Foreword

Acute and chronic viral hepatitis make a substantial contribution to the burden of chronic diseases and the premature mortality they cause. Infections with hepatitis B and C viruses cause liver cirrhosis and primary liver cancer. Ethiopia is one of the sub-Saharan African countries where viral hepatitis is endemic. The availability of a vaccine that offers lifelong protection against infection with the hepatitis B virus gives public health an opportunity to prevent a leading cause of cancer and chronic liver disease.

The significance of the challenges and opportunities related to viral hepatitis were formally acknowledged in 2010, when the World Health Assembly adopted its first resolution on a comprehensive approach to the prevention and control of viral hepatitis. The Federal Ministry of Health (FMOH) considers viral hepatitis Prevention and Control measures in line with the current drive to strengthen health systems which includes reaching every child with immunization programs that include hepatitis B vaccine, protecting against mother-to-child transmission of viruses, ensuring the safety of blood, transfusion services and injection practices.

The FMOH recognizes the urgency to generate a comprehensive strategic document as a foundation for building prevention and control measures that match the local epidemiological profile and health system capacities. These Guidelines are developed as part of the national effort in the prevention and Control of Viral Hepatitis in general and Hepatitis B and Hepatitis C virus infections, in particular.

Hence, these guidelines are intended to scale-up viral hepatitis preventive measures, and standardize screening, diagnosis, treatment and care of patients with viral hepatitis to improve outcomes through reducing morbidity and mortality associated with the disease. The guidelines will serve as a framework and a quick reference in line with current scientific evidence and recommendations considering patient factors and local resource settings.

The FMOH urges all care providers and implementing partners to strictly use these guidelines as a reference in the program implementation of Viral Hepatitis Prevention and Control Programs in the country.

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Contents

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Glossary

ALP	Alkaline Phosphatase
ALT	Alanine Amino transaminase
APRI	Aminotransferase/Platelet Ratio Index
ART	Antiretroviral Therapy
AST	Aspartate amino transaminase
BCC	Behaviour Change Communication
BMI	Body Mass Index
CBC	Complete Blood Count
CCC DNA	Covalently Closed Circular DNA
CHB	Chronic Hepatitis B
CLD	Chronic Liver Disease
CMV	Cytomegalo virus
EBV	Epstein Barr virus
IEC	Information Education Communication
EPHI	Ethiopian Public Health Institute
EOT	End of Treatment Response
EVR	Early Virologic Response
FMHACA	Food, Medicine and Health Care Administration and Control Authority
FMOH	Federal Ministry of Health
GO	Government
HAV	Hepatitis A virus
HBIG	Hepatitis B Immunoglobulin
HBV	Hepatitis B Virus
HBcAb	Hepatitis B core Antibody
HBsAB	Hepatitis B surface Antibody
HBeAG	Hepatitis B e Antigen
HBsAG	Hepatitis B surface Antigen
HCC	Hepatocellular Carcinoma

HCV	Hepatitis B Virus
HCW	Health Care Worker
HAD	Health Development Army
HDV	Hepatitis D Virus
HEV	Hepatitis E Virus
HEW	Health Extension Worker
HGV	Hepatitis G Virus
HIV	Human Immunodeficiency Virus
HMIS	Health Management Information System
HSV	Herpes simplex virus
IFN	Interferon
INR	International normalized ratio
LFT	Liver Function Test
MSM	Men who have Sex with Men
NGO	Non-Governmental Organization
NTWG	National Technical Working Group
NUKes	Nucleoside analogues
PEG-INF	Pegylated Interferon
PEP	Post Exposure Prophylaxis
PFSA	Pharmaceuticals Fund and Supplies Agency
PI	Protease Inhibitor
RBV	Ribavirin
RFT	Renal Function Test
RHB	Regional Health Bureau
RVR	Rapid Virologic Response
SC	Sub-cutaneous
SVR	Sustained Virologic Response
TB	Tuberculosis
TTV	Transfusion Transmitted Virus
VCT	Voluntary Counseling and Testing
WHO	World Health Organization

Chapter One: Background and Epidemiology of Viral Hepatitis

Introduction

Hepatitis is a term which refers to the inflammation of the liver. It occurs as a result of infection with various pathogens, exposure to alcohol, medications, chemicals, poisons, as well as immune disorders. Hepatitis viruses are a diverse group of medically important viruses which affect millions globally. To date the following hepatitis viruses are known: hepatitis A, B, C, D, E, F and G. The alphabetical naming of these viruses indicates the order in which they were discovered. In the 1960s only two types were known (A and B), but by the late 1970s and beyond, new varieties were discovered. Hepatitis viruses are either RNA viruses (hepatitis A, C, D, E and G), or DNA viruses (hepatitis B and hepatitis F). They are similar in the symptoms they cause, but have markedly different epidemiologies. Infection with hepatitis viruses can be a self-limiting type, or it could lead to chronic infection (lasting for six months or more).

Hepatitis viruses are broadly classified into two groups: enteric and parenteral. Enteric hepatitis viruses consist of hepatitis A, E and F. They are transmitted primarily by the fecal-oral route and are usually associated with outbreaks of acute illness which may be mild to severe. This usually occurs after ingestion of contaminated food and/or water. Infection with these viruses usually results in acute infection without further sequelae. The notable exception is the unusually high mortality caused by hepatitis E virus (HEV) in pregnant women, in which there is up to 25% mortality associated with this virus. Measures to improve personal and environmental hygiene are adequate to prevent the spread of these enteric hepatitis viruses. Viruses of the second group are parenterally transmitted or blood borne hepatitis viruses consisting of hepatitis B, C, D and G. The parenterally transmitted viruses are transmitted primarily by contaminated blood and blood products (blood transfusion), as well as by sexual contact, and use of contaminated medical instruments such as syringes and needles. In contrast to enteric hepatitis viruses which cause acute illness, parenterally transmitted hepatitis viruses, mainly HCV and HBV, cause more insidious disease. They are associated with the development of chronic liver disease which progresses to hepatocellular carcinoma (HCC) in a significant number of cases. From this perspective, HBV and HCV have significant public health significance. Furthermore, the earlier the age that these viruses are acquired the higher the risk progressing to chronicity. Blood banks in many countries routinely screen the blood supply for these two viruses, in addition to HIV.

Someof the hepatitis viruses are not vaccine preventable, as they do not easily grow in cell cultures. Currently effective and licensed vaccines are available for HAV, HEV and HBV.HDV can also be prevented, as HBV immunization is protective for HDV.

Epidemiology of Enteric Hepatitis Viruses

- ***Hepatitis A virus (HAV)***

HAV mainly occurs in the form of outbreaks/epidemics, and is one of the most frequent causes of food-borne infection. Globally it affects around 1.4 million people annually. High infection rates are found in developing countries having very poor environmental sanitation. As such, in developing countries, the commonest cause of viral hepatitis in children is HAV in as high as 80-90%. In such places 90% of children become infected with HAV before the age of 10 years. In children the infection is asymptomatic. Epidemics due to HAV are rare in such communities since most people are already immune. In situations of improved economic and sanitary conditions, there is an intermediate level of infection. Older people may be more susceptible, and such areas may experience large outbreaks. Areas of low infection are found in developed countries where hygienic conditions prevail. However in such circumstances HAV may continue to circulate in certain high risk groups (IV drug users, MSM, and travelers to areas of high endemicity). HAV transmission is principally fecal-oral (person-to-person contact, or through consumption of contaminated food and water).

- ***Hepatitis E Virus (HEV)***

Global infections of HEV are estimated to reach around 20 million cases annually. HEV predominantly affects young adults (15-40 years). Infection with HEV may cause fulminant hepatitis in up to 25% of pregnant women, and can lead to the death of both mother and baby. Transmission is fecal-oral. In endemic areas HEV is transmitted through ingestion of contaminated water from sewage, including from animal wastes. In Europe HEV may be zoonotic, as the virus is found in pigs, wild boar, deer, rabbits and rats. The animals are transmitters without getting sick themselves. Persons may acquire HEV from infected animals, through consumption of raw or uncooked meat.

Epidemiology of Parenteral Hepatitis Viruses

- ***Hepatitis B Virus (HBV)***

HBV causes both acute and chronic hepatitis. The global burden of HBV is significant. It is estimated that one third of the world's population (about 2 billion people) have been infected with Hepatitis B at some point in their lives and of these 350 – 400 million people are chronically infected. Some 780,000 people die annually due to consequences of hepatitis B virus infection. The prevalence of HBV is highest in sub-Saharan Africa and East Asia. Most people living in these regions become infected during childhood, and up to 5-10% of the adult population is chronically infected. HBV accounts for over 80% of the adult patients with sporadic hepatitis in sub Saharan Africa. HBV is transmitted by blood and/or body fluids from infected individuals, and use of contaminated traditional and medical equipment. In highly endemic areas it may also be transmitted vertically (from mother to child). HBV is extremely infectious (about 100 times as infectious as HIV), and is an important occupational hazard for health workers. The vast majority of healthy adults infected with HBV will completely clear the infection within 6 months. However infants and children are more likely to develop chronic infection; 80-90% of infants infected during the first year of life develop chronic HBV infection and 30-50% of children infected before the age of 6 years similarly develop chronic HBV infection. Furthermore, 15-25% of adults who become chronically infected during childhood go on to develop hepatitis B related liver cancer or cirrhosis.

- ***Hepatitis C Virus (HCV)***

The global burden of HCV infection is huge. An estimated 115 million people are antibody positive and an estimated 80 million have chronic infection. Most HCV infections are in North Africa and East and Central Asia. Each year, approximately 700,000 people die from hepatitis C-related liver diseases. HCV is a blood borne infection that is most commonly transmitted through use of unscreened blood supplies, unsafe injections and inadequately sterilized medical equipment. Less commonly HCV transmission may also be through sexual contact, or from infected mother to her baby. Certain population groups have an increased risk of acquiring HCV infection (those who inject drugs, those receiving unsafe blood transfusions, children born to HCV infected mothers, sexual partners of HCV or HIV-infected individuals, persons using intranasal drugs and those people who have had tattoos or body piercings). HIV and HCV have common routes of transmission, and it is estimated that, globally, 4 – 5 million persons are co-infected with these two viruses. In addition, up to 25% of HCV- infected persons may be co-infected with HBV in some areas.

The studies that are done thus far in Ethiopia are hospital based. Therefore, generalization of the outcomes of these studies to the general population will not be possible. .

- ***Hepatitis D Virus (HDV)***

Hepatitis D virus (HDV) causes a serious liver disease known as type D hepatitis (or delta hepatitis). HDV has the unusual property of being a defective or incomplete virus, which requires the presence of HBV in order to replicate. For this reason, it only occurs in persons who are infected with HBV. Therefore its pattern of distribution follows that of HBV infection.

Epidemiology of viral hepatitis in Ethiopia

Since the 1980s, over 30studies have been conducted in Ethiopia by different groups of investigators to determine the seroprevalence of various hepatitis viruses in the country. The aim here is not to try and present an exhaustive summary of the entire medical literature but rather to highlight significant trends and observations over time. The bulk of the studies have focused on hepatitis B and hepatitis C virus infections, mainly due to the involvement of these 2 viruses in causing chronic liver disease, which is a significant public health problem nationally. It was reported that 12% of the hospital admissions and 31% of the mortality in medical wards in Ethiopian hospitals were due to chronic liver disease (CLD) .

Seroprevalence estimates for HBV and HCV infections have been generated in different studies, with varying sample size. A nationwide national hepatitis B study conducted in the 1980s, and involving more than 5,000 young males, reported finding 10.8% prevalence of HBsAg %. Out of the group, 7.3% exhibited positivity for at least 1 HBV marker. Another large sample size community-based study involving both genders and conducted a decade later in Addis Ababa, revealed an HBsAg prevalence of 7% . However in the study less than 1% of women of child bearing age were HBeAg positive, indicating that vertical transmission of HBV was not significant in this community, confirming earlier findings by other investigators. The same community-based study in Addis Ababa also reported an overall HCV prevalence of 0.9%, with a markedly higher prevalence of HCV in HIV-coinfected individuals.

Studies conducted in blood donors across the country have shown varying seroprevalence estimates for HBsAg, which was as high as 14.4% in the mid-1990s but declining thereafter. In a study from Gondar conducted in 2004, HBsAg prevalence was 8.2% among blood donors, whilst another study from Jimma involving over 6,000 adult blood donors, showed a prevalence of 2.1% and 0.2% for HBsAg and HCV respectively.

Several of the studies have focused on pregnant women, or women who just delivered, with or without HIV infection. Recent studies conducted in Dessie (2014), Bahir Dar (2013) and Addis Ababa (2012) found an HBsAg prevalence of 4.9%, 3.8% and 3% respectively. The study from Dessie also determined seroprevalence for HCV, which was found to be low (0.8%). All HCV positives were among the HIV-infected group. Other studies were carried out previously in Shashemene (2008), Gondar (2006) and Jimma (2002/2003) which reported HBsAg prevalence rates of 6.1%, 7.3%, and 3.7% respectively (11,12,13). Several of these studies also determined HBV/HIV co-infection rates, with the Bahir Dar study reporting 19% HBV/HIV co-infection (9), in contrast to just 0.6% from Shashemene.

At least 2 recent studies have investigated HBsAg prevalence among healthcare workers . In Gondar, medical waste handlers working at health institutions had a significantly higher HBsAg prevalence compared to non-clinical waste handlers employed in the same place, 6% and 1% respectively. Similarly HCV prevalence amongst medical waste handlers was higher (1%), compared to 0% amongst the non-clinical waste handlers (14).Another study from Oromia likewise compared an equal number of healthcare workers and non-HCWs working at government health institutions. Prevalence of HBsAg in HCW was 7.3%, significantly higher than the 0.9% observed in non-HCW. The study further noted that 22.7% of HCWs had been exposed to needle-stick injuries while few if any, had received HBV vaccine.

The highest prevalence rates of HBsAg have been reported in patient populations presenting with chronic hepatitis or chronic livers diseases to health facilities. In Bale Robe, Oromia region, out of 578 patients with chronic hepatitis, HBsAg prevalence reached 22.3% and 35.8% in Addis Ababa (16, 17). HCV prevalence was 3.6% and 22.5% respectively in the two locations. The study from Addis Ababa which was conducted in 2010/11, reported an HBV/HCV co-infection rate of 2.5%. In still another study, data from 2007-2011 was reviewed from 2,684 clinically suspected hepatitis patients from Gondar. The research found 14.2% and 12.4% prevalence for HBsAg and HCV respectively.

