Republic of Ghana

NATIONAL GUIDELINES FOR PREVENTION, CARE AND TREATMENT OF VIRAL HEPATITIS

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GHANA HEALTH SERVICE
Your Health Our Concern

MINISTRY OF HEALTH

NATIONAL GUIDELINES FOR PREVENTION, CARE AND TREATMENT OF VIRAL HEPATITIS

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Viral hepatitis is an inflammation of the liver caused by viruses. The common causes of viral hepatitis include the five unrelated hepatotropic viruses, namely Hepatitis A, B, C, D, and E. Hepatitis A and E viruses typically cause acute and self-limiting infections. Hepatitis B and C (HBV and HCV) infections may progress into chronicity.

Viral Hepatitis has become a major public health problem in Ghana. Globally Ghana is considered a high prevalence country for both chronic hepatitis B (HBV) (≥8%) and chronic hepatitis C (HCV) (5-10%) virus infections. HBV and HCV are currently the most important viral hepatitis in Ghana because they cause chronic infections. Infection is associated with increased risk of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC). The latter is one of the commonest cancers in the country and with a high mortality. Suppression of HBV and HCV leads to reduction or delay in the development of cirrhosis and hepatocellular carcinoma (HCC).

These guidelines was adapted from the World Health Organization (WHO) and other internationally accepted guidelines for prevention, care and treatment for Viral Hepatitis. It covers the management of five different types of viral hepatitis namely; Acute Viral Hepatitis A, B, C, D and E and Chronic Hepatitis B and C.

These Guidelines are primarily intended for the use of all healthcare workers including clinicians, nurses, pharmacist, laboratory personnel, disease control and surveillance officers, public health experts etc. working at all levels of the healthcare delivery system (from Community-Based Health Planning and Services (CHPS) to Tertiary level).

The purpose of these guidelines is to provide evidence based step by step instructions for healthcare workers required in the prevention, detection and reporting, care and treatment of viral hepatitis cases.

I will therefore entreat all health workers to study and use these guidelines in order to reduce the disease burden of viral hepatitis on the populace of Ghana.

Hon. Kwaku Agyeman-Manu
Minister of Health

PREFACE

These treatment guidelines have been revised in collaboration with Hepatitis Society of Ghana (HepSoG) in line with current information. Several newer drugs since the last edition, have expanded the scope of treatment, however some of these are not yet available in Ghana.

Ghana is also yet to embark on any organized therapy countrywide. Hopefully this situation will change with time. Co-infection is recognized as a growing problem with important implications on management. These guidelines will assist clinicians in managing patients with viral hepatitis, in particular chronic hepatitis B and C.

Dr Kofi N. Nkrumah

(President of Hepatitis Society of Ghana).

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ABBREVIATIONS AND ACRONYMS

Ag	Antigen
ALT	Alamine aminotransferase
anti-HAV	Antibody against hepatitis A virus
anti-HBc	Antibody against hepatitis B core antigen
anti-HCV	Antibody against hepatitis C virus
anti-HEV	Antibody against hepatitis E virus
ANC	Antenatal care
APRI Score	Aminotransferase/platelet ratio index
AST	Aspartate Aminotransferase
ART	Antiretroviral Therapy
ARV	Antiretroviral
BUE and Cr	Blood Urea, Electrolytes and Creatinine
CHPS	Community-Based Health Planning and Services
CCTH	Cape Coast Teaching Hospital
CMV	Cytomegalovirus
CHB	Chronic hepatitis B
CKD	Chronic Kidney Disease
CIF	Case-based Investigation Form
DAA	Direct-acting antiviral (drugs)
DDCC	Deputy Director Clinical Care

ABBREVIATIONS AND ACRONYMS

DDI	Drug-drug Interactions
DHIMS	District Health Information Management System
DPT-HepB-Hib	Diphtheria-Tetanus-Pertussis-Hepatitis B-Haemophilus Influenzae type b Vaccine
DPM	Deputy Programme Manager
DSD	Disease Surveillance Department
EPI	Expanded Programme on Immunization
FBC	Full Blood Count
FDA	Food and Drugs Authority
FIB-4	Fibrosis-4 Score
GHS	Ghana Health Service
gGT	gamma glutamine transpeptidase
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HBcIgG	Hepatitis B core Immunoglobulin G
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HCC	Hepatocellular carcinoma
HEV	Hepatitis E virus
HCW	Health Care Worker

ABBREVIATIONS AND ACRONYMS

HELLP Syndrome	H (Haemolysis), EL (Elevated Liver enzymes) LP (Low Platelets)
HIV	Human Immunodeficiency Virus
HPD	Health Promotion Division
ICD	Institutional Care Division
IDSR	Integrated Disease Surveillance and Response
Ig	Immunoglobulin
IgM	Immunoglobulin M
IgG	Immunoglobulin G
KATH	Komfo Anokye Teaching Hospital
KBTH	Korle-Bu Teaching Hospital
LFT	Liver Function Test
MoH	Ministry of Health
NCD	Non-Communicable Disease
NHIA	National Health Insurance Authority
NMIMR	Noguchi Medical Institute of Medical Research
NPHRL	National Public Health and Reference Laboratory
NAs	Nucleos(t)ide Analogues
NVHCP	National Viral Hepatitis Control Programme
OEHU	Occupational and Environmental Health Unit
PWID	Persons who inject drugs
PHD	Public Health Division

PMTCT	Prevention of Mother to Child Transmission
PLHIV	People Living with HIV
PM	Programme Manager
PRO	Public Relations Officer
PNO	Principal Nursing Officer
PHU	Public Health Unit
SPH	School of Public Health
SVR	Sustained Virological Response
ULN	Upper Limit of Normal
RNA	Ribonucleic acid
TB	Tuberculosis
VL	Viral Load
WHO	World Health Organization

1. INTRODUCTION

1.1 Background

Hepatitis (plural:hepatitides) is inflammation of the liver characterized by the presence of inflammatory cells in the liver. Hepatitis can be caused by infectious or non-infectious agents or substances such as viruses, bacteria, toxins, drugs, and alcohol use. Viral hepatitis is inflammation of the liver caused by viruses. Viral Hepatitis is commonly caused by one of several viruses[2,3,4]. The commonest causes of viral hepatitis include the five unrelated hepatotropic viruses, namely; Hepatitis A, B, C, D and E. In addition to the nominal hepatitis viruses, other viruses that can also cause liver inflammation include Herpes simplex, Cytomegalovirus (CMV), Epstein-Barr virus, Yellow fever virus, Coxsackie viruses and Adenovirus among others[2, 3, 4]. Hepatitis A and E viruses typically cause acute and self-limiting infections. Hepatitis B and C (HBV and HCV) infections may progress into chronicity with long term sequelae. HBV and HCV are currently the most important viral hepatitides in Ghana because they cause chronic infections. Both may be acquired in childhood and any time thereafter. Infection is associated with increased risk of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC). The latter is one of the commonest cancers in the country and has a high mortality. Suppression of HBV and HCV leads to reduction or delay in the development of cirrhosis and hepatocellular carcinoma (HCC). The introduction of standard interferon (alpha -2a & 2b) monotherapy in 1992 marked the beginning of drug therapy in Ghana, although the overall response was low. Subsequently, several other molecules have been developed all in attempt to improve response.

1.2 Scope and Objectives

The general objectives of these guidelines is to provide evidence based step by step instructions for healthcare workers required in the prevention, detection and reporting, care and treatment of viral hepatitis. These guidelines cover the management of five different types of viral hepatitis namely; acute viral hepatitis A, B, C, D and E and chronic viral hepatitis B and C.The specific objectives are:

- To provide measures required in prevention of viral hepatitis
- To provide steps in early detection and response to viral hepatitis cases
- To provide guidance in the care and treatment for all persons living with chronic viral hepatitis B and C

1.3 Applicability of the Guidelines

These Guidelines are primarily intended for the use of all healthcare workers including clinicians, nurses, pharmacist, laboratory personnel, disease control and surveillance officers, public health experts etc. working at all levels of the healthcare delivery system (from Community-Based Health Planning and Services (CHPS) to Tertiary level).

1.4 Epidemiology

Viral hepatitis has become a major public health concern globally. Over 3 billion people world-wide are exposed to the infection yearly. Hepatitis B and C are major causes of cirrhosis and liver cancer and the second leading cause of cancer death in the world. The Global Burden of Disease study estimates that approximately 1.46 million persons die each year from viral hepatitis [4], most of these from hepatocellular carcinoma (HCC) and cirrhosis

secondary to chronic hepatitis B and C [4, 5]. Systematic reviews of biomarker surveys suggest that approximately 240 million persons live with chronic hepatitis B, and between 130 and 150 million live with chronic hepatitis C [6,7]. Hepatitis A and E also contribute to mortality through fulminant disease (14,900 and 52,100 annual deaths, respectively) [4].

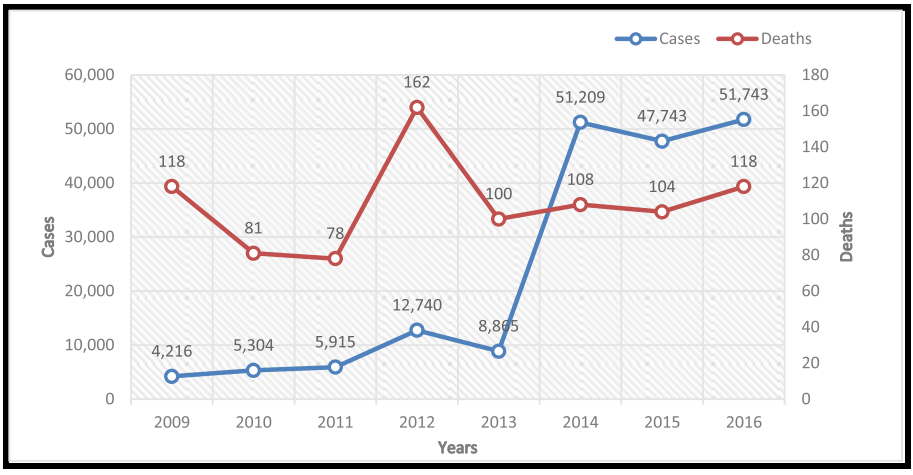
Unfortunately, most persons with chronic viral hepatitis are unaware of their infections and may present late with complications. Viral Hepatitis has become a major public health problem in Ghana. Surveillance data on clinical viral hepatitis from the Disease Surveillance Department (using the Integrated Disease Surveillance and Response (IDSR) standard case definition for viral hepatitis) shows an increasing annual trend of reported clinical viral hepatitis cases from all the ten regions of Ghana[1] (Figure 1).

