofovir are the preferred agents. Lamivudine, adefovir and telbivudine are no longer recommended as first line regimens due to low genetic barrier and/or adverse effect profiles.

Combination therapy either with IFN and NA or two NAs is not recommended in treatment naïve patients, either HBeAg negative or positive. It can be considered in special populations on an individual-based approach (2,11,16,17).

A. Tenofovir disoproxil fumarate (TDF)

Tenofovir disoproxil fumarate is a nucleotide analogue and a potent inhibitor of both HBV polymerase and HIV reverse transcriptase. TDF is approved by FDA for HBV treatment in 2008. TDF is found to have superior antiviral efficacy and a similar safety profile compared to adefovir in both HBeAg positive and negative patients (18). After 1-year of treatment with TDF, viral suppression occurred in 93% in HBeAg - negative and 76% of HBeAg - positive subjects (18). Long-term use of TDF results in histological improvement and even regression of cirrhosis. In one study, 87% of subjects showed histological improvement at 240 weeks of TDF treatment, while 51% showed regression of fibrosis. Of the 96 (28%) patients with cirrhosis (which is defined as an Ishak score of 5 or 6 at baseline), 74% showed ≥1 unit decrease in the score (19).

In another study which followed patients for up to 7 years, 99.3% achieved viral suppression defined as HBV DNA <69 IU/ml. Of HBeAg - positive patients, 54.5% achieved HBeAg loss and 11.8% achieved HBsAg loss. Only one of 375 HBeAg - negative patients achieved HBsAg loss. 1.7% of subjects had elevation of serum creatinine more than 0.5 mg/dL above baseline. No significant change in bone mineral density was observed. No resistance to TDF was detected throughout 7 years (20). Another study showed that at 10th year, 100% of HBeAg - negative and 98% of HBeAg - positive subjects had undetectable HBV DNA levels. Of HBeAg - positive patients, while 52% achieved HBeAg loss, 27% achieved anti-HBe seroconversion (21).

TDF is converted in the gut to tenofovir (TFV) and enters the bloodstream. TFV is removed from the bloodstream by glomerular filtration and active tubular secretion (22). The major potential toxicity of TDF is tubular dysfunction, ranging from low level proteinuria to Fanconi's syndrome. Small, non-progressive increases in serum creatinine with a progressive sustained slow decline in renal function are observed with TDF (23). Hypophosphatemia, decreased bone mineral density, serum transaminase elevations, and dyspeptic symptoms are the other side effects seen with TDF.

B. Tenofovir alafenamide (TAF)

Tenofovir alafenamide is a novel prodrug of tenofovir. TAF is hydrolyzed to tenofovir and then phosphorylated to tenofovir diphosphate, which is the active metabolite. TAF is more stable in plasma and can achieve higher intracellular levels with lower levels of circulating TFV compared to TDF. This results in fewer renal and bone safety concerns (23,24). In both HBeAg-positive and -negative patients with CHB, TAF is non-inferior to TDF. Of 285 HBeAg - negative subjects, 94% had HBV DNA levels <29 IU/ml and of 581 HBeAg - positive subjects, 64% had HBV DNA levels <29 IU/ml at week 48. A higher proportion of ALT normalisation is seen in subjects receiving TAF compared to TDF (25,26).

C. Entecavir (ETV)

Entecavir is a deoxyguanin nucleoside analogue and was approved for CHB treatment in 2005. ETV is a first-line agent used in CHB due to its high genetic barrier, favorable safety profile, and rapid suppression effect of viral load (27).

A randomized controlled trial performed in HBeAg - positive CHB patients showed that ETV treatment at year 5 resulted in normal ALT in 80% of subjects and HBV DNA levels <300 copies/ml in 94%. 23% of subjects achieved HBeAg seroconversion while 1.4% had HBsAg loss (28). In a study comparing the efficacy of TDF and ETV, entecavir normalized the ALT levels earlier, but there was no difference at 144 weeks (29). Another study showed comparable rates of HBeAg loss, ALT normalization, and viral suppression (30).

NA-naïve CHB patients treated with ETV show substantial histological improvement and regression of fibrosis and cirrhosis. In another study, after 3-7 years of follow-up, 88% of patients had ≥1 point improvement in the Ishak fibrosis score (31).

D. Lamivudine (LAM)

Lamivudine is a nucleoside analogue and the first NA approved for CHB treatment in 1998. After one year of lamivudine treatment, patients show favorable histological, biochemical, and virological outcomes (32,33). Among HBeAg - positive subjects, 32% achieved HBeAg loss (32). However, the longer the duration of treatment, the higher the rates of lamivudine resistance. In one study, the proportion of patients with LAM-