In patients with comorbidities, principally HIV infection, a study conducted in Debretabor, Amhara

region, reported an HBsAg and HCV prevalence of 6.1% 1.3% respectively (19). Another study in HIV-infected individuals from Gondar which was carried out in 2011, found an overall HIV-viral hepatitis (HBV and HCV) co-infection rate of 11.7%. Co-infected patients had increased liver enzyme levels and lower CD4 counts, suggesting a deleterious effect of superimposed HBV and HCV infections in HIV infected persons.

A series of studies have also been conducted to determine HBV or HCV prevalence in persons attending voluntary counseling and testing (VCT) for HIV in Ethiopia. The studies from VCT sites in Mekelle and Hawassa only investigated HCV prevalence in HIV-negative and HIV-positive individuals. HCV prevalence was significantly higher in HIV-positive individuals in both Mekelle and Hawassa. Another study conducted in Addis Ababa among persons attending VCT, found an overall HCV prevalence of 3.6%. The Addis Ababa study was also the first report for the country to identify circulating HCV genotypes (23).In both the Hawassa and Addis Ababa studies the overall HCV prevalence dropped to below 1% after confirmatory testing was conducted on all initially positive samples.Two other studies from VCT sites in Shashemene and a second study from Addis Ababa, investigated only HBV prevalence in HIV-positive and negative individuals (24,25).The overall HBsAg prevalence in the 2 studies was similar (5.7% in both). However, stratifying by HIV status yielded markedly different results. In Shashemene there was a significantly higher prevalence of HBsAg in HIV+ individuals (14% versus 4.3% in HIV-negative individuals), whereas the Addis Ababa study failed to note a significant difference in HBsAg prevalence between the two groups. However the same study reported an anti-HBc prevalence of 44.8%, indicating that previous exposure to HBV in this community was high. The same trend was reported 2 decades earlier by other investigators who documented finding a mean carrier rate of hepatitis B surface antigen of 6.2%, and a mean overall hepatitis B virus marker prevalence of 42%, which rose to 76% in those over 14 years of age.Delta antibody (anti-HDV) was found in 3 of the 31 HBsAg positive patients from the same study.

Comparatively less work has been done to define the epidemiology of other viral hepatitis viruses in Ethiopia. Although the literature here is scanty, a few studies on hepatitis A and E have been described. A study conducted in 1990 showed evidence of HAV infection in 50% of the population before the age of 5 years, which increased rapidly with age and became universal after 15 years of age. Studies to compare hepatitis E prevalence among 32 pregnant and 34 non-pregnant women in Ethiopia have demonstrated a higher HEV infection rate in the pregnant women, 59% and 22% respectively. In the same study, a total of 10 maternal deaths were recorded, 9 of which occurred in the pregnant group, the majority during the third trimester. Eight of the maternal deaths were associated with HEV infection.

In summary, the many different studies conducted in Ethiopia, mainly on HBV and HCV have produced varying seroprevalence estimates. However arriving to a consensus estimate for each of the hepatitis viruses for the country as a whole, remains a significant challenge. This is because the studies have been conducted in different population groups (having increased or lower risk probability), utilized different sample sizes, and most of all, used different laboratory screening methods, some with, and others without, the benefit of confirmatory testing, to arrive at seroprevalence estimations. In addition the studies have a wide geographical distribution. In light of the above limitations, further large scale seroprevalence studies are warranted to achieve more recent national seroprevalence estimates. Recent national data from different sources may also be utilized to generate more current seroprevalence estimates, such as from ANC surveillance or blood banks. Having recent information on hand can provide more concrete evidence-based input for policy making on prevention and care of viral hepatitis in Ethiopia.

Table 1.1: Special Populations (considered being at high risk for viral hepatitis infection in Ethiopia)

No		ETHIOPIA
1	Pregnant women	Information available (though old)
2	Health care workers	Information available
3	School children	Information not available
4	Food handlers	Information not available
5	People receiving blood transfusion	Information not available (we have it only for blood donors)
6	Patients on dialysis	Information not available
7	Unsafe sexual practices (high number of sexual partners, etc)	Information available
8	Men who have Sex with Men (MSM)	NA*
9	HIV co infection /comorbidity	Information available
10	Refugees living in overcrowded camp conditions	Information available
11	Traditional practices (tattoos, body piercing) and inadequate sterilization of medical devices	Information available
12	IV drug injection	NA

*NA = not applicable.

Chapter Two: Prevention of Viral Hepatitis

Prevention of hepatitis A and E virus infection

Both HAV and HEV infection are principally transmitted through the fecal-oral route. And certain environmental and behavioral factors predispose certain group of people to high risk of infection. These groups includes children living in poor sanitation and in areas with low hygiene, people living in crowded environments (military recruits, prison camps, immigration camps, psychiatry and other rehabilitation centers, pre-school …) and health care workers. Besides, severe fulminant hepatitis may occur in pregnant women due to HEV infection.

Thus, the most important approaches in preventing both HAV and HEV infection are improvement of sanitation, adequate supplies of safe drinking water and proper sewage system, combined with personal hygiene practices such as regular hand washing.

Thus, transmission of HAV and HEV could be controlled by adopting the following two measures:

1. General public health approach

- Maintaining quality standards for public water supplies
- Establishing proper disposal systems to eliminate sanitary waste
- Within household and individual level

2. Promote behavior change for improved hygienic practices. Thus, good personal hygiene, including frequent and proper hand washing after bowel movement and before food preparation, are important measures to reduce the risk of transmission from infected individuals. Thus promote behaviors such as:

- Hand washing with soap and water after using the toilet and changing diapers and before preparing food, eating or feeding baby
- Cook food well and eat it while it's hot
- Only drink safe water
- Disinfection in place who cares for high risk groups: - Chlorination and certain disinfecting solutions (household bleach 1:100 dilution) are sufficient to inactivate the virus.
- Peel fruits and vegetables, wash salads in clean water
- Provide HAV and HEV vaccination when available

Prevention of hepatitis B and C virus infection

Both HBV and HCV are parenteral viruses whose transmission is usually by contact with blood or other body fluids (i.e. semen and vaginal fluid) of an infected person. The main transmission route includes sexual contact, transfusion of infected blood and blood products, sharing of contaminated needles, other sharps, and tooth brushes, vertical transmission and close muco-cutaneous contacts.

Primary Prevention: Non-vaccine prevention

Generally the non-vaccine prevention of hepatitis B and C virus infection could be possible through promotion of personal behaviors as well as standard practices in the healthcare setting that included:

- Hand hygiene: Including surgical pre procedure cleaning of hand, hand washing and use of gloves
- Safe handling and disposal of sharps and waste
- Safe cleaning of equipment
- Screening of blood and blood products for transfusion against hepatitis B, C virus and other viruses
- Improved access to safe blood
- Training of health personnel
- Practice protectedsex: promotion of correct and consistent condom use
- Routine screening of sex workers in high prevalence settings
- Increase access to medical and social services for vulnerable persons
- Avoid sharing intravenous drug paraphernalia (equipment)
- Immunize at risk individuals for Hepatitis B
- Clear up blood or fluids using water and detergent
- Ensure surgical instruments are disposable or adequately sterilized
- It is recommended to wear goggles if there is risk of infected material splashing into the eye
- Use safety engineered devices like syringes
- Screen and vaccinate health care workers

Primary Prevention: Hepatitis B immunization

- Hepatitis B vaccine is safe and effective, but is not been seen as an alternative to a strategy of prevention of transmission.
- Generally, vaccination should be offered to all neonates and non-exposed Ethiopians though special emphasis to high risk populations.

Infant immunization

All infants should receive the hepatitis B vaccine: this is the mainstay of hepatitis B prevention. In areas where mother-to-infant spread of HBV is common, in high- and intermediate-prevalence countries, the first dose of monovalent vaccine should be given as soon as possible after birth (within 24 hours).

Hepatitis B vaccine is part of EPI program in Ethiopia and currently is given at 6, 10 and 14 weeks for newborns. However, WHO strongly recommends provision of HBV vaccine at birth because of high risk of transmission during birth with subsequent sequelae of chronicity.

Risk of chronic infection from HBV varies by age at time of infection. Over 90% of individuals infected during neonatal period will develop chronic hepatitis B infection, while that proportion significantly reduced to about 50% for infection acquired during infancy, 20% in childhood and less than 5% in adulthood (see graph below). In accordance, in countries like Ethiopia where prevalence is estimated intermediate or above, introduction of birth dose is highly recommended.

Thus, Ethiopia being one of the countries with high to intermediate-prevalence countries in consultation with the National EPI strategy and immunization schedule guidelines recommend introduction of a

monovalent HBV vaccine at birth. Accordingly, neonates will receive HBV immunization at birth (within 24 hrs), 6, 10 and 14 weeks integrated with the routine national immunization schedule.

Vaccination of people in high-risk groups

Individuals other than neonates identified as high-risk groups (such as healthcare workers, immune-compromised individuals including HIV; Organ transplant, patients on hemodialysis, children 1-5 years who missed immunization for HBV, sexual partners and close contacts of infected individuals) shall also receive three doses of HBV vaccine. The standard course of immunization for non-neonates involves the injections at 0, 1 and 6 months. However, an accelerated course of 0, 1 and 2 months is possible like in PEP as well, for hepatitis B vaccines. Adults who need protection very quickly (e.g. within 48 hours of exposure) can have schedule of 0, 7 and 21 days. After an accelerated course, a booster at one year is recommended.

A course of HBV vaccine may give lifelong immunity. However it is recommended that individuals at continuing risk of infection (immune-compromised patients and those on hemodialysis) should be offered a single booster dose vaccine once every five year after primary immunization. Measurement of hepatitis B surface antibody (anti-HBs) levels is not required either before or after this booster dose. Where available, antibody levels should be monitored annually for high risk groups and if they fall below 10mIu/ml a booster dose of vaccine should be given to individuals who have previously responded to the vaccine.(Optional)

Also, anti HBs testing is recommended in patients with chronic renal failure on dialysis. The role of immunological memory in patients with chronic renal failure or renal dialysis does not appear to have been studied, and protection may persist only as long as anti-HBs levels remain above 10mIU/ml. Booster doses should also be offered to any haemodialysis patients who are at a high risk of exposure if they previously responded to the vaccine particularly if they are to receive haemodialysis and have not received a booster in the preceding 12 months

Hepatitis B Immunoglobulin

Prophylactic treatment to prevent hepatitis B infection after exposure to hepatitis B virus (HBV) should be considered in several situations:

- Perinatal exposure of an infant born to a HBsAg positive mother within 24 hrs
- Accidental percutaneous or permucosal exposure to HBsAg-positive blood preferably within 24-48 hrs
- Sexual exposure to an HBsAg-positive person

HBIG must be provided to individuals who have not been immunized against HBV or are being immunized against HBV but have not yet received all the three shots in the vaccination series and are exposed to the virus. It provides passive immunity and can give immediate but temporary protection. HBIG is given concurrently with hepatitis B vaccine and does not affect the development of active immunity. If the injection occurred at the time of immunization, administration of HBIG may still prevent the development of carrier status.

Complications of HBV vaccine

Hepatitis B immunoglobulin is well tolerated. Adverse reactions to the vaccine are few and usually mild.

- There may be some soreness and erythema around the injection site
- Fatigue, malaise and influenza- like symptoms are rare

- An association with Guillain – Barre – type syndrome has not been substantiated

Post Exposure Management

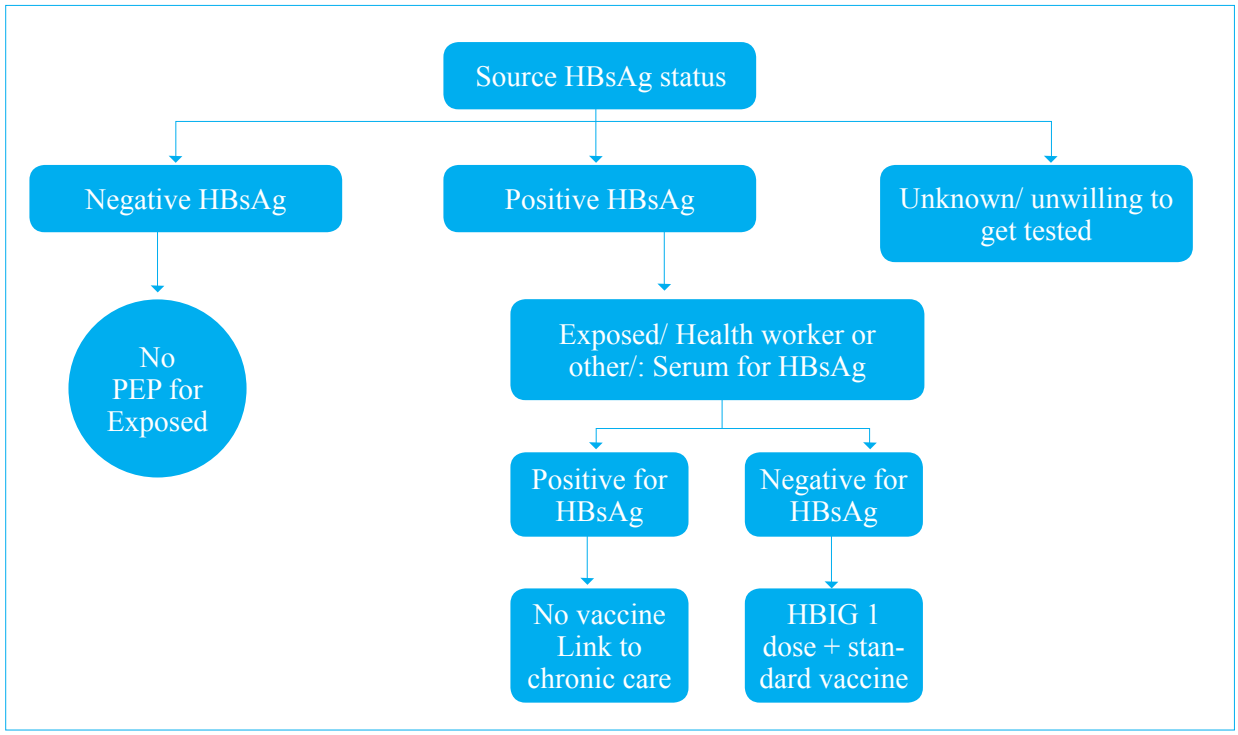
- After confirmed exposure, test for HBsAg, Anti-HBs Ab, and Anti-HBcAb, if negative provide vaccine and possibly HBIG if required. For testing the exposed person sample should be collected before the vaccine. The vaccine should be given within 48 hours and certainly not later than seven days after exposure.