Globally Ghana is considered a high prevalence country for both chronic hepatitis B (HBV) [≥8% [2]] and chronic hepatitis C (HCV) [5-10% [3]] virus infections. Recent studies have revealed HCV sero-prevalence rates of 2.8% to 5.4% in Ghana [12,14].

The seroprevalence of HCV is between 1·3 and 8·4 % among blood donors in Ghana[14, 17, 18], 5·4 % among children in a rural district in Ghana[20] and 2·5 % among parturient in Accra, Ghana[22].

The risk of developing cirrhosis increased 8-fold in patients with HBV infections than those without [21]. Hepatitis E (HEV) sero-prevelance was 28.66% (45/157) among pregnant women seen between the months of January and May, 2008 at the Obstetrics and Gynaecology Department, Korle-Bu Teaching Hospital, Accra, Ghana [13].

Figure 1: Annual Trend of Reported Acute Viral Hepatitis Cases and Deaths; Ghana, 2009-2016



Source: DHIMS GHS, 2016

1.5 Risk Factors for Viral Hepatitis

1.5.1 Risk factors for Viral Hepatitis A and E

- Over-populated communities (slum and refugees camps) characterized by poor sanitation and use of unsafe drinking water
- Poor personal hygiene (low soap utilization, or poor hand washing practices)
- Poor food hygiene
- Floods leading to contamination of domestic water sources
- Broken down water and waste disposal systems
- Open defecation

1.5.2 Risk Factors for Viral Hepatitis B, C and D

- High-risk sexual behaviour;
    - Persons with multiple sexual partners
    - Commercial sex workers
    - Men having sex with men
    - Unsafe sex practices
- Non-immune partners and household contacts of HBV infected persons
- Intravenous and percutaneous drug use e.g. Injection Drug Users
- Individuals in prisons and persons born in countries with high rates of endemic disease.
- Persons who frequently require blood or blood products e.g. regular renal dialysis patient, sickle cell patients
- Recipients of solid organ transplantation
- Those at occupational risk of HBV infection, including health care workers; and international travelers to countries with high rates of HBV
- Practices such as scarification, bloodletting, circumcision with unsterile instruments, tattooing and body piercing.

1.6 Mode of Transmission of Viral Hepatitis

Hepatitis A and E viruses are transmitted primarily by the faecal-oral route, that is, when an uninfected person ingest food or water that has been contaminated with the faecal matter of an infected person. The virus can also be transmitted through close physical contact of an infected person.

Hepatitis B, C and D viruses are transmitted by exposure to blood and various body fluids. This may be through;

i. Percutaneous or mucosal exposure to infected blood, blood products or body fluids (vaginal fluids, seminal fluids, menstrual fluids)

This can happen through;

- Un-protected sexual contact with an infected person, either heterosexual or homosexual.
- Direct contact with infected or contaminated blood
- Use of contaminated sharps, needles and syringes, e.g. shared needles in drug abusers
- Circumcision with unsterilized instruments
- Tattooing, body piercing, sharing razors
- Sharing personal items, such as toothbrushes, razors, syringes
- Direct contact with open sores of an infected person

ii. An infected mother passing it to her baby at birth (mother to child transmission); an important route of transmission in Ghana.

iii. Horizontal transmission (exposure to infected blood) especially from an infected child to an un- infected child during the first 5 years of life. This may occur through biting and scratching when young children are playing together.

iv. Transfusion with contaminated blood and other blood products (This is less likely now that blood donors are screened)

Modes of transmission for HBV are the same for the human immuno-deficiency virus (HIV), but HBV is 50 to 100 times more infectious. Unlike HIV, HBV can survive outside the body for at least 7 days. During that time, the virus can still cause infection if it enters the broken skin or mucosal lining of a person who is not infected.

1.6 Clinical Presentation

The presentation of Viral Hepatitis can be in two forms namely; Acute and Chronic. Viral Hepatitis is defined as acute when it lasts less than six months and chronic when it persists longer.

The clinical presentation of acute hepatitis is similar for all five viruses. It ranges from the absence of symptoms to mild or moderate features such as jaundice, poor appetite and malaise. In a minority of cases it may result in fulminant hepatitis with a potentially fatal outcome.

Non-specific features are flu-like symptoms, common to almost all acute viral infections and may include malaise, muscle and joint aches, fever, nausea or vomiting, diarrhea, and headache.

More specific features include profound loss of appetite, jaundice (yellowing of the skin and eyes), dark urine and abdominal discomfort.

Less common features are tender hepatomegaly, lymphadenopathy and splenomegaly. Acute viral hepatitis is more likely to be asymptomatic in children. Majority become chronic. Only 30% to 50% of adults develop significant symptoms during acute infection.

2.0 PREVENTIVE MEASURES FOR VIRAL HEPATITIS

2.1 Prevention of Hepatitis A and E

- The following intervention areas should be implemented to prevent acquiring Viral Hepatitis A and E;
    - Vaccination
    - Regular hand washing with soap under safe running water; before eating, after visiting the wash room and before cooking
    - Drink safe water , Practice good sanitation and personal hygiene
    - Safe food handling and hygiene practice; eat food whilst hot, wash plates and cutleries with safe water and soap before use.

2.2 Prevention of Viral Hepatitis B, C and D

The following intervention areas should be implemented to prevent acquiring Viral Hepatitis B, C and D.

1) Vaccination

1a) Vaccination against Hepatitis B (No Vaccine for Hepatitis C)

Vaccination is recommended for the non-infected (No detectable HBsAg), and non-immune patients (No detectable Anti-HBs) and all infants.

1b) Hepatitis B Vaccination schedule

- **For adults:** Three doses of hepatitis B vaccine given 0,1 and 6 months interval
- **For Children:** Four doses of Hepatitis B vaccine given at 0 (at birth),1,16 and 24 months

1c) Persons eligible for Hepatitis B vaccination

The following categories of persons should be vaccinated with hepatitis B vaccine;

- All new-born infants should be given birth dose of hepatitis B vaccine. Continue with three doses as part of routine childhood immunization at child welfare clinics starting from six weeks as part of DPT-HepB-Hib vaccine

- Infants born to HBsAg positive women. Hepatitis B immuno-globulin should also be added (Prevention of Mother to Child Transmission (PMTCT) of Hepatitis B infection)

- At risk populations such as health workers (including trainee students and newly recruited staff), partners and household members of Hepatitis B positive persons should be screened and those negative for hepatitis B vaccinated.

- All people in hyper endemic areas

2) Practice safe sex

- Use condoms appropriately. Avoid multiple partners

3) Blood safety

- All blood should be screened for Hepatitis B and C before transfusion

4) Infection Prevention and control measures

- Process all instruments/sharps (by decontamination with 0.5% chlorine solution, cleaning and high level decontamination or sterilization) before use at all health and non-health facilities. (Refer to Ministry of Health Infection Prevention and Control Policy guidelines, 2015).

- Practice safe injections, use only sterile needles and syringes.
- Avoid sharing sharps (blades, needles and syringes) and tooth brushes etc with others.

5) Organize regular health promotion activities to educate the population on preventive measures of viral hepatitis.

See Annex 8: Sample Messages on Viral Hepatitis for use during health talks on radio, television, community durburs, health facilities e.t.c

2.3 Role of diet and healthy lifestyle in preventing hepatitis

Eating balanced diet including lots of fruits and vegetables protects the liver. Agents that damage the liver such as alcohol and smoking are particularly harmful in patients who already have hepatitis. For this reason, it is recommended that persons with viral hepatitis should avoid drinking alcohol and smoking.

2.4 Screening

Periodic mass screening of persons at risk for viral hepatitis especially viral hepatitis B and C should be conducted. This will enable early detection of persons with viral hepatitis B and C, so as to institute early preventive measures to forestall the patients from acquiring liver cirrhosis and hepatocellular carcinoma. The screening also prevents transmission of viral hepatitis infection.

2.4.1 Who to conduct screening

A team of trained health care professionals working in accredited public and private health institutions should be deployed to conduct screening exercises.

The team should include; Doctors (Gastroenterologist, Medical Officers), Physician Assistants, Clinical Nurses, Public Health Nurses/Community Health Nurses, Pharmacist, Laboratory Technicians/Biomedical Scientists and Epidemiologist/Disease Control Officers.

2.4.2 Eligibility criteria for screening

Planned periodic mass screening of special populations at risk e.g. schools, churches, prisons, commercial sex workers should be conducted.

The following persons should be screened for Hepatitis B and C routinely:

- All health care professionals (additionally pre-employment and exit screening would be required)
- All health care trainees
- All pregnant women reporting at ante-natal care
- Pre-school children and before hepatitis B vaccination
- All blood donors, donated blood, body fluid, tissue or organ
- All suspected cases reporting to health facilities
- Patients with haemoglobinopathies

- Any person offering to be screened (voluntary screening)
- Routine medical examination
- Patient with abnormal liver function tests (LFT's) particularly elevated ALT of unknown cause
- Patients with cirrhosis, or suspected hepatocellular carcinoma (HCC)
- Spouses or children or first degree relatives of HBsAg or anti-HCV positive patients
- HIV and HCV positive patients
- Patients with an Acute kidney injury or Chronic kidney disease (CKD) patients, especially if haemodialysis is planned

The following persons should be screened for Hepatitis A and E routinely:

- All Food Vendors before issuing certificates
- Persons working in food processing industries before issuing certificates
- Day-care employees and families of children in day-care
- Participants in oro-anal sex
- Pregnant women (mostly for Hepatitis E)

2.4.3 Screening Procedures

The screening should be conducted for individuals reporting to a health facility or a mass group of population. A screening centre should be established at all the medical health facilities and manned by trained health professionals for routine screening of individuals reporting to the health facilities. The request for individual(s) screening should be done by the attending clinician (doctor, physician assistant etc.) who has established the eligibility of the individual(s) for the screening. However, for mass screening, a screening centre should be set-up close to the selected population to be screened e.g. School Park, conference halls, etc.

The screening centre should be manned by trained health professionals. Before a mass screening exercise is conducted, an awareness creation activities should be conducted among the population group selected for the screening. This can be done in the form of information, education and communication through the mass media, posters/leaflets, durbars etc. in and around the selected area/premises of the selected population.

Pre-and-post screening counselling

All persons should be counselled before and after screening. It is important that clients or patients are fully informed, in simple comprehensible language in the following areas:

- The main mode of transmission, possibility of transmission to non-immune spouse, children and close household relatives
- Health implications of chronic hepatitis B and C infection
- Reassure that not all will develop complications

- Avoidance of certain health risks e.g. Alcohol use, unprotected indiscriminate sex
- Vaccination of non-immune partner and household
- Stress on long term follow up if positive

Screening Logistics

The following logistics are required for screening;

- Adequate infection prevention and control materials such as gloves, disinfectants etc.
- WHO pre-qualified testing kits and reagents (Refer to Section 4; Laboratory Diagnosis of Viral Hepatitis)
- Viral Hepatitis Case Investigation Form (CIF) and line listing form to capture information on all persons screened (Refer to Section 3.5; Data management and Reporting).
- Hepatitis A, B and E vaccines. Only Persons who test negative should be vaccinated
- Designated treatment centres: All persons who test positive should be referred to health facilities for care and treatment (Refer to Section 5; Care and Treatment for Viral Hepatitis)

Steps in screening

Step 1: The individual is first counselled by the Counsellor (pre-test counselling) and the CIF/Line Listing form is completed by the Disease Control Officer

Step 2: The individual now goes for blood sample collection and testing by the Laboratory Technician/Biomedical Scientist

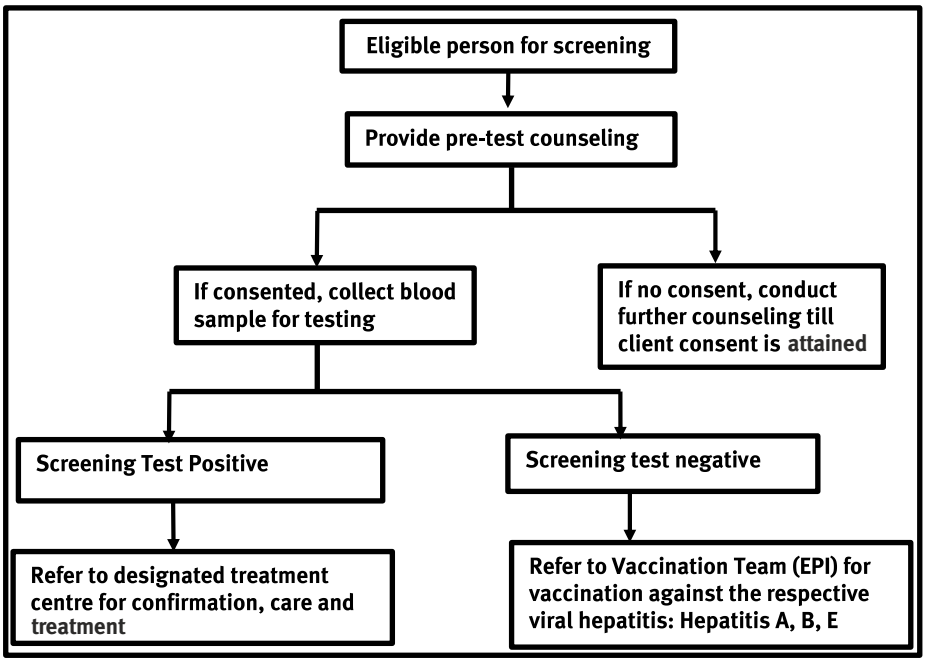
Step 3: The individual is counselled by the Counsellor (post-test counselling) on the outcome of the test results. If the test is negative for Viral Hepatitis, then he or she is referred to the vaccination team (Public Health Nurses/Community Health Nurses) for vaccination against the respective viral hepatitis e.g. Hepatitis A, B and E vaccines.

However, if positive for any of the Viral Hepatitis tested for e.g. Viral Hepatitis B or C, he or she is referred to the doctor in the designated treatment centre for further confirmatory test like ELISA. Only confirmed cases that require treatment are then put on care and treatment (Refer to section 5: Care and Treatment for Viral Hepatitis).

2.4.4 Screening Data Management

The demographic and health data including laboratory test results will be captured using the Hepatitis Case-Based Investigation Form (CIF). The District Disease Control Officer should collate the completed CIFs from all the screening centres within his/her jurisdiction and enter into Epi-Info. This is then transmitted by e-mail to the region for onward transmission to the national level-NVHCP. The Data should be cleaned before entering into Epi-Info. Analysis should be done at all levels. The following variables will be analysed: Age-sex distribution, distribution by region, district, occupation; professional groupings, hepatitis sero-positives and negatives.

Figure 2: Algorithm for Screening Persons for Viral Hepatitis



3. SURVEILLANCE FOR VIRAL HEPATITIS

3.1 Definition of Surveillance

Disease Surveillance is the **ongoing** **systematic** and **regular** collection, collation, analysis and interpretation of data on the occurrence, distribution and trends of a disease with sufficient accuracy and completeness and the dissemination of information to those who need to know to **take action (disease control).**

Importance of viral hepatitis surveillance:

Surveillance of viral hepatitis is essential for generating information that may lead to:

- Early Detection of outbreaks, monitor trends in incidence and identify risk factors for new (incident) infections. This is done through surveillance for acute viral hepatitis in health facilities
- Forecasting acute viral hepatitis outbreaks
- Monitor trends of acute and chronic viral hepatitis cases and deaths
- Evaluate control measures that are being instituted
- Estimate the prevalence of chronic infections and monitor trends in the general population and in sentinel groups. This is by keeping surveillance on chronic infections
- Estimate the burden of sequelae of chronic hepatitis, including cirrhosis and Hepatocellular carcinoma (HCC)

3.2 Sources of Surveillance Information

The following are the sources of surveillance information:

1. Acute viral hepatitis cases reporting to health facilities.
2. Reports from community based surveillance workers on outbreak of fever with jaundice cases
3. Analysis of daily/weekly/monthly routine surveillance data on acute and chronic viral hepatitis cases by health workers in the health facility (both outpatient and in-patient records).
4. Surveys-e.g. screening of populations at risk and identifiable groups (churches, schools etc.)
5. Reports from print and electronic media
6. Rumours from communities

3.3 Types of Viral Hepatitis Surveillance

There are three domains of viral hepatitis surveillance namely; surveillance of acute hepatitis, surveillance of chronic infections and surveillance for sequelae i.e. the complications of chronic viral hepatitis such as hepatocellular carcinoma.

a) Surveillance of acute hepatitis is done to identify and understand the sources of new infections and prevent them. This is done through collecting information on persons with acute hepatitis in health care settings.

b) Surveillance for chronic prevalent infections is done to estimate how common these are. That is done through approaching persons without signs and symptoms of acute hepatitis, mostly in biomarker surveys-by screening general populations, specific at risk population e.g. health workers, prisoners, commercial sex workers etc.

c) Surveillance for sequelae is done to measure the impact of control measures/treatment on mortality reduction. To this effect, data is captured on persons diagnosed with hepatocellular carcinoma or cirrhosis in Regional and Tertiary centres.

3.4 Viral Hepatitis Standard Case Definition

Case definitions are a set of criteria used to determine whether a person has a disease condition. Viral Hepatitis is a weekly and monthly notifiable disease in Ghana. These case definitions are for the purpose of reporting and surveillance. These definitions may differ from criteria to be used for the management of patients. The following standard case definitions are used:

3.41 Suspected Acute Viral Hepatitis Case definition:

Any person with discrete onset of an acute illness with signs/symptoms of;

(i) Acute infectious illness (e.g. fever, malaise, fatigue) and

(ii) Liver damage (e.g. anorexia, nausea, jaundice, dark coloured urine, right upper quadrant tenderness of body),

AND/OR

(iii) Raised alanine aminotransferase (ALT) levels more than ten times the upper limit of normal

3.42 Confirmed Acute Viral Hepatitis Case definition:

A suspected case that is laboratory confirmed by virus specific biomarkers

- Acute Hepatitis A: IgM anti-HAV positive or positive RNA HAV
- Acute Hepatitis B: HBsAg, IgM anti-HBc (IgG) positive
- Acute Hepatitis C:
    - HCV RNA positive (Viral Load) and anti-HCV negative

      OR

    - Seroconversion to anti-HCV[1]

      OR

    - Anti-HCV positive AND IgM anti-HBc negative **AND** anti-HAV IgM negative AND anti-HEV IgM negative
- Acute Hepatitis D: IgM anti-HBc positive plus anti-HDV positive (only as co-infection or super-infection of hepatitis B)
- Acute Hepatitis E: IgM anti-HEV positive

[1]Among patients tested regularly at short time intervals, seroconversion to anti-HCV suggests a recent HCV infection, which may take place in the absence of clinical, acute hepatitis. Seroconversion to anti-HCV should be followed by a reflex RNA test (when available).