- Immunoglobulin is given at different site and it does not reduce the immune response to the vaccine. If the status of the source is not known assume HBV infected source.

- If the type of exposure is a "needle stick" injury, cut or abrasion, the site should be washed immediately with soap and water

- In addition to vaccine at birth, HBIG is indicated for babies born to mothers who are chronic carriers of hepatitis B virus or to mothers who have had acute HBV hepatitis during pregnancy.

Fig 2.1: Algorithm for provision of PEP in Ethiopia for HBV infection exposure



Chapter Three: Diagnosis, Treatment and Care of Hepatitis B infection

Introduction

Hepatitis B Virus (HBV) is a DNA virus, which causes acute and chronic hepatitis that could range from asymptomatic carrier states to fulminant liver failure. It has 10 genotypes identified unto now, A to J based on nucleotide divergence. For details of epidemiology and transmission refer to chapter 1 & 2. Acute Hepatitis B virus is usually self-limited and resolves but in few groups of individuals it may progress. Diagnosis and treatment of HBV should aim in viral suppression and prevention of complications, cirrhosis, and hepatocellular carcinoma and end stage liver disease. HBV is prevalent in Ethiopia and based on few studies it has a prevalence of 8-12 %. Diagnosis of HBV should be based on serology detection of surface antigen on a validated test kit.

Natural history of HBV infection

Hepatitis B virus causes both acute and chronic infection. Left untreated, chronic HBV infection can cause liver cirrhosis, liver failure and hepatocellular carcinoma.

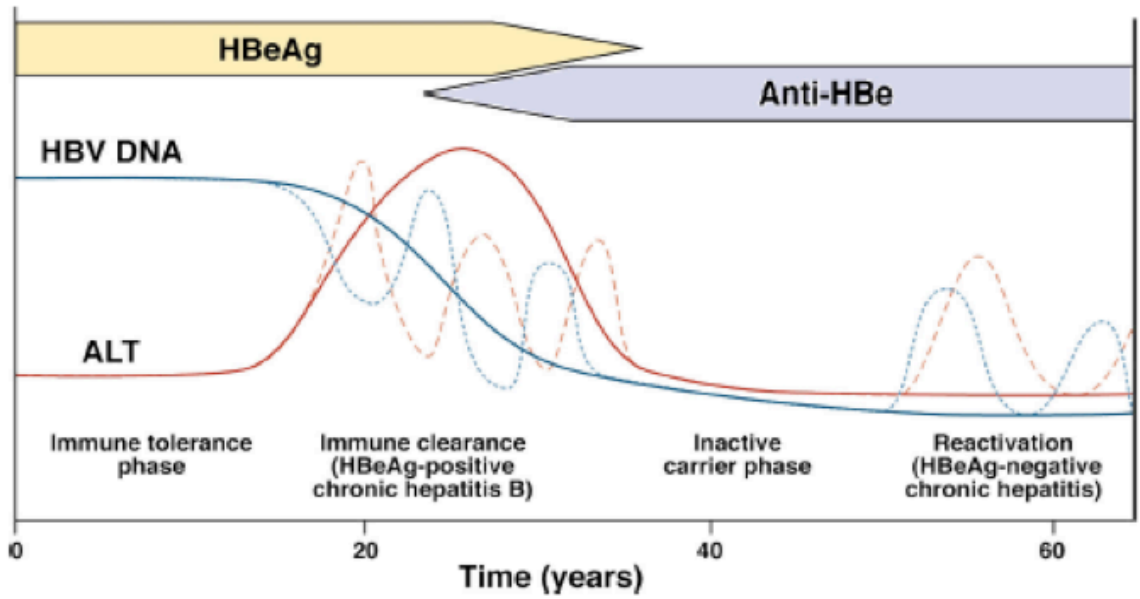
Acute HBV infection

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 (antibodies to hepatitis B surface antigen), usually within 3 months.

Chronic HBV infection

Defined as, persistence of hepatitis B surface antigen (HBsAg) for six months or more after acute infection with HBV. Throughout the guidelines, the term chronic hepatitis B (CHB) has been used to indicate chronic HBV infection.

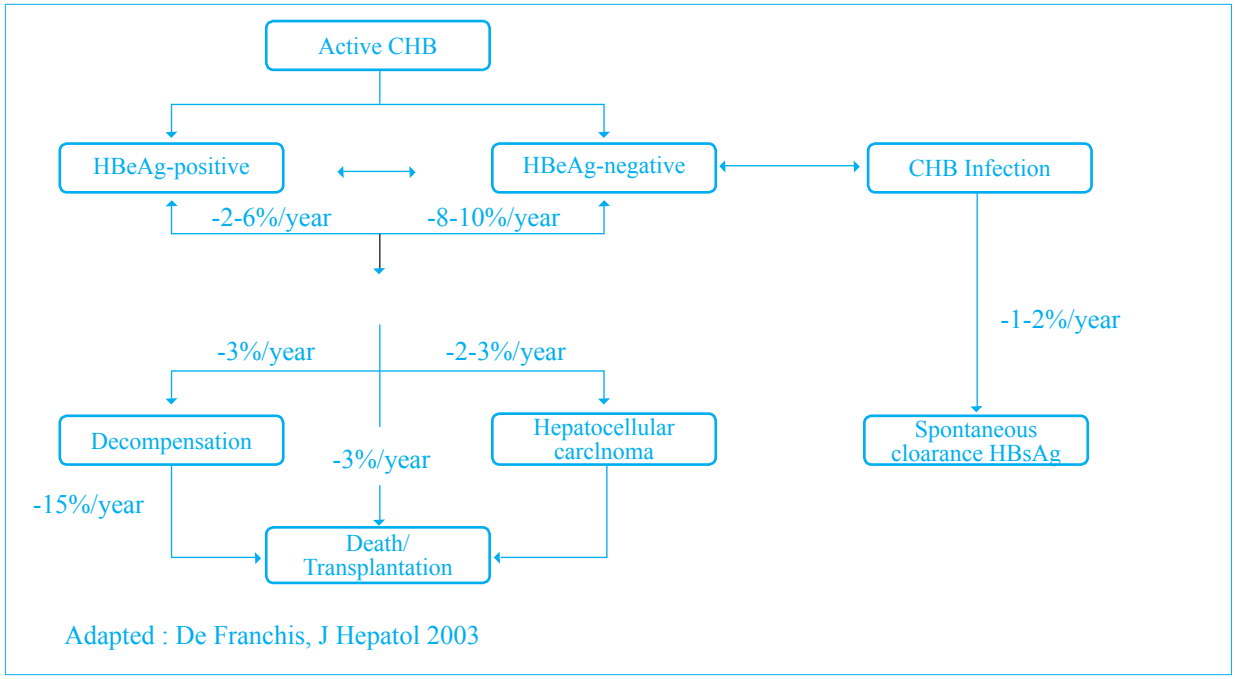
Fig 3.1 Schematic presentation of progression of HBV infection



Phases of Progression of chronic Hepatitis B virus infection

The different phases of HBV help to understand the progression of the disease and help in guiding for treatment.

Fig 3.2The different phases of chronic hepatitis B progression



1. "Immune tolerant" phase

- Stage seen in many HBeAg - Positive children and young adults, particularly among those infected at birth
- High levels of HBV replication (HBV DNA levels > 20, 000 IU/ml)
- Persistently normal ALT
- Minimal histologic disease

2. "Immune active" (HBeAg-positivea chronic hepatitis)

- Abnormal or intermittently abnormal ALT
- High or fluctuating level of HBV replication (HBV DNA > 2,000 IU/ml)
- Histological necroinflammatory activity present
- HBeAg to anti-HBe seroconversion possible with normalization of ALT leading to "immune- control" phase

3. Inactive chronic hepatitis "Immune control"

- Persistently normal ALT
- Low or undetectable HBV DNA levels (HBV DNA levels <2000 IU/mL)
- Risk of cirrhosis and HCC reduced
- May develop HBeAg negative disease

4."Immune escape" (HBeAg-negative chronic hepatitis)

- HBeAg negative and anti_HBe positive
- Abnormal ALT (persistently or intermittently abnormal)
- Moderate to high level of HBV replication (HBV > 20, 000 IU/ml)
- Older persons especially at risk for progressive disease (fibrosis/cirrhosis)

5. "Reactivation" or "acute-on- chronic hepatitis"

- Can occur spontaneously or be precipitated by immunosuppression from chemo– or immunosuppressive ther-

apy, HIV infectionor transplantation, development of antiviral resistance, or withdrawal of antiviral therapy

- Abnormal ALT
- Moderate to high level of HBV replication
- Seroreversion to HBeAg positivity can occur if HBeAg negative
- High risk of decompensation in presence of cirrhosis

6. Occult HBV Infection:

- Persons who have cleared hepatitis B surface antigen, i.e. they are HBsAg negative but HBV DNA positive, although at very low levels (invariably <200 IU/mL)
- Most are also anti-HBcpositive . These individuals are at risk of reactivation of HBV with immune suppression and require prophylactic antiviral therapy prior to chemotherapy.
- Factors that increase the risk of cirrhosis and HCC
- Factors that increase the risk of cirrhosis includes: male gender, alcohol intake, persons with hepatitis C, HIV co-infection and immunosuppressed individuals

Host factors:

- Age > 40 at infection
- Extremes of age
- Male gender

Environmental factors:

- Alcohol,
- Immunosuppression: HIV
- Co-infection with acute HDV, HCV and/or HIV
- Viral factors:

Viral load

- Genotype
- Viral Mutations
- HBeAg status

Serologic Markers of HBV

Hepatitis B surface antigen (HBsAg)

HBV envelope protein and excess coat particles detectable in the blood in acute and chronic hepatitis B infection

Hepatitis B core antigen (HBcAg)

HBV core protein: The core protein is coated with HBsAg and therefore not found free in serum

Hepatitis B e antigen (HBeAg)

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 antibody (anti-HBs)

Antibody to HBsAg: Develops in response to HBV vaccination and during recovery from acute hepatitis B, denoting past infection and immunity

Anti-HBe

Antibody to HBeAg: Detected in persons with lower levels of HBV replication but also in HBeAg-negative disease (i.e. HBV that does not express HBeAg)

Hepatitis B core antibody (anti-HBc)

Antibody to hepatitis B core (capsid) protein: Anti-HBc antibodies are not neutralizing antibodies and are detected in both acute and chronic infection

IgM anti-HBc

Subclass of anti-HBc. Detected in acute hepatitis B but can be detected by sensitive assays in active chronic HBV

IgG anti-HBc :-
Subclass of anti-HBc detected in past or current infection

Extrahepatic manifestations of HBV

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

Natural history of HIV/HBV co-infection

HIV coinfection has been shown to have a profound impact on almost every aspect of the natural history of HBV infection and includes more rapid progression to cirrhosis and HCC, higher liver-related mortality, and decreased treatment response compared with persons without HIV coinfection

HIV/HBV-co-infected persons also demonstrated more rapid HIV disease progression compared to those who were HIV-infected alone, and had an impaired recovery of CD4 cells.

Screening for HBV infection

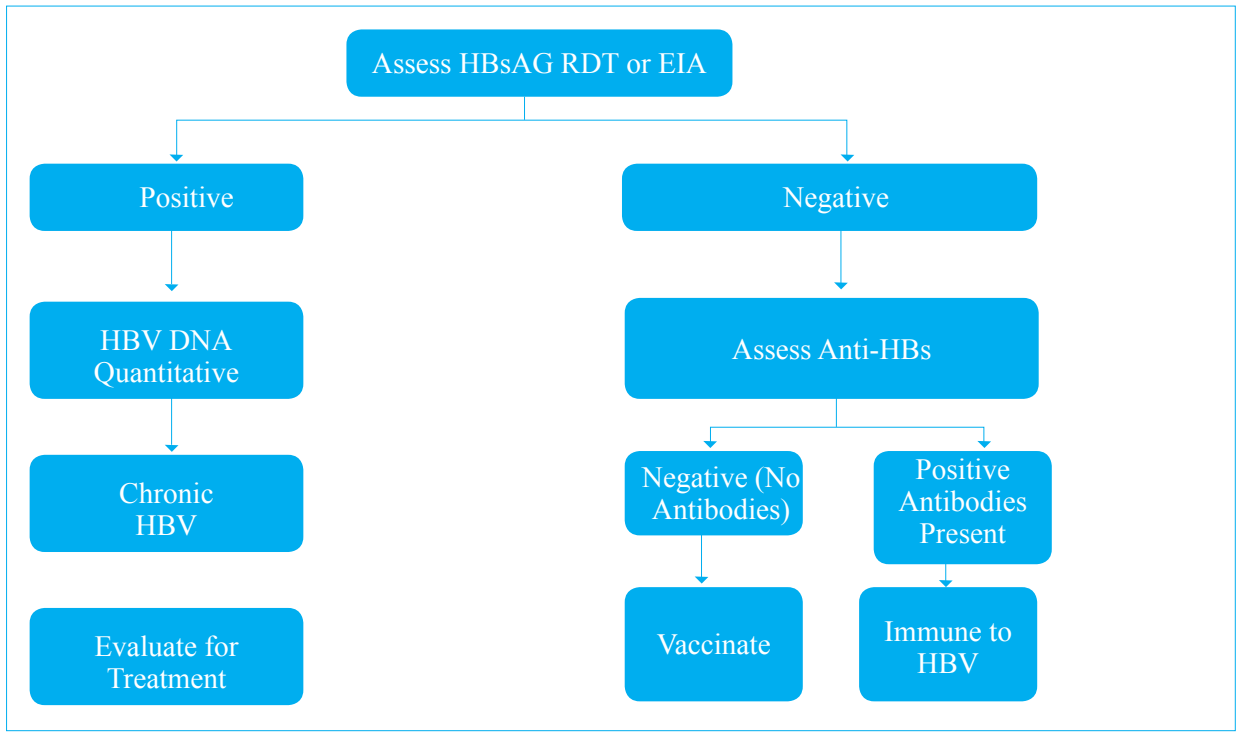
Screening for HBV infection is done using HBV serological testing for high risk groups which include pregnancy, HCV, HIV, CLD, Commercial sex workers and prisoners. Screening for other infections, for example TB, is also indicated in some groups at risk, such as people living with HIV and prisoners. After test result, vaccination or treatment and care for reactive patients are recommended when resources permit.