3.43 Chronic Viral Hepatitis Case definition (HBV and HCV):

Any person not meeting the case definition for acute viral hepatitis and has specific biomarkers (e.g. person tested in the context of the evaluation of a chronic liver disease, a check-up or a survey)

Chronic Hepatitis B:

- HBsAg is the first serological marker to appear. Persistence of HBsAg for at least 6 months indicates chronic infection
- HBsAg is present with positive anti HBcIgG

Chronic Hepatitis C:

- Hepatitis C virus RNA present in a person with antibodies against hepatitis C (Anti-HCV positive)
- HCV RNA positive OR HCV core antigen positive

NB: Antibody detection (i.e HCV Ab positive) cannot differentiate between acute, chronic infection and past infection.

3.5 Data management and Reporting

For all suspected/confirmed acute or chronic Viral Hepatitis cases, some basic patient information should be collected using the Viral Hepatitis case-based investigation form (CIF) and summarized on the line listing form. The Viral Hepatitis data capture and reporting tools are annexed (see annexes 5,6A, 6B and 7).

Data Capture and Entry

At Health Facility Level

Use of Case-based Investigation form: For each suspected Viral Hepatitis case reporting at all health facilities and meeting the case definition, the attending clinician (Doctor, Physician Assistant, Senior Nurse Prescriber etc.) should notify the Disease Control Officers (DCO) or designated Focal Persons and request for blood sample collection and testing by the Laboratory Officer.

The DCOs or designated Focal Persons are to ensure that blood sample is collected by the Laboratory Officer and fill the Viral Hepatitis Case-based Investigation Form (CIF) (see annex 6). The DCOs or designated Focal Persons also fills the unique identification number (Epidemiological Number) to link the laboratory results with the patient clinical and epidemiological records. The Epidemiological Number should be provided at the district level by the District Disease Control Officer (DDCO). A copy of the completed CIF is kept at the facility, copy sent by e-mail to the district level, and the other copy together with the blood sample is sent to the referral laboratory (Regional Hospital Laboratory, Zonal Public Health Laboratory or National Public Health and Reference Laboratory or other designated laboratory) for testing.

Use of Viral Hepatitis Summary Reporting Form: The Health Information Officer (HIO)/DCO at all health facilities weekly and monthly compiles summary data on acute and chronic viral hepatitis cases and deaths from the Out Patient and In-patient Registers using the Viral Hepatitis Summary Reporting Forms. This is then entered into the DHIMS2 platform weekly.

Use of District Health Information Management System (DHIMS2): The DHIMS2, a web-based platform should be used to capture and transmit viral hepatitis data at all health facilities. The Health Information Officers (HIO) and Disease Control Officers at all health facilities should enter the summary data on suspected or confirmed acute or chronic Viral Hepatitis into the District Health Information Management System (DHIMS2) platform weekly and transmit same weekly and monthly. Facilities to report weekly and monthly even when no cases are recorded ("Zero reporting"). The District Disease Control Officer, the Regional Disease Control Officer and Regional HIO should validate the data entered weekly and monthly.

Data on blood screened: The Disease Control Officer and Laboratory Officers should capture summary data on all blood screened for Viral Hepatitis B and C at the health facilities using the District/Health Facility Viral Hepatitis Blood Donors Screening Reporting form (see annex 7). This should then be entered into the DHIMS2 platform monthly.

Cancer Registers: All persons diagnosed with hepatocellular cancer should be captured in a designated cancer register at health facilities especially in the Teaching hospitals. The District Disease Control or Surveillance Officer and the Regional Surveillance Officer in collaboration with Physician Specialist should complete the register and monthly enter summary data on the hepatocellular cancer cases and deaths into the DHIMS2 platform (refer to National Cancer Register)

At District Level

The District Disease Control Officer compiles all completed CIFs from all health facilities under their jurisdiction and enters same into a computer programme, e.g. Epi-Info. Provide a unique identifier (Epid. Number: Country code (CCC)-Region code (RRR)-District code (DDD)-Year code (YY)-Case Number (NNNN): [CCC-RRR-DDD-YY-NNNN] to link the laboratory results with the patient clinical/epidemiological records. They should also enter the laboratory data and tests results on the same database. The completed data base should then be sent by e-mail to the regional level on a weekly and monthly basis.

The District Disease Control Officer (DDCO) should also validate the summary viral hepatitis data entered into DHIMS2 platform weekly and monthly. Ensure that all fields on forms are filled completely.

At Regional Level

The CIF Epi-info data base received from the districts should be merged by the Regional Data Manager in collaboration with the Regional Disease Control Officer into a single database and sent to the national level on a weekly and monthly basis. The Data Manager at the Regional level should check for data entry flaws and clean the data base on a weekly basis. He/She should make sure that clinical and laboratory data of each patient are linked, before analysis.

Regional Disease Control Officer and Regional HIO should validate the summary data on viral hepatitis entered into the DHIMS2 platform weekly and monthly.

At National Level

The data bases received from the regions should be merged into a single national database using preferably Epi-Info before sharing with Health Developmental Partners on a monthly basis. The Data Manager at the National Viral Hepatitis Control Programme (NVHCP) should check for data entry flaws and clean the data base on a weekly basis. He/She should make sure that clinical and laboratory data of each patient are linked, before analysis.

The Data Manager at the National Viral Hepatitis Control Programme (NVHCP) should validate the summary data on viral hepatitis entered into the DHIMS2 platform weekly and monthly.

The National Public Health and Reference Laboratory (NPHRL) should collate all Viral Hepatitis test done at all laboratories. The data from the NPHRL will be computerized using Epi-info then sent to the NVHCP where they will be linked to the clinical data using the Epid-number. The results will then be sent to the regions and districts where the specimen came from.

Data Reporting

Acute Viral Hepatitis data should be reported weekly, whilst Chronic Viral Hepatitis B and C is reported monthly throughout the year. Facilities and Districts should report weekly/monthly, even when no cases are recorded ("Zero reporting").

During outbreaks of Acute Viral Hepatitis, the reporting of cases and deaths should be done on a daily basis. The line list should be completed at the health facility level, compiled at district level and a copy sent to the regional and national levels, on a daily basis.

All summary data on viral hepatitis captured in DHIMS2 should be reported monthly.

Data analysis

The Disease Control Officers at each level should calculate the Incidence Rate for Acute Viral Hepatitis cases and Prevalence Rate for Chronic Viral Hepatitis B and C cases and Case Fatality Rate. The data should be analysed further by person (age, sex distribution of cases and deaths), place (affected communities, districts) and time (weekly/monthly trends of cases and deaths). The results should be illustrated with tables, spot maps and graphs every week/month. During outbreaks epidemic curves should be constructed to monitor the outbreak. The supervisors at regional and national levels should ensure that all districts keep an up-to-date weekly and monthly trend of Acute and Chronic Viral Hepatitis cases and deaths respectively. Every month, the Data Manager of the NVHCP should make a map showing the distribution of cases and deaths by district, as well as the laboratory results by district. The details of the indicators to be analysed are captured under section 6: Supervision, Monitoring and Evaluation of these guidelines.

The DCO/HIO should monitor the timeliness and completeness of reporting from all levels using monitoring chart.

4. LABORATORY DIAGNOSIS OF VIRAL HEPATITIS

For all suspected cases of Acute Viral Hepatitis, blood samples should be taken by Laboratory Officers and sent to the referral labs for testing on Viral Hepatitis A, B, C, D and E. The referral laboratories are all the 10 Regional hospital Laboratories, all Public health Reference laboratories (Tamale, Sekondi-Takoradi, Kumasi, and Accra) and any other designated laboratory. The District and Regional Disease or Surveillance Officers shall coordinate the collection and transportation of the blood samples.

4.1 Laboratory Diagnosis for Acute Viral Hepatitis

Table 1 on page 42 describes sample collection, storage, transportation and laboratory test for confirmation of all types of Viral Hepatitis: Only WHO pre-qualified standard hepatitis testing kits/reagents should be used.

Table 1: Sample collection, storage, transportation and laboratory test for confirmation of all types of Acute Viral Hepatitis

Diagnostic test	Initial test with WHO prequalified Rapid Diagnostic test (RDT) and confirmed using ELISA test. Hepatitis A: IgM anti-HAV positive or RNA positive Hepatitis B: positive for Hepatitis B surface antigen (HbsAg) or IgM anti-HBc positive Hepatitis C: Anti-HCV positive or positive RNA Hepatitis D: HBsAg positive or IgM anti-HBc positive plus anti-HDV positive (only as co-infection or super-infection of hepatitis B) Hepatitis E: IgM anti-HEV positive
Sample to collect	Serum, whole blood or stool (for hepatitis A and E viruses)
When to collect the sample	Samples should be collected from suspected patient/during screening. IgM anti-HAV becomes detectable 5-10 days after exposure. HBsAg can be detected in serum from several weeks before onset of symptoms to days, weeks or months after onset; it persists in chronic infections. IgM anti-HBc positive usually disappears within 6 months. AntiHBc IgG then appears.
How to prepare, store and transport the sample	Use universal precautions to minimize exposure to sharps and any body fluid. Collect at least 5 mls of venous blood. Let clot retract for 30 to 60 minutes at room temperature or centrifuge to separate serum from red blood cells. Aseptically transfer serum into sterile, screw capped tubes. Store serum at 4°C. For storage >5 days, samples are held at -20°C Transport serum samples using appropriate packaging to prevent breakage or leakage.
Results	Results are usually available within 1 to 3 days from arrival at the laboratory.

4.2 Laboratory Tests for Chronic Viral Hepatitis

Chronic Viral Hepatitis B (HBV)

Basic initial laboratory investigations:

The following laboratory tests should be requested after thorough history and physical examination in HBsAg positive individuals;

a. Establish chronicity: HBcIgG positive or Repeat HBsAg after 6 months if HBcIgG test is unavailable

b. Establish e antigen/antibody status: HBe Ag & Ab

c. Establish inflammatory activity: LFTs,

d. Determine the Level of viraemia – viral load: HBV DNA

e. Screen for complications using Alpha fetoprotein, Abdominal ultrasound, Coagulation profile, Full blood count

f. Screen for other co-infections: HCV Ab, HIV, HDV if available

g. Supportive investigation: determine blood urea and creatinine

h. Consider liver biopsy or fibroscan if indicated

Chronic Viral Hepatitis C (HCV)

Initial Investigations for HCV Patients:

The screening test for HCV is HCV Ab test. Unlike HBV testing, a positive HCV screening test (anti-HCV Ab) does not equate to active infection.

Also, the HCV testing is bedevilled with several false positive results. The following steps are recommended to establish active infection;

- Confirm HCV Ab testing using ELISA
- Confirm active infection using RNA testing; detectable RNA confirms active infection; if RNA undetectable, no further testing is indicated. It indicates past infection
- Further testing for RNA positive cases include LFT, abdominal ultrasound, Genotyping, FBC, alpha fetoprotein, BUE and Cr; Screen for co-infections - HIV, HBV
- Assess degree of inflammation and fibrosis by conducting the following test:
    - Aspartate aminotransferase-to-platelet ratio index (APRI) Score
    - Fibrosis-4 (FIB4) score
    - Fibroscan
    - Liver biopsy is the gold standard.

5. CARE AND TREATMENT FOR VIRAL HEPATITIS

5.1 Care and Treatment for Acute Viral Hepatitis

Management of acute viral hepatitis is mainly supportive and often may not require hospitalization or medication.

It is important to establish which virus is involved, as the risk of progression differs as indicated below:

Hepatitis A: This is usually self-limiting. The rate of fulminant hepatic failure (FHF) is very low; there is a 1% fatality rate in those over the age of 40 years. FHF during pregnancy has a high mortality.

Hepatitis B: It is self-limiting in 95% of adult cases, but for children under the age of five, it is self-limiting in only 5-15%.

Hepatitis C: It is mostly self-limiting in 5-30% of cases.

Hepatitis D: It requires the presence of HBV and follows the course of HBV.

Hepatitis E: It is mostly self-limiting. The overall mortality rate in FHF is 1–3%; however in pregnant women the rate is 15–25%. Pregnant women, children and adults above the age of 40 years and those with background chronic liver disease are at increased risk of developing a more severe disease.

The next session will discuss the five hepatotropic viruses;

5.1.1 Acute Hepatitis A Infection

Hepatitis A virus (HAV) is an RNA-containing virus of the Picorna viridae family. The average incubation period is 28 days, but it can vary from 15 to 45 days.

Hepatitis A transmission is faeco-oral and therefore poor hygiene and sanitation enhance its transmission. At risk group include children, participants in oro-anal sex, consumers of high-risk foods (e.g., raw shellfish), day-care employees and families of children in day-care. HAV infection confers a lifelong immunity.

Diagnosis of Hepatitis A infection

HAV is reliably diagnosed by anti-HAV immunoglobulin M (IgM). The presence of anti-HAV immunoglobulin G indicates a previous infection or immunity.

Management of HAV infection

HAV infection is self-limiting and treatment should be conservative and supportive. There is no specific medication for HAV infection. Hygiene is very important. Hands should always be washed after visiting the toilet.

Prognosis

The risk of FHF is very low (0.01–0.1%), but increases with age, pregnancy and in those with pre-existing liver disease. In patients above the age of 40 years, there is a 1% mortality rate.

5.1.2 Acute Hepatitis B Infection

Hepatitis B virus (HBV) is a DNA-containing virus of the Hepadnaviridae family. The virus is present in most body fluids of individuals with acute or chronic hepatitis. In Ghana, HBV is often transmitted vertically (infected mother to child) or horizontally among young children playing together (through biting and scratching).

Other modes of transmission are through unsafe injections, unsafe blood/blood products and non-sterile instruments (scarifications). Sexual transmission is less common.

The incubation period for HBV is 60 days, and it can vary from 28 to 160 days. Approximately 30% of infections among adults present as icteric hepatitis, and 0.1– 0.5% of patients develop fulminant hepatitis. Infection resolves in 1%, 5%, 30% and 95% in neonates, under 1 year old, under 5 year old and adults respectively, with loss of serum HBsAg and subsequently the appearance of anti-HBs (HBsAb).

Diagnosis of Acute HBV Infection

Acute HBV infection is confirmed by a positive HBsAg and HBcIgM tests and a negative HBcIgG test. A follow-up re-check of HBsAg should always be carried out 6 months after the acute onset to confirm clearance.

Management of Acute HBV Infection

Management is often conservative and supportive. In fulminant hepatitis, meticulous intensive care may improve the survival, but orthotopic liver transplantation is the only therapy that has been shown to improve patient outcomes.

Prognosis: Full recovery with development of **anti-HBsAb** provides long-term immunity.

5.1.3 Acute Hepatitis C Infection

Hepatitis C virus (HCV) is an RNA-containing virus of the Flaviviridae family. The incubation period varies from 14 to 160 days. Transmission is from blood to blood and blood products. HCV may potentially be transmitted sexually, mainly in individuals with other sexually transmitted diseases.

The perinatal transmission rate is around 5%, much lower than the rates for HIV and HBV. Breast feeding does not pose a risk. Health-care workers are at risk, mostly due to nosocomial transmission (needle stick injury carries a 3% HCV risk). Also at risk are individuals in prisons and persons born in countries with high rates of endemic disease. Most acute infections are asymptomatic, but if symptoms occur, they usually last 2– 12 weeks.

Diagnosis of acute HCV infection

Distinguishing acute from chronic HCV can be challenging. The presence of HCV antibodies signifies exposure; however in an acute infection, HCV antibody may remain undetectable up to 4 weeks. Testing for HCV RNA is the best method of diagnosing acute HCV, particularly if it is then followed by the development of anti-HCV. **NB:** Anti-HCV is not protective and does not confer immunity.

Management of Acute HCV Infection

Early identification of HCV is important, because there is evidence that early intervention with standard interferon alpha can markedly reduce the risk of chronic infection from 80% to 10%. The patient with acute HCV infection should be counseled to reduce behaviors that could result in transmission, such as sharing of injection equipment or high-risk sexual practices. Because the risk of transmission of other infections is higher in the acute infection phase.

Patients with acute HCV infection are often asymptomatic or have nonspecific symptoms (fatigue, anorexia, mild or moderate abdominal pain, low-grade fever, nausea, vomiting) that frequently are not recognized as being associated with acute HCV infection. A small proportion (<25%) of patients with acute HCV infection will develop jaundice.

Patients diagnosed with acute HCV infection should be initially monitored with hepatic panels (ALT, aspartate aminotransferase [AST], bilirubin, and international normalized ratio [INR] in the setting of increasing bilirubin level) at 2- to 4-week intervals. Laboratory monitoring should continue until the ALT levels normalize and HCV RNA becomes repeatedly undetectable, suggesting spontaneous resolution. If this does not occur, frequency of laboratory monitoring for patients with persistently detectable HCV RNA and elevated ALT levels should follow recommendations for monitoring patients with chronic HCV infection. Those with spontaneous clearance should not be treated with antiviral therapy, but they should be counseled about the possibility of reinfection and tested routinely for reinfection if risk behaviors are ongoing

NB: There is no vaccine for HCV.

Prognosis of Acute HCV infection

HCV infection will spontaneously clear in 20% to 50% of patients. In at least two-thirds of patients, this will occur within 6 months of the estimated time of infection (median, 16.5 weeks); only 11% of those who remain viraemic at 6 months will spontaneously clear infection at some later time. Thus, detectable HCV RNA at 6 months after the time of infection will identify most persons who need HCV therapy. Unfortunately, most acute infections are missed as they are asymptomatic, and the opportunity to treat is therefore rare.

5.1.4: Acute Hepatitis D infection

Hepatitis D virus (HDV) is a defective single-stranded RNA virus of the Deltaviridae family. It is an incomplete RNA virus that needs the hepatitis B surface antigen to transmit its genome from cell to cell. It therefore only occurs in people who are positive for the hepatitis B surface antigen.

The mean incubation period varies from 60 to 90 days, but it can vary as widely as 30 to 180 days.

The mode of transmission of HDV is similar to that of HBV. HDV infection can occur either as a co-infection with HBV or as a super-infection in those with chronic HBV. HBV /HDV Co-infection leads to severe acute disease, indistinguishable from acute HBV and with a relatively low risk of chronicity. Super-infection usually develops as acute exacerbation of chronic hepatitis with a high risk of progression to chronic liver disease.

Diagnosis of Acute HDV Infection

Positive HDV Ag and HDV-RNA (PCR) confirm a diagnosis of acute HDV infection. The anti-HDV (IgM class) appears 30–40 days after the first symptoms.

Management is conservative and supportive.

5.1.5 Acute Hepatitis E Infection

Hepatitis E virus (HEV) is an RNA-containing virus of the Caliciviridae family. The average incubation period is 40 days, and it can vary from 15 to 60 days. HEV is transmitted primarily by the faeco–oral route, and faecally contaminated drinking water is the most frequent vehicle for transmission. Transmission may occur vertically. Transmission between persons is minimal.

Diagnosis of acute Hepatitis E infection

HEV antigen and IgM/IgG antibody testing.

Acute hepatitis E treatment

Management is conservative and supportive.

Prognosis of Acute HEV Infection

The prognosis is generally good, except in pregnant women. Pregnant women with acute hepatitis E infection have an approximately 15% risk of fulminant liver failure. The mortality rate is high, ranging from 5% to 25% in different studies. HEV infection causes mortality in up to 25% of pregnant women in the third trimester of pregnancy.

NB 1. Acute Hepatitis E infection should be considered as a differential for HELLP syndrome.