High risk groups should be given priority for screening:

- Infants born to infected mothers
- Health care workers (including health professionals and supporting staff)
- Hemodialysis patients
- I.V drug users(rare)
- People with high risk sexual behavior
- Partner of HBV Infected Persons
- HIV positive patients
- HCV Positive patients
- Pregnant mothers as high risk and priority population

- Prior to immunosuppressive or cancer therapy
- Organ transplant recipients
- Blood or organ Donors
- Persistently elevated liver enzymes (AST, ALT)

Figure 3.3: Algorithm for Screening and Diagnosis of HBV Infection in Ethiopia



Care of patients with HBV infection

The spectrum of disease with CHB is diverse. In some people, CHB is inactive and does not lead to significant liver disease. In others (approximately 10or example TB, is also indicated in some groups at risk, such as people livid-stage liver disease, and a markedly increased risk of hepatocellular carcinoma (HCC), usually many years after initial infection. Unlike patients with other causes, HCC due to hepatitis B virus infection can occur with normal liver parenchyma i.e. before the development of cirrhosis.

The diagnosis of decompensated liver disease is based on both clinical examination and laboratory monitoring, and therefore a careful medical examination of patients must be made prior to commencing therapy. The stage of disease may be assessed using non-invasive methods using APRI and FIB4 which are validated and need only blood tests which are simple to perform.

Treatment of patients with HBV infection

The objective of treatment is to prevent the adverse outcomes of CHB. The decision to initiate antiviral therapy is usually based on a combined assessment of the stage of liver disease (from clinical features, liver histology [where available], and increasingly on blood or ultrasound-based NITs), together with levels of serum ALT and HBV DNA. The decision to treat is usually clear in persons who present with life-threatening or advanced liver disease, such as acute liver failure, and compensated or decompensated cirrhosis and acute-on-chronic liver failure. In persons who have not yet progressed to cirrhosis, decisions are also based on ALT and HBV DNA levels. However, not all persons will have elevated ALT and HBV DNA levels. It is important that antiviral therapy is targeted to the active phases of CHB when the risks of disease progression (fibrosis) are greatest and, conversely, that persons with minimal fibrosis and low risk of CHB progression are identified, as they do not require antiviral therapy. Based on the different phases, treatment is not recommended to immune tolerant and inactive carrier phases of hepatitis.

Pretreatment evaluation

Laboratory Evaluation:

- Priority Tests:
- Serological markers: HBsAg, HBeAg,
- Complete blood test (CBC)
- Liver chemistry tests (ALT, AST, Bilurubin, INR, Total protein and Albumin) ,
- calculate APRI /AST to platelet ratio/ score or FIB4, which will be calculated as depicted below
- HIV and HCV rapid test
- Viral load: Quantitative HBV DNA
- Imaging: Abdominal Ultrasonography

Optional

- HBsAg titer levels
- AFP if hepatic mass and suspicion of HCC
- U/S guided liver biopsy if indicated
- Fibro scan/elastography when available to assess liver stiffness / degree of fibrosis
- Abdominal tri-phasic CT scan/ MRI to diagnose HCC when available

Assessment of liver fibrosis by non-invasive tests:

Simple laboratory tests

- APRI:-

  Aspartate aminotransferase (AST)-to-platelet ratio index (APRI) is a simple index for estimating hepatic fibrosis based on a formula derived from AST and platelet concentrations.
  A formula for calculating the APRI is given: APRI = * (AST/ULN) x 100) / platelet count (10^9/L).

- FIB-4:-

  A simple index for estimating hepatic fibrosis based on a calculation derived from AST, ALT and platelet concentrations, and age. Formula for calculating FIB-4: FIB-4 = (age (yr) x AST (IU/L)) / (platelet count (109/L x [ALT (IU/L) 1/2]).

Low and high cut-off values for the detection of significant cirrhosis and fibrosis

For APRI:- A level of 1(low) to detect significant fibrosis and 2 (high cut-off) for cirrhosis and for FIB-4 a 1.45 (Low) and 3.25 (High) cut-off for significant fibrosis and cirrhosis respectively

Alternative method of assessment of degree of fibrosis

- Fibroscan

$$FIB4 = Age(yr) \times AST/Platelet(10^9/lt) \times ALT(u/lt)^{1/2}$$

- For significant fibrosis: Lower cu off=1.45 and higher cut off=3.25

Indication of treatment

Those who are at risk or with ongoing inflammation of the liver are eligible for treatment. However priorities should be given to those are at increased risk of progression and with advance liver fibrosis and liver disease. Hence treatment is indicated or should be prioritized in those with the following conditions;

- All adults, adolescents and children with detectable HBV DNA and clinical evidence of cirrhosis (both compensated and decompensated).
- All adults, adolescents and children with detectable HBV DNA and APRI score > 2 regardless of HBV DNA level, HBeAg status and degree of ALT elevation.
- All adults greater than 30 years of age with persistent elevation of ALT above upper limit of normal and HBV DNA > 20,000u/ml, regardless of HBeAg status. (for HBeAg negative and HBeAb positive treat at HBV DNA >2000 IU/ml)
- Patients with HBV and are to undergo immunosuppressive therapy like chemotherapy
- Co-infection with HIV - see below (Section HBV/HIV co-infection)

NB: Patients with HBV, advanced liver disease and Hepato-cellular carcinoma (HCC) recommended counseling for treatment of HCC than for treating HCC

Serial ALT measurements are recommended to make treatment decisions, as single result may not be reliable.

Monitor HBV DNA, ALT, APRI assay every 12 months to make treatment decision.

- If Liver biopsy is done then treat if necro inflammation is moderate to severe.
- If available and fibroscan revealed a score of > 7.9 Kpa it is equivalent to significant fibrosis treatment is indicated
- Fibroscan score > 9.5 is a sign of cirrhosis and treatment is indicated after other possible causes has been excluded / Obesity, alcoholic, drugs ,,../ and other evidence of cirrhosis including low platelet count, low albumin, clinical evidence of ascites or other evidences of portal hypertension.

If treatment is not indicated close monitoring is required for the following group of individuals because inactive disease may reactivate and cause subsequent risk of liver damage.

No cirrhosis, APRI score ated close monitoring is required for the following group of individuals because inactive Adults age toring is required for the following group of individualsbec

- Adults age toring is required for the folloHBeAg negative, HBV DNA 2000-20,000U/ml. or Intermittently abnormal ALT.

Drug choice and duration of therapy

There are some future hopes in drug treatment for hepatitis B as new drug target therapies are also evolving. Currently 7 agents are approved for the treatment of HBV infection. These include five nucleo(s)tide analogues and an injectable peg-interferon. The nucleotide analogues are

Tenofovir, Entecavir, Telbivudine, Lamivudine , Adefovir ; Tenofovir and entecavir have high barrier of resistance, but the other agents are associated with high viral resistance profile especially lamuvidine with a resistance profile that could reach > 70 % after 5 years of treatment.

Recommended treatment in Ethiopia

Preferred Therapy:

The currently recommended first line treatment options (Preferred) for chronic Hepatitis B infection are Tenofovir and Entecavir.. Also to be considered is presence of HCV, HIV & Hepatitis D Co-infection(s).

- Tenofovir:
- For those with renal dysfunction (AKI or CKD), consider alternative treatment / and adjusted drug regimen based on renal dysfunction
- Entecavir: can be considered for those with history of AKI or CKD or risk factor for renal disease.
- Telbuvidine :- an alternative in renal failure and patients at risk of having renal compromization (Type 2 DM) and in pregnancy with high viral load

Alternate therapy:

In the absence of the above recommendations, Lamivudine or Telbivudine could be used for interventions intended for < 12 months due to its related high risk of resistance. Telbivudine can also be preferably used for prevention of mother to child transmission of HBV as it is safe during pregnancy.

Table 3.1: circumstances where a certain first line anti-HBV agent may be preferred over others

Setting	Anti-HBV Agent
Decompensated cirrhosis	Tenofovir may be appropriate
Renal insufficiency	Entecavir preferred (with dose modification) Telbuvidine – alternative
Pregnancy, woman of child-bearing age planning pregnancy in the near term	Tenofovir preferred
Pregnant mother requires treatment	Tenofovir is preferred, Telbivudine can also be used as alternative
HIV co infection	Tenofovir plus emtricitabine or lamivudine + Efavirenz(fixed dose)

Treatment Duration and Dose

Dose and duration: All Nucleos(t) iseanologue should be given for at least 12 months. Decision when to stop treatment will be based on HBeAg status and achieving targets for each (discussed below).

- Tenofovir: 300mgs oral daily for adults
- FDC of TDF with emitrictabine 200mg/day or Lamivudine can also be used.
- Entecavir 0.5 mg oral daily if no prior exposure to lamivudine and 1mg oral daily for those with prior exposure to Lamivudine.
- Telbivudine: 600mg oral daily with low Viral load at baseline, no evidence of cirrhosis and close HBV DNA monitoring at 24th week of therapy. If HBV DNA at 24 week is l load at baseline, no evidence of cirr

- Lamivudine 100mg oral daily
- Adefovir: 10mg oral daily

Monitoring therapy

- Initially every 3 months for the first one year and subsequently 6 monthly.

The following investigations are recommended while on treatment where resources are available.

- Every three months in the first year and subsequently every 6 months
- Liver enzyme and function test
- Renal function test (for those on TDF)
- After the first year
- HBV DNA (quantitative) annually
- HBeAg (for those with HBeAg positive CHB)
- HBsAg for Hbe Ag negative CHB (optional)
- Abdominal sonography for patients with advanced cirrhosis and AFP Q 6mos

When to stop treatment

All persons with cirrhosis based on clinical evidence (or APRI score >2 in adults) require lifelong treatment with nucleos(t)ide analogues (NAs), and should not discontinue antiviral therapy because of the risk of reactivation, which can cause severe acute-on-chronic liver injury. Discontinuation can be considered exceptionally in the following condition and all of the criteria should be fulfilled.

- persons without clinical evidence of cirrhosis (or based on APRI score ≤2 in adults);
- and who can be followed carefully long term for reactivation;
- and if there is evidence of HBeAg loss and seroconversion to anti-HBe (in persons initially HBeAg positive) and after completion of at least one additional year of treatment;
- and in association with persistently normal ALT levels and persistently undetectable HBV DNA levels (where HBV DNA testing is available).

Where HBV DNA testing is not available: Discontinuation of NA therapy may be considered in persons who have evidence of persistent HBsAg loss and after completion of at least one additional year of treatment, regardless of prior HBeAg status.

Retreatment

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

Treatment for special Groups

These include: pregnancy, patients on dialysis, prior to immunosuppressive or cancer therapy, transplant patients, co-infections with HCV infection

Pregnancy:

In HBV-monoinfected pregnant women, the indications for treatment are the same as for other adults, and tenofovir is recommended. No recommendation was made on the routine use of antiviral therapy to prevent mother-to-child HBV transmission. Other alternative drug includes Telbuvidine, which is also pregnancy category B.

In HIV co-infected pregnant woman, a once-daily fixed-dose combination of tenofovir + lamivudine (or emtricitabine) + efavirenz is recommended as first-line ART

All infants should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours, followed by two or three doses and HBIG at birth within24 hrs.

Treatment protocol in Hemodialysis or Renal Transplant patients:

- Vaccination

Give hepatitis B vaccination in HBsAg negative, anti HBs negative patients with end stage chronic kidney disease.

There is however inefficient response to HBV vaccination in patients with end stage renal disease. This could be improved by administering double dose with intensified time schedule 404 hrs.herapy to prevent mother-to-child HBV transmission..

With regard to HB vaccination it is currently recommended to maintain anti-HBsAg antibody titers at > 100mIU (10 times higher than with normal population), to achieve adequate seroprotection in hemodialysis patients.

- **Drug Treatment**

- Pegylated interferon (not in end stage) or nuclesos(t)ide analogue can be used in renal impairment. Pegylated interferon should be avoided in haemodialysis and renal transplant patients because of risk of rejection.
- Entecavir is recommended as 1st line oral therapy in patients with kidney disease
- Telbuvidine is an option of treatment alternative
- Lamivudine is good but its problem is development of YMDD resistance on long term use, thus monitor by HBV DNA.
- For patients with renal dysfuctionn, at baseline, consider either avoidance of tenofovir and use of entecavir instead, or dose reduction of tenofovir, if the estimated glomerular filtration rate (eGFR) is <50 mL/min, or in those with risk factors for renal dysfunction, including long-term diabetes, uncontrolled hypertension or severe osteopenia/osteoporosis.
- For individuals with normal renal function, a minimum monitoring package could include annual urine dipstick testing and creatinine measurement for eGFR where possible.
- Persons with renal dysfunction with a CrCl<50 mL/min should have follow -up in tertiary care center

- **Drug prophylaxis Pre-Transplant**

- All HBsAg positive patients who are to undergo renal transplant should receive anti HBV prophylaxis with a nucleos(t)ide analogue. This is started just at time of transplant (at least a week before) and continued indefinitely, so long as the patient is still on immunoprophylaxis
- Entecavir is the preferred 1st line nucleo(t)ide analogue, because it offers high antiviral potency with low risk to resistance. Adjust dose in patients with glomerular filtration rate <50ml/min.
- Tenofovir can be used in renal transplant patients as an alternative but the renal parameters must be monitored.
- Lamivudine is safe but problem is development of resistance on long term us. It could be considered in patients with HBV DNA <2000 IU/ml. When used monitor HBV DNA (6 monthly). If rising change to entecavir or tenofovir.

Co-Infections in Chronic Hepatitis

- HBV/HDV co-infection: Treat for HBV as above
- HBV/HCV co-infection: Treat for HCV and treatment for HBV may follow accordingly

- HBV/HIV co-infection: Consider starting treatment for both infections regardless of CD4 count with HIV treatment including TDF for duration of life /see below/

- HBV/HCV/HIV co-infection: Treat cautiously according to indications and monitor drug interactions, toxicity, and resistance.