NB 2. There has been reported evidence that HEV can progress to chronicity in the Genotype 3 sub-type but this guideline will not address that aspect

5.2 Care and Treatment for Chronic Hepatitis B

Chronic hepatitis B (CHB) is defined as persistence of hepatitis B surface antigen (HBsAg) for six months or more. The major complications of CHB are cirrhosis and hepatocellular carcinoma

5.2.1 Transmission

Most infections are acquired via perinatal (vertical) or horizontal transmission during childhood. Other routes of transmission include contaminated blood used for transfusion or contact with infected body fluids (sexual transmission, contaminated needles and unsterilized instruments used for circumcisions, tattoos and manicure).

HBV is highly infectious, compared to HCV; a tiny innoculum of blood or blood products may cause infection. More than 90% of childhood infections become chronic whereas only 5 to10% of acute adult infections become chronic. This emphasizes the importance of perinatal HBV vaccination in Ghana.

5.2.2 Natural history and Terminology

There are 4 phases of chronic hepatitis B infection namely 1) Immune Tolerant 2) Immune Clearance/Active 3) Immune Control/Inactive and 4) Immune Escape/Reactive. See table 2.

Table 2: Natural History and Terminology for Chronic Hepatitis B

	Immune Tolerant	**Immune Clearance /Active**	**Immune Control /Inactive**	**Immune Escape /Reactivation**
ALT	Normal	High	Normal	High
HBeAg Status	Positive	Positive	Negative	Negative
Viral load	Very High	High	Low	High
Liver Histology	Normal	Active Necro-Inflammation	Normal	Active Necro-Inflammation
Comments	Common & prolonged following perinatal or childhood infections	Common following adult infection	Spontan-eous HBsAg loss at 1-3%/year	Linked to mutations
Treatment	No	Yes	No	Yes

5.2.3 Who should be investigated or screened?

Ideally all persons reporting for medical care should be screened. Screening during blood donation and routine medical examination are particularly recommended (see section 2.4 Screening).

5.2.4 Pre-and Post-test Counselling

It is important that patients are fully informed, in simple comprehensible language on basic information about hepatitis B (see section 2.4 Screening)

5.2.5 Basic initial laboratory investigations

The following laboratory tests should be requested after thorough history and physical examination in HBsAg positive individuals

Phase 1: Confirmed HBsAg Positive

- Establish Chronicity: HBcIgG positive or Repeat HBsAg after 6 months if HBcIgG test is unavailable
- Request hepatitis B profile
    - HBeAg and HBeAb
    - HBsAg and HBsAb
    - HBcAb (IgG and IgM)

- Explain the significance of parameters identified in the profile
- Establish function activity: LFTs, Consider liver biopsy if indicated
- Determine the Level of viraemia – viral load
- Screen for complications: Alpha fetoprotein, Abdominal ultrasound, Coagulation profile, Full blood count
- Screen for other co-infections: HCV Ab, HIV and HDV
- Supportive: determine blood urea and creatinine

Phase 2: Pretreatment Counselling

- Accessibility and availability of antivirals
- Need for long term follow up
- Objectives of treatment and the likely outcomes must be discussed namely:
    - Normalization or improvement of hepatic damage in the long term
    - Virological clearance
    - Prevention or delay of further liver damage and progression to Chronic liver disease and HCC
    - HBeAg seroconversion
    - HBsAg seroconversion ideal but seldom achieved (with current therapy)

- Overall improvement of the quality of life
- Some of the misinformation by lay public must be discouraged.
- The guilt feeling of those affected must be dispelled.

- It must be stressed that most patients are healthy; treatment is aimed at preventing future complications in a small minority at risk.
- Un-recognised forms of treatment including herbs should be avoided.
- Drug compliance is vital. The protracted treatment schedule and the need for rigorous compliance must be stressed.
- Side effects of therapy should be discussed with the patient. The importance of avoiding other drugs unless indicated must be emphasized.
- Likewise treatment failure must be explained.

Diet and lifestyle: The patient is encouraged to eat balanced diet normally but avoid those foods that upset him / her. Healthy lifestyle including regular exercises, managing any concurrent illnesses e.g. diabetes, and the avoidance or reduction of alcoholic beverages must be encouraged.

Patients who do not qualify for treatment must be given explanation, reassured and followed up regularly.

5.2.6 Patients Follow-up

All patients including those not needing immediate treatment require long term follow-up to identify any changes in clinical status and to identify early any complications.

Depending on HBeAg status, 3-6 monthly viral load (VL) and LFTs in the first year and thereafter according to results. Abdominal ultrasound (USG) 6-12 monthly.

5.2.6.1 Patients Follow-up Procedures

Health Facility level follow-up: Detailed (traceable) residential addresses including the contact telephone numbers of all patients should be collected and entered into the treatment centre (hospital) register. The clinical nurses at the treatment centres (hospitals) should call all patients as per their schedule of next visit to remind them of their review date and ensure that the patients come for reviews.

Community level follow-up: The treatment centre (hospital) team works with the District Health Management Team (DHMT) to map up where the patients that require follow-up are resided and identify the Community Health Nurses (CHN) working in the respective areas of residence of the patients. The names and contact details of all patients that require follow-up are then given to the CHNs who visits the patients at home on scheduled periods to ask of the status of their health and remind them of their review dates to the treatment centres. The CHNs counsel the patients on the need for regular medical check-ups and ensures that the patients attend the reviews at the treatment centres (hospitals).

5.2.7 Treatment of Chronic Hepatitis B Infections

Goals of Treatment:

- To achieve clearance of HBV viraemia
- To prevent or delay chronic liver disease progression
- To minimize risk of hepatocellular carcinoma
- To prevent transmission of HBV infection
- To improve quality of life and survival of affected patients

Patients should preferably be referred to tertiary or specialist centres or designated treatment centres for treatment. Treatment End points: HBsAg seroconversion is the ideal end point but this is not commonly achieved with all forms of current therapy (Table 3).

Table 3: Treatment End Points for Chronic Hepatitis B

	HBeAg positive	**If HBeAg negative**
End points	ALT Normalization	ALT Normalization
	HBV DNA viral suppression	HBV DNA viral suppression
	HBeAg Seroconversion	HBsAg Seroconversion
	HBsAg Seroconversion	

5.2.8 Who Should Be Treated

The following categories of patients should be treated:

- All patients with **chronic active HBV infection** (HBeAg Positives and HBeAg Negatives)
- All HBV related cirrhosis or advanced fibrosis (APRI Score >2) patients with detectable viraemia

Criteria for **HBeAg Positives CHB** (see algorithm Figure 2)

- Persistently elevated ALT (>2x ULN)
- Viral load > or = 20,000 IU/ml
- Moderate – severe inflammation or fibrosis on liver histology

Any two of the above criteria qualifies patient for treatment.

Criteria for **HBeAg Negative CHB** (see algorithm Figure 3)

- Persistently elevated ALT (>2x ULN)
- Viral load > or = 20,000 IU/ml
- Moderate – severe inflammation or fibrosis on liver histology

Any two of the above criteria qualifies patient for treatment.

Figure 3: Algorithm for HBeAg positive patients

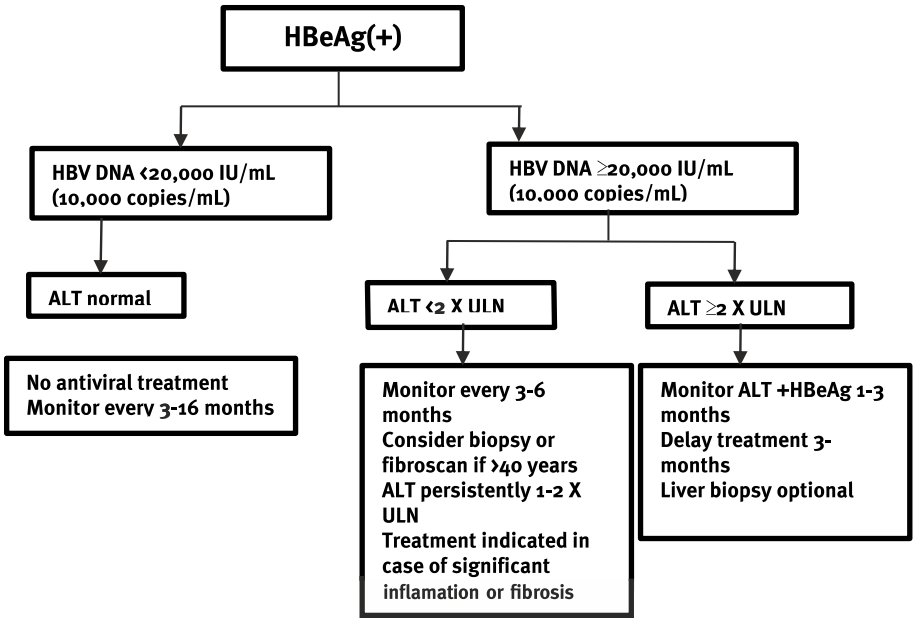
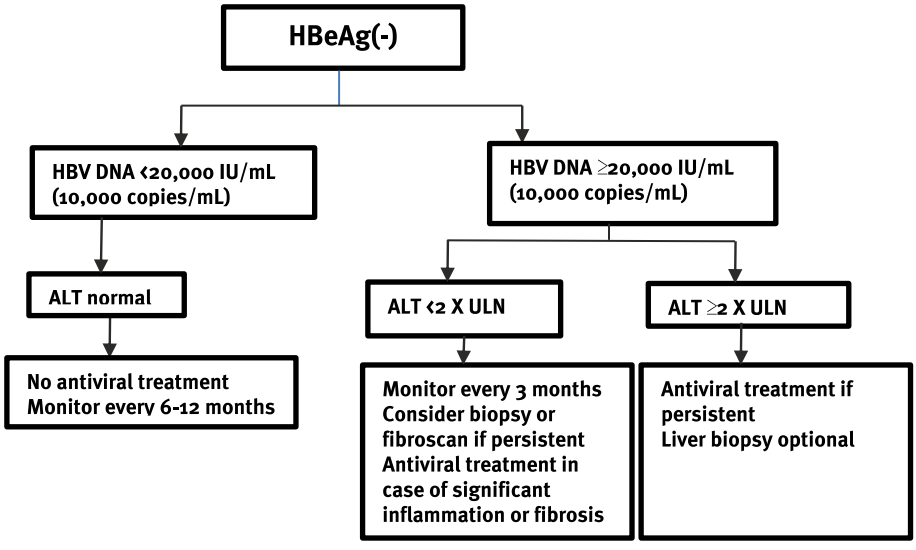


Figure 4: Algorithm for HBeAg negative patients



5.2.9 Antiviral Therapy for Chronic Hepatitis B

Approved Antiviral Agents (Table 4)

1. Tenofovir dixopoxil fumarate: Is a nucleotide analogue with very potent activity against HBV replication with a high genetic barrier.

2. Entecavir: Is a nucleos(t)ide analogue (NA) with very potent activity against HBV replication with a high genetic barrier.

3. Pegylated interferons: This is conventional interferon modified by pegylation to have longer half-life and therefore used as a once a week injection. They have been shown to increase and sustain the response rates in both HBeAg negative and HBeAg positive patients with a defined duration of treatment. See table 4 for comparative analysis.

4. Lamivudine: This is a nucleos(t)ide analogue with antiviral activity against HBV. It has been shown to have a good on-therapy viral suppression but low off-therapy sustained viral suppression rate. It also has a significantly increased risk of treatment failure due to emergence of resistant mutants. The best results with lamivudine are obtained when the duration is indefinite provided there is no development of resistance. **Currently not recommended as first line drug.**

5. Other approved anti-HBV drugs are Adefovir and Telbivudine.

Recommended First Line Antiviral Therapy for Chronic Hepatitis B

Recommended first line anti-viral therapy for HBV treatment are Tenofovir, Entecavir, Pegylated Interferon and Emtricitabine (Table 4, 5 and 6).

Tenofovir is the recommended first choice treatment for chronic hepatitis B. Entecavir is the drug of choice for children 2-11years. Pegylated interferon α-2a (Pegasys) is used in well selected category of patients (very high ALT, moderate –severe necro-inflammatory changes on liver histology and moderately high viral loads)

NB: Pegylated Inteferon is contraindicated in children under 12 years of age.

Table 4: Comparison of different treatment options in CHB

	Treatment duration	**Advantages**	**Disadvantages**
Pegylated Ifn α -2a	Defined (• 48 weeks)	• Finite treatment duration • Favourable response rates in both HBeAg+ve and HBeAg-ve disease. • More durable HBeAg seroconversion. • HBsAg loss in HBeAg+ve& -ve disease. • No resistance	Response rates may be low in HBeAg-ve. • Low tolerability • Less favourable safety profile. • Injection (sc)
Lamivudine Adefovir	Potentially indefinite	• Well tolerated • Safe in patients with compensated or decompensated liver disease. • Oral administration.	•HBeAg seroconversion less durable. • ALT flare up on discontinuation may be serious. • Increasing drug resistance with long term therapy. • Expensive (Adefovir)
Tenofovir Entecavir	Potentially indefinite	• Well tolerated • Potent • Better resistance profile • Oral administration	• Caution in renal impairment. • Caution in decompensated Liver disease. • Flare up hepatitis may occur on discontinuation.

Table 5: Recommended medicines for the treatment of CHB and their doses in adults

Medicines	Dose
Tenofovir	300 mg once daily
Tenofovir plus emtricitabine	Tenofir 300 mg; emtricitabine 200mg daily
Entecavir (adult with compensated liver disease and lamivudine naive)	0.5 mg once daily
Entecavir (adult with decompensated liver disease or previous exposure to Lamivudine)	1 mg once daily
Telbivudine	600 mg once daily
Lamivudine	100 mg once daily
Adefovir	10mg once daily
Pegylated interferon alpha-2a	180ug once per week
Pegylated interferon alpha-2b	0.5 or 1.0ug per kg per week

Table 6: Recommended medicines for the treatment of CHB and their doses in children

<table>
<tr><th>Medicines</th><th colspan="2">Dose</th></tr>
<tr><td>Tenofovir (in children 12 years of age and older, and weighing at least 35 kg)</td><td colspan="2">300 mg once daily</td></tr>
<tr><td>Entecavir (in children 2 years of age or older and weighing at least 10 kg. The oral solution should be given to children with a body weight up to 30 kg)</td><td colspan="2"><table>
<tr><td colspan="2">Recommended once-daily dose of oral solution (mL)</td></tr>
<tr><td>Body weight (kg)</td><td>Treatment-naive persons*</td></tr>
<tr><td>10 to 11</td><td>3</td></tr>
<tr><td>>11 to 14</td><td>4</td></tr>
<tr><td>>14 to 17</td><td>5</td></tr>
<tr><td>>17 to 20</td><td>6</td></tr>
<tr><td>>20 to 23</td><td>7</td></tr>
<tr><td>>23 to 26</td><td>8</td></tr>
<tr><td>>26 to 30</td><td>9</td></tr>
<tr><td>>30</td><td>10</td></tr>
</table></td></tr>
</table>

*Children with body weight more than 30 kg should receive 10 mL (0.5 mg) of oral solution or one 0.5 mg tablet once daily.

Monitoring during treatment

The aim of monitoring while on treatment is to assess adherence, evaluate effectiveness of therapy, check for evidence of progression of liver disease, adverse events and assess for indications for stopping treatment (Table 7).

1. At each visit check for adverse events
2. At 12 weeks perform the following test:
    - HBV DNA viral load
    - Liver Function Tests (LFTs)
    - FBC
    - BUE and Cr
    - HBsAg quantification for patients on Pegylated Interferon *

    *(End of Treatment Response)
3. At 24 weeks perform the following test:
    - HBV DNA (Viral Load)
    - Liver Function Test
    - FBC if indicated
    - BUE and Cr
    - HBsAg quantification

4. At 48 weeks perform the following test:
    - HBV DNA Viral Load
    - Liver Function Test
    - FBC, Thyroid function tests (pegylated interferon).
    - HBsAg quantification
5. At least annually thereafter
    - HBV DNA Viral Load
    - Liver Function Test
    - Abdominal ultrasound
    - FBC
    - BUE and Cr

Table 7: Monitoring Chart for Chronic Hepatitis B Antiviral Therapy

Test	Weeks on therapy				
	Baseline	**12**	**24**	**36**	**48**
HBV Viral Load	✓	✓	✓	✓	✓
Liver Function Test (LFTs)	✓	✓	✓	✓	✓
FBC if indicated	✓	✓	✓	✓	✓

5.2.10 Management of Treatment failure

Definition of treatment failure:

In settings where HBV DNA testing is available: Primary antiviral treatment failure may be defined as failure of an antiviral drug to reduce HBV DNA levels by ≥1 x log10 IU/mL within 3 months. Secondary antiviral treatment failure may be defined as a rebound of HBV DNA levels of ≥1 x log10 IU/mL from the nadir in persons with an initial antiviral treatment effect (≥1 x log10 IU/mL decrease in serum HBV DNA).

In settings where HBV DNA testing is not available: Treatment failure and drug resistance may be suspected based on the following features: receiving antiviral drugs with a low barrier to resistance together with documented or suspected poor adherence, and laboratory measures such as an increase in serum aminotransferases, and/or evidence of progressive liver disease.

Recommendations:

- In persons with confirmed or suspected antiviral resistance (i.e. history of prior exposure or primary non-response) to Lamivudine, Entecavir, Adefovir or Telbivudine, a switch to Tenofovir is recommended
- Treatment adherence should be reinforced in all persons with confirmed or suspected antiviral resistance
- For Adefovir resistance, a switch to either tenofovir or entecavir can be considered.
- To date, there has been no reported resistance with Tenofovir. If there is primary non-response, then treatment adherence should be reinforced and monitored. At present, there is therefore no indication to switch to an alternative drug regimen.

5.2.11 Antiviral Therapy for Special Groups

HBV and Pregnancy

All pregnant women should be screened for HBV infection during antenatal care (ANC). Acute HBV infection during pregnancy should be managed as for the non-pregnant population. However acute infections are more likely to be fulminant. In such situation, antiviral therapy may be considered on a case by case basis. Chronic HBV is not at increased risk of progression during pregnancy. Evaluation remains the same as for the non-pregnant population.

HBV DNA should be tested at the end of the 2nd trimester and persons with viral loads greater than 100,000 IU/ml and no other contraindication for treatment should be started on antiviral therapy and continued throughout the 3rd trimester. This is to prevent transmission of infection to the baby. Treatment in this case is stopped upon delivery and monitored thereafter.

Tenofovir is currently the safest and preferred drug for HBV treatment in pregnancy. Entecavir has not been studied adequately in pregnancy. Pegylated interferon is contraindicated in pregnancy.

NB: The risk of mother to child transmission is not influenced by the mode of delivery

Babies Born to Mothers with HBsAg Positivity

New born babies to HBsAg positive mothers MUST receive the mono-valent HBV vaccine preferably within 24hours and also the Hepatitis B Immuno-globulin (HBIG) soon after delivery but preferably not more than 72hours after birth. The injections should be given on the different sites of lateral thigh.

The baby thereafter should be enrolled into the National Childhood Immunization Programme at the Child-welfare clinic to complete all routine childhood immunizations.

Prior to immunosuppressive therapy

All HBsAg positive persons scheduled for immunosuppressive therapy who otherwise do not qualify to start treatment must start antiviral therapy or prophylaxis at least one week before starting chemotherapy. Treatment should be with the most potent nucleos(t)ide available and must be continued for up to 6 months after cessation of chemotherapy. They should be monitored with monthly LFT and 3 monthly Viral loads.

Renal dialysis and Transplant patients

HBV is prevalent in persons with Chronic Kidney Disease including renal transplant recipients. All such patients should be tested prior to initiation of renal dialysis and sero- negative patients should be vaccinated in consultation with a gastroenterologist. All the nucleos(t)ide analogues require dose adjustments and should be used with caution. Renal function monitoring should be done in consultation with a nephrologist during therapy. Interferons are not recommended.