About 70-90% of all HIV patients show evidence of past or active HBV infection. The carriage of chronic HBsAg varies geographically but ranges from 1.9% to over 40%. Studies in Kenya and Ethiopia report rates between 10 to 40% of HIV/HBV co-infection but it should be noted that in these studies only the HBs Ag alone was tested (13,20). Cohort studies suggest that HBV does not appear to influence progression of HIV

Negative Influence of HIV on HBV:

- Lower rates of HBeAg clearance

- Increased serum HBV DNA levels

- Reactivation of hepatitis in asymptomatic carriers occurs

- Faster progression to fibrosis, cirrhosis, and HCC

- Higher morbidity and mortality rates

Screening for Hepatitis B and C in HIV patients:

All HIV patients should be offered screening for hepatitis B and C and vice versa as a routine.

If negative for HBsAg, HBsAb,and HBcAb,vaccinate against HBV .

Treatment options for patients with HIV –HBV Co-infection:

- ART should be initiated in all individuals with HIV regardless of WHO clinical stage or CD4count in the following situations:

- Individuals coinfected with HIV and HBV with evidence of severe chronic liverdisease

During HBV/HIV co-infection if treatment is indicated for HBV, combination antiretroviral therapy should be initiated with drugs containing TDF + 3TC (or FTC) + EFV as a preferred regimen

Rational Drug Use:

- Determine if both diseases require treatment.

- Determine when to treat HBV alone or HIV alone

- Monotherapy for either virus is not recommended as it leads to rapid development of drug resistance.

- For HIV positive patients who require treatment with HAART and are HBV positive, the backbone of treatment should include 2 drugs that are active against Hepatitis B.

- For HIV positive patients who are co infected with HBV and qualify for treatment of both the diseases i.e. HIV and HBV, oral drug therapy is first line for these patients with at least 2 of the drugs having activity against HBV like combination of Tenofovir, Emtricitabine/ lamuvidine and Efavirenz.

- The use of lamivudine as monotherapy in any of these diseases is contraindicated due to high YMDD resistance.

- When switching treatment in patients with HIV on ART failure, the regimen that will continue should have two of the drugs having activity against HBV
- If tenofovir-associated renal toxicity occurs, the dose of tenofovir should be adjusted according to the renal clearance.

Monitoring for Toxicities:

Monitor as in HIV negative patients although more adverse effects are expected in the co-infected patients than in those who have mono infection with HBV.

When to Refer:

Primary care Physicians who are engaged in the management of HBV are advised to refer to specialist with experience in the management of hepatitis when there is:

- Patients with established portal hypertension or decompensated liver disease
- Patients with co-morbidities e.g. diabetics
- Patients with complications while on treatment
- All co-infected - such HCV/HBV infection
- Cancer Patients on chemotherapy
- Other special groups such as pregnant women and children
- Decompensated cirrhosis

Chapter Four: Diagnosis, Treatment and care for Hepatitis C Infection

Introduction

The hepatitis C virus is a small, positive-stranded RNA-enveloped virus that is approximately 9.6 kb in length.

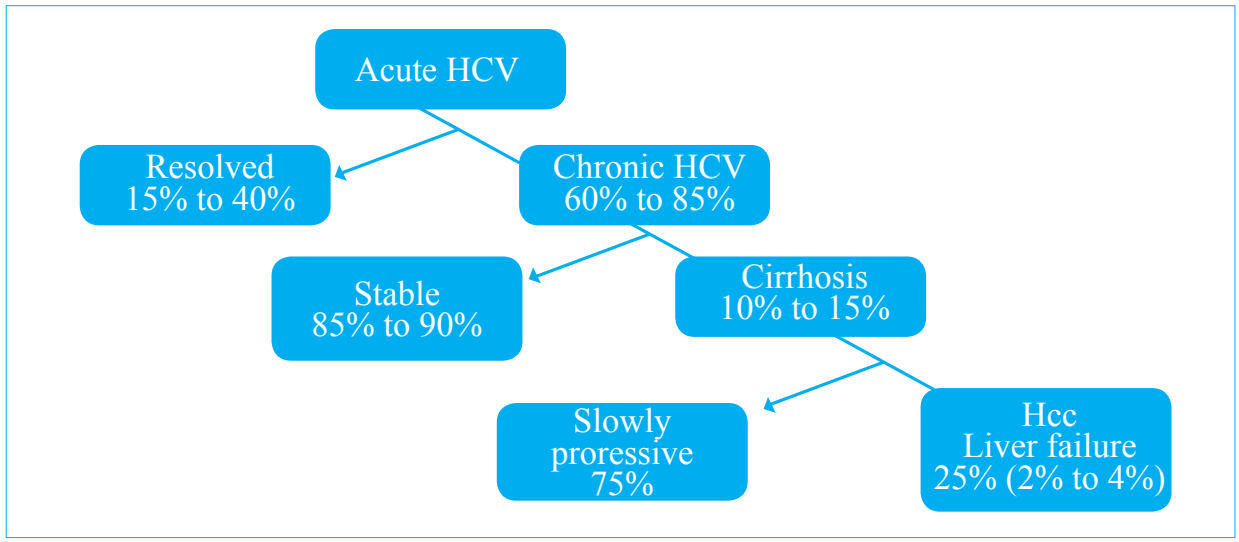
It has a highly variable genome and multiple genotypes and sub genotypes. The distribution of HCV genotypes and sub genotypes varies substantially in different parts of the world. There are currently seven genotypes identified.

Diagnosis and treatment of HCV should aim in eradication of the virus and ultimately cure. HCV is prevalent in Ethiopia and based on few studies the commonest genotype is 4 (60%)followed by 1(20%) The rest are rarely seen. Diagnosis of HCV should be based on serological detection of antibodies and to be confirmed by demonstration of HCV RNA in the blood.

Natural history of HCV infection

Hepatitis C virus causes both acute and chronic infection.Left untreated, chronic HCV infection can cause liver cirrhosis, liver failure and hepatocellular carcinoma.

Figure 4.1: Natural History of HCV Infection. (NIH management of Hepatitis C; conference statement June 10-12, 2012)



Factors that increase the risk of cirrhosis includes: male gender, alcohol intake, persons with hepatitis B, HIV co-infection and immunosuppressed individuals.

- **Host factors:**
  - Age > 40 at infection
  - Advancing age with the infection
  - Male gender
- **Environmental factors:**
  - Alcohol,
  - Immunosuppression: HIV
  - Co-infection with acute HBV
  - Steathosis, obesity
  - Insulin resistance or type 2 DM

Extra hepatic manifestations of HCV include: - Cryoglobulinaemia, glomerulonephritis, thyroiditis and Sjögren syndrome, insulin resistance, type-2 diabetes mellitus, and skin disorders such as porphyria cutaneatarda and lichen planus.

Natural history of HIV/HCV co-infection

Co-infection with HIV adversely affects the course of HCV infection, and co-infected persons have a significantly accelerated progression of liver disease to cirrhosis, decompensated liver cirrhosis and HCC than HCV-monoinfected persons, particularly those with advanced immunodeficiency (CD4 count <200 cells/mm^3).

HIV/HCV-co-infected persons also demonstrated more rapid HIV disease progression compared to those who were HIV-infected alone, and had an impaired recovery of CD4 cells.

Screening for HCV infection

If anti-HCV rapid diagnostic test (RDT) or immunoassay (IA) is positive, a confirmatory HCV RNA viral load test using either quantitative or qualitative PCR is needed to confirm chronic HCV infection.[6]

Screening for other infections, for example TB, is also indicated in some groups at risk, such as people living with HIV and prisoners.

It is recommended that HCV rapid tests instead of enzyme immunoassayto be offered to individuals who are part of a population with high HCV sero-prevalence or who have a history of HCV risk exposure/ behavior to improve access to care. If Anti HCV Anti body is detected, it is recommended to measure HCV RNA to confirm an ongoing infection.

High risk groups should be given priority for screening:

- Persons who have received medical and surgical or dental interventions
- Persons who have received blood transfusions
- Persons who inject drugs
- Persons who have had tattoos, body piercing or scarification
- Persons with HIV infection
- Pregnant mothers during ANC follow-up
- Prisoners and previously incarcerated persons
- Patients with chronic liver disease
- Infants born from HCV positive mothers

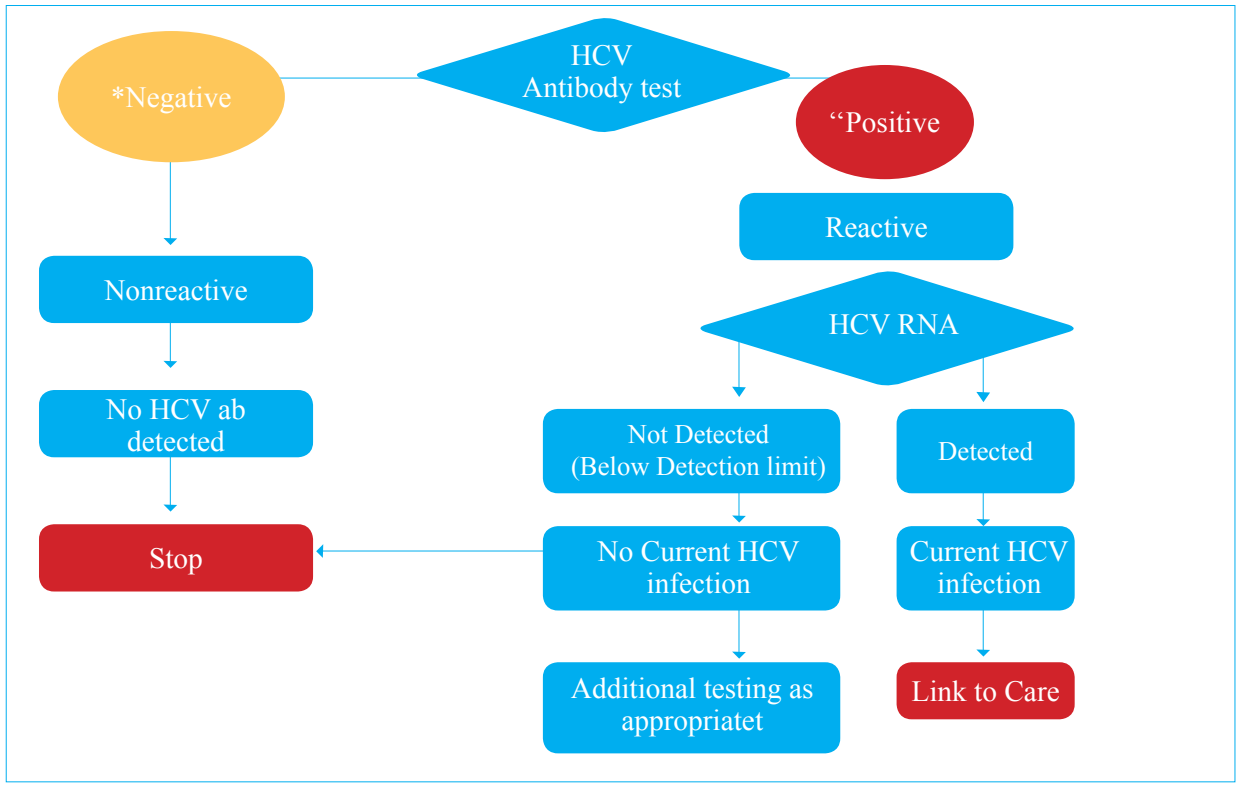
WHO- or SRA-approved rapid diagnostic tests can be used to screen for HCV infection. Several RDTs have been developed but only very few are on the process of prequalification.[7] Validation of rapid diagnostic tests will be done and specific RDT will be recommended accordingly.

Confirming diagnosis of chronic HCV infection

It is suggested that detection of HCV RNA be performed directly following a positive anti-HCV serological test to confirm chronic HCV infection. Quantitative nucleic acid testing for HCV RNA as part of the assessment is important before starting treatment for HCV infection. Quantitative HCV RNA measurement is recommended to confirm HCV infection and prepare for treatment with anti HCV. When it is available qualitative HCV RNA detection can also be used to confirm the diagnosis of HCV.

N.B. Persons who are infected with both HIV and HCV can have false-negative HCV serological test results. This may occur in up to 6% of persons withHIV.

Figure 4.2: Screening algorithm for HCV



* *For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are Immunocompromised, testing for HCV RNA can be considered.*

† *Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.*

Care of patients with HCV infection

The spectrum of disease in persons infected with chronic HCV extends from mild fibrosis to cirrhosis and HCC. Compensated cirrhosis may progress over time to decompensated cirrhosis associated with ascites, esophageal and gastric varices, and eventually to liver failure, renal failure and sepsis, all of which are life-threatening. HCC may also occur at a rate of 2–4% per year in persons with cirrhosis. The diagnosis of decompensated liver disease is based on both clinical examination and laboratory monitoring, and therefore a careful medical examination of patients must be made prior to commencing therapy. The stage of disease may be assessed using non-invasive methods using APRI and FIB4 which are validated and need only blood tests which are simple to perform.[9, 10]

In our set-up where treatment access is limited, the stage of fibrosis may be used to prioritize treatment for patients with more advanced disease (e.g. patients with cirrhosis or those with ≥F2 fibrosis based on the simple formula-APRI).

Treatment of patients with HCV infection

HCV is a now a curable disease, and advances in HCV therapy have resulted in significantly higher cure rates. Therapies can be either be classified as interferon-based or new interferon free therapies containing direct acting antivirals (DAA).DAAs have higher cure rates and which will potentially have a big impact to the public, if enough patients are treated, as it decreases incidence. Because of the high rate of side effects to interferon-based therapy, treatment with interferon-free directly acting antivirals (DAAs) is now accepted worldwide. [11]

Genotyping of HCV can be used to select different combinations of DAAs and decide on the duration of therapy. However some combinations of DAA are pan-genotypic, which can cover all genotypes with high sustained virologic response (SVR) exceeding 90% which can be given for fixed duration of 3-6months based on the type of combination of DAAs selected. Hence it is optional to determine genotype especially in countries where resources are limited and universal access is planned.

Goals of therapy

The goals of treating HCV with effective antiviral drugs are: [12]

- Viral eradication and achieving cure. The proxy indicator for cure is sustained virologic response (SVR) demonstrated by undetectable HCV RNA three months after end of therapy.
- Preventing progression of liver disease and related comorbidities and liver related death.
- Reducing the risk of hepatocellular carcinoma

Pretreatment evaluation

Detailed history and thorough examination is needed before commencing antiviral therapy for HCV. History should address: risk assessment, family status, alcohol use and risk behaviors, factors that may affect disease progression including insulin resistance, other causes of liver disease, HIV status and socioeconomic status.[13] It is recommended to look for potential drug-drug interactions. The following investigations are needed before starting therapy

- **Mandatory tests:**
    - AST and Platelet count are the only required tests for initiating patients on the recommended all-oral DAA regimens
    - Other tests required for patients with suspected advanced disease or who will be administered interferon or ribavirin containing regimens
- **Complete blood cell count (CBC)**
- **Liver enzymes and function test (AST, ALT, ALP, Bilirubin, ALB and INR)**
- **RFT (Creatinine, BUN)**
- **Quantitative HCV RNA (IU/ml)HIV and HBV screening with RDT**
- **Pregnancy test for females of Child bearing age.**
- **Optional:**
    - Genotyping (only required when pan-genotypic DAA regimen is not available)
    - Abdominal Ultrasonography to assess obvious signs of cirrhosis and complications, to exclude or look for other causes of liver disease
    - AFP if hepatic mass is detected on abdominal Ultrasonography
- **Assessing the degree of liver fibrosis and cirrhosis**

Based on availability and ease of application, non-invasive assessment of fibrosis that requires minimal resources is recommended over non- invasive tests that require more resources such as Elastography or Fibroscan or invasive way of assessing fibrosis.[9, 10]

- Preferred method of assessment of degree of fibrosis

APRI refers to ratio of liver enzyme-AST to Platelet and is a non-invasive fibrosis tests based on blood indices which will be more suitable for use in our country

APRI = [(AST(IU/L)_ULN(IU/L)X100]/Platelet count(^{109}/L)

- Alternative method of assessment of degree of fibrosis
- FIB4: (FIB4=AGE(yr)XAST(IU/L)/Platelet count(109/LX(ALT)(IU/L)1/2
- Fibroscan

Table 4.2: Low and high cut-off values for the detection of significant cirrhosis and fibrosis; (WHO. Guide lines for screening, care and treatment of persons with HCV infection, April 2014.P 60.)

	APRI(low cut-off)	APRI(high cut-off)	FIB4(low cut-off)	FIB4(high cut-off)	Transient elastography (Fibroscan)
Significant fibrosis (METAVIR ≥F2)	0.5	1.5	1.45	3.25	7-8.5kPa
Cirrhosis (METAVIR)	1.0	2.0	-	-	11-14kPa

Indication of treatment:

All chronic HCV infected individuals should be treated to eradicate the virus and achieve cure so that complications can be avoided. However It is recommended to give priority of treatment to those confirmed HCV infection (Detectable HCV RNA) and have at least one of the following:[11,15]

- Evidence of liver cirrhosis on clinical and/or imaging.
- Show worsening of liver disease while on follow up
- Evidence of advanced fibrosis based on simple formulas like APRI score ≥ 2
- Detection of clinically significant on or more extra-hepatic manifestation of HCV such as Cryo-globulinaemia, Glomerulonephritis, thyroiditis and Sjögren syndrome, insulin resistance (type-2 diabetes mellitus), Porphyria cutaneatarda and lichen planus.
- Co-infection with HBV and or HIV
- Co-existence with other known causes of liver disease such as NAFLD, Alcoholic liver disease etc.

Drug choice and duration of therapy

Treatment of HCV can be administered in three ways: interferon-based,all directly acting antiviral-based (DAA) orthrough a combination of interferon and DAAs. DAAs are all oral, well tolerated and highly efficacious. Sofosbuvir (SOF), polymerase inhibitor, is the back bone of DAA therapy and can be combined with several combinationsDAAsto improve efficacy. It is recommended to select based on: high efficacy with SVR rate of > 90%, ability to cover all genotypes especially in an area where routing genotype testing is difficult, minimal side effect profile, short duration of therapy and availability and affordability of the combinations.

According to the criteria mentioned and available most recent data, the following three DAA combinations and one Interferon and DAA combination have been selected to use in this guideline: Sofosbuvir (SOF) and Daclatasavir (DCV), Sofosbuvir and Ledivasvir (LDV) also called Harvoni in fixed drug combination, Sofosbuvir and Ribavirin (RIB) and Peglated interferon (PIFN), Sofosbuvir and Ribavirin combinations.

Genotype coverage, duration of therapy and factors affecting drug selection and treatment duration has been mentioned. (See table below: table 4.3). Available drug combination with shorter duration of therapy, low side effect, pan genotype coverage and low cost will be given priority for selection.[16-23.]

Table 4.3.: Treatment recommendations for HCV (including HCV/HIV co-infected with chronic hepatitis without cirrhosis.(Journal of Hepatology 2015 vol. 63/199 – 236)

Genotype	SOF/DCV	SOF/LDV	SOF/RIB	PIFN/SOF/RIB
1a	12 weeks	8-12 weeks	Not recommended	12 weeks
1b	12 weeks		Not recommended	12 weeks
2	12 weeks	Not recommended	12 weeks	12 weeks
3	12 weeks	Not recommended	24 weeks	12 weeks
4	12 weeks	12 weeks	Not recommended	12 weeks
5	12 weeks	12 weeks	Not recommended	12 weeks
6	12 weeks	12 weeks	Not recommended	12 weeks

Preferred combinations:

1. Sofosbuvir 400 mg oral once daily + Daclatasvir 60mg oral once daily for 12 weeks (dose of DCV be adjusted to 90 mg with Efavirenz and 30 mg with Atazanavir/r)

2. Sofosbuvir400mg oral once daily + Ledipasvir 90mg oral once daily for 12 weeks.

Alternate combinations:

1. Peglated Interferon 2a SC weekly + Sofosbuvir 400mg oral once daily + Ribavirin 1000 mg (weight < 75kg) , 1200mg (weight ≥ 75Kg) twice on divided doses for 24 weeks.

2. Sofosbuvir 400mg oral once daily + Ribavirin 1000 mg (weight < 75kg) , 1200mg (weight ≥ 75Kg) twice on divided doses for 24 weeks.

It is recommended to thoroughly evaluate Chronic HCV infected person with cirrhosis and treatment duration be decided according to the genotype, type of drug selected and addition of ribavirin.

Table 4.4.: Treatment recommendations for HCV (including HCV/HIV co-infected with chronic hepatitis and compensated cirrhosis (Child A); (Journal of Hepatology 2015 vol. 63/199 – 236)

Genotype	SOF/DCV	SOF/LDV	SOF/RIB	PIFN/SOF/ RIB
1a	weeks (12 weeks with 24 (RIB	weeks (12 weeks with 24 †(RIB	Not recom-mended	*weeks 12
1b	weeks 12		Not recom-mended	*weeks 12
2	(weeks (without RIB 12	Not recommended	weeks 16-20	*weeks 12
3	.weeks with RIB 24	Not recommended	Not recom-mended	*weeks 12
4	weeks (12 weeks with 24 (RIB	weeks (12 weeks with 24 (RIB	Not recom-mended	*weeks 12
5	weeks (12 weeks with 24 (RIB	weeks (12 weeks with 24 (RIB	Not recom-mended	*weeks 12
6	weeks (12 weeks with 24 (RIB	weeks (12 weeks with 24 (RIB	Not recom-mended	*weeks 12

† extend RIB/SOF/LDV combination to 24 weeks if there is negative predictor of response like Low platelet count < 75,000 u/ml.

* Be careful with Peglated interferon in advanced cirrhosis, it may worsen the condition.

Virological Treatment Follow up on Therapy:

Changes in viral load during therapy are used to determine if a patient is responding to treatment and to predict whether the patient is likely to eradicate the virus. In general, the earlier the HCV RNA becomes undetectable during treatment, the more likely the eradication of the virus will be achieved. The main aim of treatment is viral eradication which is equivalent to sustained Virological response defined as HCV RNA below limit of detection (< 25u/ml) 12 weeks or 24 weeks after cessation of therapy which is also called SVR12 and SVR24 respectively. Several other terms are used to describe the response to antiviral therapy in patients with chronic HCV infection.

Monitoring treatment response

Follow up quantitative or qualitative HCV RNA viral load is required to confirm if the patient has achievedSVR. This should be performed 12 weeks after the completion of therapy.

Subsequent follow up based history and physical exam, laboratory assessment of liver status and function needed for those with advanced liver disease including cirrhosis. Routine Quantitative HCV RNA follow-up measurement once SVR achieved is not recommended.

If SVR12 is not achieved:

- Refer patients to specialist
- Monitor laboratory parameters such as LFT, CBC, INR every 6-12 months,
- Re-evaluate for retreatment, determine the genotype and
- Counsel on alcohol abstinence and against use of hepatotoxic drugs.
-

Monitoring for adverse reactions

Monitor for any adverse events using clinical parameters and additional basic laboratory parameters such as Liver enzymes, complete blood count (CBC) and renal function test (RFT-BUN and Creatinine) when there is clinical clue of toxicity.

SOF is well tolerated but commonest side effect of combination of SOF/RIB, SOF/DCV or SOF/LDV is fatigue and headache.

HCV/HIV co-infection

Treatment HCV in HIV infected individuals is not different from non HIV infected or HCV mono-infected. All combination of DAA including SOF/LDV, SOF/RIB and SOF/DCV can safely be used. However attention should be given to drug-drug interaction interactions and shared side effects like head ache, fatigue and anemia.

When to Refer

Primary care Physicians who are engaged in the management ofHCV are advised to refer to specialist with experience in the management of hepatitis when there is:

- Patients with established portal hypertension or decompensated liver disease
- Patients with co-morbidities e.g. diabetics
- All non-responders (detectable HCV RNA-SVR12)
- Patients with complications while on treatment
- co-infection of HCV and HBV
- Cancer Patients on chemotherapy
- Other special groups such as pregnant women or treatment can be delayed until after birth.

Chapter Five: Diagnosis, treatment, and care for hepatitis A and E infection

Hepatitis A

Hepatitis A virus (HAV) is an RNA-containing virus of the Picornaviridae family. The key feature is that it is a self-limiting disease with no chronic infection. It induces lifelong immunity. HAV is usually transmitted fecal-orally either by person-to-person contact or ingestion of contaminated food or water.

Clinical Course

The clinical course of HAV infection varies greatly, ranging from asymptomatic, sub clinical infections to cholestatic hepatitis or fulminant liver failure. Most infections in children are either asymptomatic or unrecognized, while 70 % of adults develop clinical symptoms of hepatitis with jaundice and hepatomegaly. The incubation time ranges between 15 and 49 days with a mean of approximately 30 days.

Cases of severe fulminant HAV infection leading to hepatic failure occur more often in patients with underlying liver disease. Fulminant hepatitis can occur in 0.01-0.1 %.

Diagnosis

Diagnosis of acute HAV infection is based on the detection of anti - HAV IgM antibodies or HAV RNA.

Other supportive laboratory clues in symptomatic individuals include elevated transaminases (ALT, AST, and ALP) and elevated bilirubin levels.

- Treatment There is no specific anti-viral treatment available to date.
- Symptomatic and supportive therapy
- ICU care for few fulminant hepatic failure cases

Hepatitis E

HEV is a non-enveloped single stranded RNA virus and transmission is usually in the fecal -oral route

Clinical course

- Most have a clinically silent and self-limited course
- Rarely associated with clinical symptoms during childhood
- In symptomatic cases the incubation period ranges from 2-8 weeks with a mean of 45 days

N.B. HEV infection can lead to more sever acute liver disease in pregnant women or in patients with underlying chronic liver disease and sometimes progress to fulminant hepatic failure.

Mortality:

In epidemics mortality ranges from 0.2% - 0.4%, but mortality is higher in infants under 2 years of age and it reaches 10% to 25% in pregnant women.

Maternal mortality occurs largely in the third trimester and is caused by fulminate hepatic failure and obstetric complications such as eclampsia or hemorrhage.

Diagnosis

The diagnosis of HEV is based upon the detection of HEV in serum or stool by PCR or by the detection of IgM antibodies to HEV. In the setting of outbreaks, IgM anti-HEV has been detected by EIA in > 90 % within one week.

N.B Pregnant individuals should be tested for HEV RNA if there is suspicion that they are infected because of associated increased mortality if they develop fulminant hepatitis

Treatment

There is no available treatment capable of altering the course of acute hepatitis. Prevention is the most effective approach against the disease.

Hospitalization is required for people with fulminant hepatitis and should also be considered for symptomatic pregnant women.

Chapter Six:Diagnosis, management and preventions of hepatitis A, B and C in children

Hepatitis A virus in children

Hepatitis A (HAV): It is an RNA Picorna Virus (Rhinovirus, Enterovirus, Cocxackievirus). It is the most common type of viral hepatitis in children, comments cause of epidemic hepatitis in children and the most common cause of community acquired hepatitis throughout the world. Hepatitis A virus is estimated to affect about 10,000new cases/year in the developed world and it believed to be much more common in developing world. Its primary mode of transmission is fecal-oral. In most cases it is benign and self-limiting. Fatalities are rare and there is no carrier state. It is a vaccine preventable infectious disease.

Here is some of the facts and clinical presentation:

- Incubation period 4 -6weeks
- Prodromal phase of about one week
- Nonspecific features like fever, loss appetite, nausea, vomiting,, diarrhea, abdominal pain, cola colored urine…..
- Jaundice usually occurs within 1 – 3 weeks
- Hepatomegaly
- Liver enzymes (ALT, AST) 20 – 100 time above the upper normal
- Spontaneous resolution is seen in 99% within 2 weeks
- 1-2% acute liver failure (fulminate hepatitis)
- 1-2% Chronic Cholestatic jaundice
- As age increases the severity increases

Variants of mode of presentation of HAV:

- Relapsing course up to 1 year
- Cholestatic up to 2 years
- Immune-complex features (vasculitis, arthritis…)

Management

- **Supportive:**
  - Fluids, vitamin B complex, Start with low dose of protein(1-2gm/kg)
- **Avoiding precipitating factors:**
  - Health education on NOT administering drugs including over the counter drugs like paracetamol, herbal medicine

Prevention

- PEP (Immunoglobulin)HAV Vaccination (above 1 year of age) 2 doses 6 months apart.
- Provide HAV vaccine with integration with EPI
- For Children >12 months (Schedule at 0, 6months

Chronic Hepatitis B in Children

There are very few published studies on prevalence of hepatitis B in Ethiopian in children. A number of seroepidemilolgical studies have shown high HBV carrier rates of between 8 and 12% with a high prevalence of hepatocellular carcinoma amongst the adult population.

Transmission

In highly endemic areas, perinatal transmission remains the most important cause of chronic infection because of high rates of disease in pregnant women.

HBV in childhood is acquired as a perinatal infection (vertical mother to child transmission), although horizontal transmission can occur in toddlers especially aged 5 to 7 Years.

Clinical Picture

The presentation of chronic viral hepatitis in children tends to be sub clinical. The incubation period lasts one to four months. A serum sickness-like syndrome may develop during the prodromal period, followed by constitutional symptoms like anorexia, nausea, jaundice and right- upper-quadrant discomfort.

The symptoms like jaundice generally disappear after one to three months, but some patients have prolonged fatigue even after normalization of serum aminotransferase concentrations.

Signs of chronic liver disease such as ascites are rare in children and only manifest in the few who develop chronic liver disease and hepatocellular carcinoma.

In children who present with acute sporadic hepatitis HBV accounts for less than 20% of these cases.

The progression of acute hepatitis to chronic hepatic disease, fibrosis, and cirrhosis, and Hepatocellular carcinoma may take years and follows the typical course as shown below:

Table 6.1: Stages of chronic Hepatitis B progression in Children

Immune tolerance phase	HBV DNA levels: increased ALT levels: Normal HBeAg status: positive histology: minimal/no necroinflammation	Do not treat
Immune clearance phase	HBV DNA levels: increased ALT Levels: increased HBeAg status: positive Histology: sever necro inflammation	Consider treatment
Chronic inactive (latent) phase	HBV DNA levels: increased ALT levels: Normal HBeAg status: Negative Histology: Minimal necro inflammation (can last 10 years or more)	No treatment
Reactivation phase	HBV DNA levels: increased ALT Levels: increased HBeAg status: Negative Histology: Significant necro inflammation	Treat

Investigations

Suspect chronic Hepatitis in paediatric patients who remain HBeAg positive for more than 6 months.

The following additional tests are required:

- HBeAg status
- ALT levels
- HBV DNA levels

Drug Therapy

Chronic hepatitis B virus (HBV) infection in children presents a therapeutic challenge for the practitioner. Decisions regarding selection of patients who may benefit from treatment, appropriate timing of treatment and the choice of antiviral therapy are complex and are compounded by the limited number of drugs that have been studied in children.

There is no established benefit of treatment of children in the immune tolerant phase, and there is a very high risk of development of drug resistance. In addition, there is no indication for treatment of children in the inactive carrier state. For children in the immune active or reactivation phases, liver histology can help guide treatment decisions, and family history of liver disease, especially hepatocellular carcinoma. Children who are on treatment require careful monitoring for development of resistance.

Goals of therapy:

- Suppressing viral replicationà reduces viral load
- Reduces liver inflammationà reduces liver cirrhosis
- Decreases HBV DNA (Viral load) to undetectable level
- Durable HBeAg seroconversion
- Normalization of ALTà indicating a decrease in liver inflammation
- HBsAg seroconversion

Treatment selection criteria:

- ALT level
- HBV DNA
- Liver histology (Optional)
- Special group of children for whom treatment can be started regardless of ALT, HBV DNA and liver histology

Figure 6.1: Algorithm for selection of children for HBV antiviral treatment.

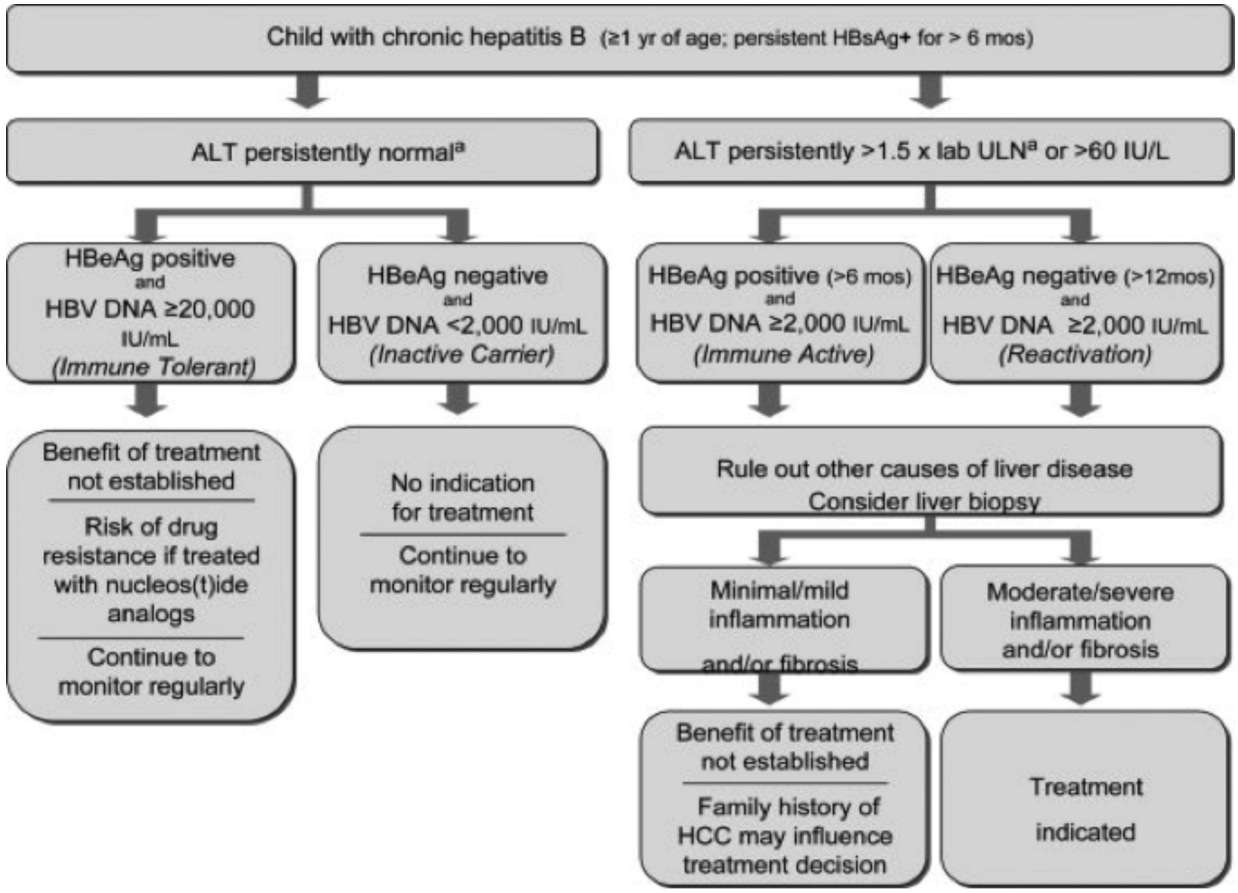


Table 6.2: HBV Treatment Guidelines

HBeAg	HBV DNA (IU/ml)*	ALT	Management
+	< 20,000	#Normal	Follow, no treatment
+	≥ 20,000	Normal	Consider biopsy; treat if diseased
+	≥ 20,000	Elevated	Treat
–	< 2,000	Normal	Follow, no treatment
–	≥ 2,000	Normal	Consider biopsy; treat if diseased
–	≥ 2,000	Elevated	Treat

N.B Liver biopsy is not an easy task in children

Special Circumstances in Which Either Temporary or Long-Term Treatment of Children with Chronic HBV Infection Should be Strongly Considered are:-

- Rapid deterioration of liver synthetic function
- Cirrhosis (compensated or decompensated)
- Glomerulonephritis due to HBV infection
- Prevention or treatment of recurrent HBV infection after liver transplantation
- Recipient of a liver graft from an anti-hepatitis B core antigen (anti-HBc)-positive donor
- Need for immunosuppression or chemotherapy
- Presence of coinfections (HBV/HIV, HBV/HCV, HBV/HDV)
- Children with a strong family history of HCC who are in the immune active phase
- Pregnant females with high viral load (>20 million IU/mL) in the third trimester, especially those who have had a previous infant with failed perinatal immunoprophylaxis

Treatment options

A conservative approach is recommended in treatment of Chronic Hepatitis B in children as experience with available drugs is not based on long term clinical trials and all available drugs are occasionally associated with severe toxicities.

IFN based Therapy: Interferon alpha

- **Licensed for use in children > 12 months of age**
- **Dose: 5-10 M units/m2 SC three times weekly**
- **Duration: 6 months**
- **It is contraindicated inpatient with cirrhosis, especially in those with decompensated liver diseases, because hepatic failure and death may be precipitated.**

Neuclos(ti)de therapy: Lamivudine/Tenofovir/ Entecavir

- **Lamivudine:**

- Lamivudine inhibits HBV DNA polymerase.
- Licensed for children> 3 years
- Dose: 3 mg/kg PO once daily (max 100mg/day)
- Duration: > 1 year

- It is most widely used and studied drug which has produced promising responses.
- However, relapse rates tend to be high after treatment is discontinued or development of resistant if it is used alone. (incidence of resistance rises from 15-32% in the first year to 67-69% by the fifth year of treatment).
- Tenofovir:
- Tenofovir is a nucleotide analogue (adenosine monophosphate) reverse-transcriptase and hepatitis B virus (HBV) polymerase inhibitor.
- Licensed for > 12 years or weigh at least 35 kg.
- Dose: 300mgs PO once daily
- Duration: > 1 year

Dosage

For HIV Infection

<2 years: Safety and efficacy not established

>2 years: 8 mg/kg PO qDay; not to exceed 300 mg/day

Hepatitis B Infection

<12 years: Safety and efficacy not established

>12 years; <35 kg: Safety and efficacy not established

>12 years; >35 kg: 300 mg PO qDay

Administration

Take with or without food

- **Entecavir:**

- A guanosine nucleoside analogue with activity against HBV polymerase, (ie, reverse transcriptase).
- Licensed: > 2 years and weigh at least 10 kg
- Dose: 0.5 mgs PO once daily
- Duration: > 1 year or + 6 months after HBeAgsero-conversion
- It is less effective for lamivudine-refractory HBV infection.
- Administer PO once daily10-11 kg: 0.15 mg (3 mL)
- >11-14 kg: 0.2 mg (4 mL)
- >14-17 kg: 0.25 mg (5 mL)
- >17-20 kg: 0.3 mg (6 mL)
- >20-23 kg: 0.35 mg (7 mL)
- 23-26 kg: 0.4 mg (8 mL)
- >26-30 kg: 0.45 mg (9 mL)
- >30 kg: 0.5 mg (10 mL oral solution or one 0.5-mg tab)

Lamivudine-experienced

Administer PO once daily

- 10-11 kg: 0.3 mg (6 mL)
- >11-14 kg: 0.4 mg (8 mL)
- >14-17 kg: 0.5 mg (10 mL)
- >17-20 kg: 0.6 mg (12 mL)
- >20-23 kg: 0.7 mg (14 mL)

- >23-26 kg: 0.8 mg (16 mL)
- >26-30 kg: 0.9 mg (18 mL)
- >30 kg: 1 mg (20 mL oral solution or one 1-mg tab)

Renal impairment

- Insufficient data exist to recommend a specific dose adjustment in pediatric patients with renal impairment
- Consider dose reductions or dosing interval increases similar to adult adjustments

Administration

- Take on empty stomach (2 hr AC or PC)
- Use oral solution for children weighing 10-30 kg
- Adefovir
- Acyclic analogue of deoxyadenoside monophosphate and inhibits amplification of circular DNA in HBV-infected hepatocytes.
- Daily for 48 weeks,

- Dosage:
- <12 years old: Not recommended
- ≥12 years old: Administer as in adults, 10 mg PO qDay

Renal Impairment

- CrCl ≥ 50 mL/min: Dose adjustment not necessary
- CrCl 30-49 mL/min: 10 mg PO q48hr
- CrCl 10-29 mL/min: 10 mg PO q72hr
- Haemodialysis: 10 mg q Week following dialysis

Interferon has limiting side effects especially hematological adverse events. However due to the resistance that is associated with oral therapy, only offer oral therapy to children who have failed interferon therapy or are intolerant to it where is IFN affordable. Life threatening flares have been reported after stoppage of oral therapy.

Treatment Monitoring

As with any therapeutic intervention, children require monitoring for adverse events while receiving treatment for chronic HBV infection.

Among the four therapies available to children, adverse events are most common in association with IFN treatment, and include fever, flu-like symptoms, fatigue, depression, thyroid dysfunction and bone marrow toxicity. Most adverse effects of IFN can be managed symptomatically, but close monitoring for bone marrow toxicity and primarily neutropenia is required with regular CBC with differential. Drug discontinuation is rarely required.

Nucleos (t) ide analogues are generally very safe, and serious sequelae such as lactic acidosis are rare.

- Adefovir may cause renal injury, and, for all of these agents, dose adjustments may be required for patients with any significant degree of renal function impairment.
- Tenofovir has been associated with decreased bone mineral density in pediatric patients treated for HIV infection, data regarding this side effect are not yet available from the adolescent HBV trial.

Post treatment flares may occur after any of the agents is discontinued, and it is prudent to check ALT at least monthly for several months after treatment is stopped, especially if HBeAgsero-conversion has not yet been achieved.

Primary nonresponse or partial response to HBV antiviral treatment can be related to pharmacologic factors, such as the level of antiviral potency of the drug and the drug's intrinsic barrier to resistance, viral factors, such as viral level and presence of resistance mutations, or to host factors such as variations in individual drug metabolism or patient compliance. Primary nonresponse is characterized by a <1 $\log_{10}$ decrease in viral load after 3 months of treatment. In non-responders, HBV genotypic testing for resistance may be useful to help differentiate between patient noncompliance and viral genotypic resistance.

Management of HCV in children

Facts about HCV in children

- Estimated 170,000,000 infected people worldwide (~ 3% of world population)à 0.1-3% in children
- Risk of chronicity: 55% – 85%
- Risk of cirrhosis: 20% within 20 years, 30% within 30 years
- Cirrhosis-related mortality: 2% – 5% / year
- Incidence of liver cancer: 3% – 10% / year among patients with cirrhosis
- HCV is curable
- No vaccine

Diagnosis of HCV: (similar with the adults)

- Anti HCV antibody
- HCV RNA(Viral load)
- Liver enzymes
- Liver biopsy
- Genotyping

Treatment

Goals of treatment

- Cure HCV (sustainable elimination of the virus)
- Avoiding extrahepatic manifestations like glomerulonephritis

Treatment options:

- Depends on genotypes
- Always dual therapy: Interferon + Ribavirin (Mentioned in the adult guideline on how and when)
- New drugs (Boceprevir and Telaprevir) resulting an excellent success

Chapter Seven:Program management of viral hepatitis

Introduction

In Ethiopia, the interventions proposed for the prevention and control of viral hepatitis will be carried out in a phased approach. The FMOH in collaboration with RHB and partners will prioritize activities that need to be implemented at all levels of the health system. Even though some key public health interventions necessary for the prevention and control of viral hepatitis already exist, standardized national guidelines are necessary to guide effective implementation. Besides, there are new interventions that require introduction of brand new essential medicines, medical technologies and/or supplies that necessitate additional programmatic directions and clinical guidelines.

Successful implementation of the national action plan on Viral Hepatitis will require involvement of all stakeholders, coordination of various activities implemented by the different stakeholders, resource mobilization and political commitment at each level of the government and health system. Accordingly, the FMOH will liaise for key activities with concerned bodies and coordinate efforts both at the national level while RHBs coordinate efforts at regional level. Resources must be allocated based on need and priority and must ensure equity so as to provide interventions and services to high risk and vulnerable populations in need of viral hepatitis related services.

Goal

To reduce morbidity and mortality related to Viral Hepatitis and mitigate the impact resulted from the silent epidemic of viral hepatitis.

Key engagement areas

In order to achieve the above mentioned goal the program will implement be the following key interventions:

A. Health Promotion and Prevention of Transmission

1. Health Education: Behaviour Change Communication/ Information Education Communication (BCC/IEC)

Educating both health providers and communities is the most important part of the viral hepatitis prevention strategies. Health workers shall be fully aware of the epidemiology and burden of viral hepatitis as well the current evidence based prevention and treatment strategies that are available. Subsequently, health workers need to educate communities and individuals on the risks of infection, methods of prevention and on available diagnosis, treatment and care technologies. This task primarily will be delivered within the structure of the primary healthcare system. Health extension workers will have a pivotal role in delivering health messages to individuals and families, whereas, health workers in health centers and hospitals while providing health education on a daily basis and to each of their encounters are also entitled to deliver health services such as screening, vaccination, diagnosis, treatment and care. The FMOH in collaboration with concerned stakeholders will develop health promotional strategies and messages, distribute to end users and monitor and evaluate effectiveness of these messages accordingly. Therefore, IEC and BCC materials on risks of viral hepatitis, methods of prevention and on available health services should be produced in sufficient quantities for distribution to all implementing partners. Various materials (e.g., posters, flipcharts, brochures, leaflets, fliers) should be developed or adapted for local use. If possible audio and video cassettes should be used as sources of practical information for different stakeholders. Arrangements should be made with the appropriate media organizations to broadcast messages on viral hepatitis.

2. Non-vaccine prevention of viral hepatitis

Some of the prevention and control strategies of viral hepatitis already exist. Such as promotion of hygiene, promotion of safe sex, infection control in health care settings, blood transfusion safety and ensuring injection safety through infection prevention in the healthcare setting. But integration and

additional evidence based interventions into the already existing system is important. But, all might need coordination, renovation and collaboration among the different departments and stakeholders. It is clear that, these control strategies have positive public health benefits, not only in terms of hepatitis control, but also for other blood borne and water borne infections, such as HIV/AIDS and diarrhoeal diseases. FMOH will ensure integration of these activities within the different programs in the FMOH, RHBs and other stakeholders.

3. Vaccination for Viral hepatitis

Among the different serotypes of viral hepatitis; vaccines have been developed and are available to prevent HBV and HAV infection and proven effective in countries where the vaccines are introduced. In Ethiopia vaccine for hepatitis B virus has already been introduced within the EPI package. However, other risk groups of public health importance did not have access to this vaccine yet. Therefore a stepwise approach will be used to introduce HBV immunization among the different risk groups based on priorities of public health importance and available resources. Accordingly in the first two years (2015 & 2016) of the program HBV vaccine will be introduced among healthcare providers (both private and public) and for students of future healthcare professionals. This will be followed by non-health professionals working inside health facilities. Other risk groups like pregnant women, children of 1 – 5 years and older children of less than 15 years etc will be considered in the due time.

B. Clinical Service Delivery

Individuals that are infected with viral hepatitis will have access to screening, diagnosis, and treatment services during the acute and chronic stage of infection. The routine provision of screening, diagnosis, and treatment and care services rests on health facilities.

The clinical care/service will be provided primarily in hospital settings and it will be integrated with other diseases. The treatment of viral hepatitis should be made by trained health care workers. Health centers are expected to refer suspected individuals to the nearby hospital for screening, diagnoses and treatment of viral hepatitis.

Health workers are expected to follow the national guidelines on prevention and treatments of viral hepatitis.

C. Human resource development

There should be a continuous training of health professionals. A national training manual for the prevention and control of viral hepatitis should be developed and used for training of health care professionals. A standalone training manual will be used for viral hepatitis till the program matures. Clinical mentoring and supportive supervision should be part of capacity building activities especially during the time of service initiation in hospitals. Job aids that containing information about strength and dosage of individual drugs and other treatment and prevention packages will be available.

Training manuals should be prepared tailored to the knowledge and skill of various levels of healthcare cadre. Pre-placement training will also be used as a means of capacity building of health professionals.

D. Supply Chain and Procurement

FMOH will ensure the availability and use of drugs, vaccine and diagnostics. In collaboration with PFSA, FMOH will build viral hepatitis treatment into existing procurement and supply chain systems to ensure adequate supply of commodities.

E. Resource mobilization

Adequate financing is important for effective and sustainable viral hepatitis service. FMOH will make the appropriate costing of strategic plan for prevention and control of viral hepatitis and mobilize resources from GOs, NGOs and other development partners. The national health insurance plan currently being rolled out will be a strong platform to push the scale up of viral hepatitis service delivery and ensure its sustainability.

F. Ethics and Human rights

Voluntary Participation: Any screening or testing of individuals for hepatitis B or C viruses should be voluntary and consent based. The respect of the individual's dignity and freedom and their right to confidentiality should be ensured. Coercion of any kind must be avoided and the disclosure of results must be strictly confidential.

Confidentiality: All information obtained from patients in the process of screening for hepatitis-B & C viruses, or any other STI should be treated with confidentiality

Anonymity: samples that are used for anonymous screening do not need patient consent, but in this case, all samples should be coded and the use of patient names should be avoided.

Informed Consent: Samples for screening of hepatitis-B or C virus should be obtained with the consent of the patients.

Developed countries have a clear policy on health care workers who become positive on screening for HBV. They recommend prevention of HBV from HCW to patients first of all by vaccination of health care workers (HCW) regardless of their HBV status and by implementation of universal precautions for infection control. Also, it recommends that HBV carriers among HCW have to be identified by testing all medical personnel and medical students prior their entering a medical school or start of work. HCW who are not vaccinated or are non-responders to vaccine should be frequently tested for possible infection during their career. HBeAg-positive HBV carriers should be recommended not to start a career in the health care system or, at least, to select a type of work where the risk of transmission is minimal or absent.

In Ethiopia HBV immunization without prior testing for HBsAg will be provided to all health workers and recruits of healthcare workers on training. And thorough program support will be provided to ensure implementation of universal precaution and high level infection prevention in the healthcare setting.

The 2014 WHO guidelines for prevention and treatment of hepatitis C underscores importance of the protection of human rights for all persons infected with HCV as a central precept of the guidelines. It also states that people with HCV infection frequently come from vulnerable groups because of low socioeconomic status, poor access to appropriate health care, or because they belong to groups that are marginalized or stigmatized such as PWID or prisoners. Thus, screening for HCV must not be used as a means to discriminate against those testing positive, for example, by denying them employment or education. The promotion of human rights and equity in access to testing and treatment are guiding principles central to these guidelines.

Thus, screening of general population and HCW for HBV in our setting needs to be conducted in such a way that the affected groups will benefit from it and it doesn't pose risk of unemployment for HCW. However HCW who become positive on screening can be advised to work in departments where parenteral transmission to patients is less risky.

Roles and responsibilities and coordination

The viral hepatitis program will be managed and coordinated at different levels of the health system: The Federal Ministry of Health (FMOH), regional health bureaus, zonal health offices and district health offices will have different areas of work and responsibilities in the prevention and control of viral hepatitis. All of them have the responsibility to ensure integration of viral hepatitis prevention and control in to the existing programs.

National level

The FMOH is responsible for setting standards, developing and revising national guidelines, preparing national action plans including target setting, mobilizing resources necessary capacity-building, monitoring and evaluation, advocacy and operational research, and for overseeing overall national coordination of the viral hepatitis programme.

Within the FMOH, different specialized agencies and directorates play key roles in implementation of the viral hepatitis programme. Coordination of these bodies is crucial for effective and efficient programme implementation and improves quality of services.

At the federal level team of experts and key implementers on viral hepatitis are organized into a TAG to advise the ministry on key policy formulations, provide technical guidance on evidence based recommendations, and propose possible solutions for implementation challenges. The TAG meets regularly on defined intervals.

Regional level

RHBs take the technical guidance from the MoH to implement interventions on the prevention and control viral of hepatitis in their own regional context. The RHBs therefore, are in charge of planning, implementing, coordinating monitoring and evaluation of the viral hepatitis program in the regions.

PFSA

Strong procurement Supply management is important to ensure sustainable supplies and responsive viral hepatitis program. The FMoH in close collaboration with PFSA will do regular quantifications of necessary commodities for prevention and control service delivery. PFSA will also coordinate the quantification, procurement and distribution of the necessary commodities by integrating into existing supply chain management system. Reporting and requisition formats will be updated to incorporate commodities needed for viral hepatitis. PFSA in collaboration with FMoH and other stakeholders will be in charge of developing orientation training manual and delivering the training for facility level dispensers.

EPHI

Setting up functional diagnostic systems/platforms for viral hepatitis at various levels will speed scale up of the program. EPHI will lead the development and revision of training manual as well as provision of training for laboratory professionals. EPHI with its regional reference laboratories will work to build the diagnostic capacities at facility level. In addition EPHI will put a mechanism for EQA by integrating into existing quality assurance mechanisms. EPHI in collaboration with FMoH will conduct operational research as needed.

FMHACA

Drug therapy for viral hepatitis especially HBV and HCV is a newly evolved global phenomenon. Accordingly, most drugs are new to Ethiopia and in most cases are not registered/ licensed in the country. The FMOH in collaboration to FMHACA will take the necessary steps so as to enlist these drugs within the national drug list and approval of their use as per the recommendation of the national guideline.

Regional laboratories

Regional laboratories will be in charge of conducting EQA within the facilities in collaboration with EPHI. They will also build the capacity of health care providers.

Hospitals

Treatment of viral hepatitis will be started in selected hospitals at the beginning and it will be scaled up in time to involve other hospitals. The selected hospitals are in charge of providing care and treatment services for viral hepatitis.

Health centres

Health centers will play a critical role in prevention and care of viral hepatitis through:

- Targeted routine screening
- Referral of suspected or diagnosed cases for further work up and treatment
- Roll out the vaccination/immunization as per national recommendations
- Create an awareness in the community on prevention and health seeking behavior for viral hepatitis in close collaboration with health posts
- Implement BCC/IEC part of the national guideline

Health posts/Community

- HEW in collaboration with HDA create an awareness in the community on key preventive intervention for viral hepatitis
- Implement BCC/IEC part of the national response to hepatitis

Development partners

- Provide the necessary technical and financial assistance to FMoH in the national response. And participate in strengthen capacity of governments at all level and other stakeholders to effectively implement the national and response.
- Enhance local and international resource mobilization and build technical and institutional capacities to sustain effective and efficient national response.
- Ensure their contributions are aligned with the national and regional responses.

Private health Sector:

The role of private sector in the prevention and treatment of viral hepatitis will be of paramount importance. Private sectors should be proactively involved in the development and implementation of national viral hepatitis guidelines and strategic documents. Private health institutions should adhere to the diagnostic and treatment standard as mentioned in the national guidelines while providing their services.

Monitoring and evaluation

A. Health facility recording and reporting

Selected viral hepatitis indicators will be incorporated into the national HMIS. Health facilities will be required to collect, compile and report these indicators through the relevant administrative level as per the reporting period.

B. Supportive Supervision

Ongoing supportive supervision will be an important component of the M&E of the viral hepatitis program. Supportive supervision is a process that promotes quality at all levels of the system by strengthening relationships within the system, focusing on the identification and resolution of problems, and helping to optimize the allocation of resources. Thus, periodical supportive supervision activities will be carried out at each level that are involved in the prevention and control of viral hepatitis.

C. Surveillances and Surveys

Efforts will be made to establish and integrate viral hepatitis surveillance system based on the availability of resources. Periodical surveys will be conducted both at a facility and population level in order to understand the level of viral hepatitis and effectiveness of interventions.

D. Research and Development

FMOH in collaboration with EPHI will encourage efforts to generate further evidences that shape and contribute to the national prevention and control of viral hepatitis. Ongoing basic, social and operational researches are important through coordinated manner and aligned with national research ethics.

E. Key indicators for viral Hepatitis program

Program Structure	Indicators	Source of data	Important assumptions
Goal	Prevalence of hepatitis B&C	Survey	
Inputs	1) Proportion of facilities providing screening services for hepatitis B&C 2) Proportion of facilities providing treatment services for hepatitis B&C	Service data/Admin report	
Outputs	1) Proportion of eligible individuals screened for hepatitis B&C 2) Proportion of individuals screened and tested positive for hepatitis B&C 3) Proportion of individuals treated for hepatitis B&C 4) Percentage of targeted risk groups get vaccination for Hepatitis B 5) Coverage of the birth dose and 6) Coverage of 3-doses of hepatitis B vaccine	HMIS…proposes	
Outcomes	1) Serological surveys of HBsAg prevalence 2) HB associated mortality data	Survey Vital registration?	

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