Liver transplant

All potential liver transplant recipients should be tested for HBV. Sero-negative persons should be vaccinated. Positive individuals should be started on treatment prior to transplant and continued thereafter, with monitoring of viral load and liver function, as recommended for the general population. Interferons are not recommended.

HIV/HBV Co-infection

For management of HIV/HBV co-infection Refer to Guidelines for Antiretroviral Therapy (ART) in Ghana (NACP). ART should be started in all PLHIV with chronic HBV infection (HIV/HBV co-infection) irrespective of the CD4 cell count or the WHO clinical stage.

The following are the treatment regimens:

- **Adults and adolescents including pregnant women:** The preferred first line regimen for the treatment of both HIV and HBV:
    - Tenofovir + Lamivudine (or Emtricitabine) + Efavirenz (TDF+3TC (or FTC)+EFV)
    - The combination of 3TC and TDF should be continued if there is good HBV response when HIV resistance to the first line ART occurs. In such situation, the second line regimen should be:
- **Children 3 years or more:** Abacavir (or Tenofovir) + Lamivudine + Efavirenz (ABC (or TDF) + 3TC + EFV)
- **For children less than 3 years:** The recommended first line regimen is:
    - Abacavir (or Zidovudine) + Lamivudine + Lopinavir/Ritonavir (ABC (or AZT) + 3TC +LPV/r

5.3 Care and treatment for Chronic Hepatitis C

Hepatitis C virus (HCV) belongs to the family of flaviviruses with several known genotypes. The HCV is a small, positive-stranded RNA-enveloped virus. It has a highly variable genome, which has been classified into six distinct genotypic groups. Existing direct-acting antiviral (DAA) treatments are significantly more effective on certain genotypes than others; thus it is important to know a patients genotype prior to initiating treatment. HCV is infectious but less so than Hepatitis B.

5.3.1 Transmission

Transmission is via contact with contaminated blood and blood products. It was regarded as the major cause of transfusion induced hepatitis prior to the advent of screening of blood products. Practices such as persons who inject drugs (PWID), sharing of needles and unsterilized scarification and tattooing are likely routes of transmission. Sexual transmission is possible but uncommon. Also through child birth; from infected mother to child.

Hepatic damage from HCV infection is thought to be an immune mediated cytotoxic T cell response. Approximately 20% and 10% of persons with HCV infection, develop cirrhosis and hepatocellular carcinoma (HCC) respectively after about 10 – 20 years. They may also develop extrahepatic manifestations such as kidney disease, arthritis and skin disorders. There is no immunity after infection, unlike HBV and this is due to the diversity and numerous strains of the HCV. Currently there are no vaccines against HCV infection.

5.3.2 Initial Investigations for HCV Patients

The screening test for HCV is HCV Ab test. High quality WHO prequalified tests should be used for screening.

Unlike HBV testing, a positive HCV screening test (anti-HCV Ab) does not equate to active infection. However, the HCV testing is bedevilled with several false positive results. The following steps are recommended to establish active infection;

- Perform HCV serology testing (HCV Ab testing)
- If HCV Ab positive, confirm active infection by nucleic acid testing;
    - Detectable Ribonucleic acid (RNA) confirms active infection
    - If RNA undetectable, no further testing is indicated
- Further testing for RNA positive cases are as following;
    - FBC
    - LFT
    - Genotyping
    - Alpha fetoprotein
    - BUE and Creatinine
    - Abdominal Ultrasound
    - Screen for co-infections - HIV, HBV, TB

The predominant genotype(s) in Ghana is not known at present, however the WHO global distribution of genotypes suggests that Ghana falls within the area where genotypes 2 and 3 are predominant.

Assess degree of inflammation and fibrosis particularly in genotype 1 (Table 8 and Figure 5).

- Aminotransferase/platelet ratio index (APRI) Score
- FIB-4
- Fibro Scan

Table8: Selected non-invasive tests to assess liver fibrosis

Test	Components	Requirements
APRI	AST, platelets	Simple serum and haematology tests
FIB-4	Age, AST, ALT, platelets	Simple serum and haematology tests
Fibro Test	gGT, haptoblobin, bilirubin, A1 apolipoprotein, α 2-macroglobulin	Specialized test. Testing at designated laboratories
Fibro Scan	Transient elastography	Dedicated equipment

Figure 5: APRI and FIB-4 Formulas

APRI= [(AST (IU/L)/AST_ULN (IU/L)) X 100] / platelet count (10^9/L)

FIB-4 = age (yr) X AST (IU/L)/platelet count (10^9) X [ALT (IU/L)$^{1/2}$

ULN: Upper Limit of Normal

In resource-limited settings, it is suggested that APRI or FIB-4 be used for assessment of hepatic fibrosis rather than other non-invasive tests that require more resources such as elastography or FibroTest.

5.3.3 Indications for treatment

- All persons with active HCV infection i.e. detectable RNA are candidates for treatment if there are no contraindications.
- Prioritize treatment to persons with moderate to severe fibrosis, risk of HCV transmission e.g. IVD users , Men having sex with men (MSM), women in their reproductive ages and persons with extrahepatic manifestations

5.3.4 Pretreatment Management

- Education or counseling on natural history of disease, modes of transmission, prevention and assurance of effective treatment
- Vaccinate against hepatitis A and B if seronegative
- Weight loss if appropriate. Obesity increases likelihood of liver fibrosis
- Stop smoking

- Avoid use of illicit drugs
- Recommend abstinence from alcohol
- Assess for and manage depression if present in interferon based treatment
- Consider referral to support groups

Goals of Therapy

Primary goal of treatment is to eradicate the virus. The secondary goals are to:

- Slow disease progression
- Minimize risk of liver cancer
- Reverse liver damage
- Enhance quality of life
- Prevent transmission of virus
- Reduce extra-hepatic manifestations

5.3.5 Antiviral Therapy for Chronic Hepatitis C

Until 2011, standard of care was combination therapy of Pegylated interferon with Ribavirin for all genotypes globally. Subsequently, there has been a paradigm shift with the development of several new medicines or direct acting antiviral agents (DAA) e.g. sofosbuvir, ledipasvir, daclatasvir etc. where these are not available interferon based treatment may be used.

NB: Because treatment tends to be complex and prolonged, patients requiring treatment should be referred to tertiary or specialist centres or designated treatment centres.

The treatment regimens for HCV infection are currently complicated with many new modalities appearing frequently and also depend on genotype, treatment naïve (not treated before) with or without cirrhosis etc. Table 9 shows the dosages and mode of administration of the recommended medicines for treating Chronic Hepatitis C.

Table9: Recommended medicines for treating Chronic Hepatitis C

Medicines	Dose
Pegylated Interferon a-2b	180microgms subcutaneous injection once weekly
Ribavirin	800mg or 1000mg (if patient weight < 75kg) or 1200mg (if patient weight >75kg) Given orally
Sofosbuvir	400mg once daily orally
Velpatasvir	100mg once daily orally
Simeprevir	150mg once daily orally
Ledipasvir	90 mg once daily orally
Daclatasvir	60mg once daily orally
Simeprevir	150mg once daily orally
Ombitasvir 150mg/Paritasvir 150mg/Ritonavir 100mg	fixed dose combination orally
Dasabuvir	150mg twice daily orally

Recommended preferred and alternative treatment durations in patients with or without cirrhosis

I. Daily fixed-dose combination of Ledipasvir (90 mg) and Sofosbuvir (400 mg) for 12 weeks; if treatment-experienced 12 weeks with ribavirin or 24 weeks without ribavirin.

II. Daily fixed-dose combination of Sofosbuvir (400 mg) and Velpatasvir (100 mg) for 12 weeks

III. Daily Daclatasvir (60 mg) plus Sofosbuvir (400 mg) for 12 weeks;

Tables 10a to 10d give the recommended preferred and alternative treatment durations in patients with or without cirrhosis, respectively.

Table 10: Summary of recommended preferred regimens with treatment durations for Chronic Hepatitis C

Table 10a: Patients without cirrhosis

Genotypes	Daclatasvir / Sofosbuvir	Ledispasvir / Sofosbuvir	Sofosbuvir/ Ribavirin	Sofosbuvir/ Velpatasvir
1	12 weeks	12 weeks[a]		
2			12 weeks	12 weeks
3	12 weeks		24 weeks	
4	12 weeks	12 weeks		
5		12 weeks		
6		12 weeks		

[a] Treatment may be shortened to 8 weeks in treatment-naïve persons without cirrhosis if their baseline HCV RNA level is below 6 million (6.8 log) IU/mL. The duration of treatment should be shortened with caution

Table 10b: Patients with cirrhosis

Genotype	Daclatasvir/ Sofosbuvir	Daclatasvir/ Sofobuvir/ Ribavirin	Ledipasvir/ Sofosbuvir	Ledispasvir/ Sofosbuvir/ Ribavirin	Sofosbuvir /Ribavirin
1	24 weeks	12 weeks	24 weeks	12 weeks[b]	
2					16 weeks
3		24 weeks			
4	24 weeks	12 weeks	24 weeks	12 weeks[b]	
5			24 weeks	12 weeks[b]	
6			24 weeks	12 weeks[b]	

[b] If platelet count <75 X 10^3/µL, then 24 weeks treatment with Ribavirin should be given

Table 10c: Summary of recommended alternative regimens with treatment durations for patients without cirrhosis

Genotypes	Simeprevi/ Sofosbuvir	Daclatasvir/ Sofosbuvir	Sofosbuvir/Pegylated interferon/Ribavirin
1	12 weeks[a]		
2		12 weeks	
3			
4	12 weeks		
5			12 weeks
6			12 weeks

[a] If genotype 1a-infected patient, is positive for the Q80K variant, a simeprevir/sofosbuvir regimen should not be chosen. For genotype 1a-infected patients, treat with Ombitasvir/ Paritaprevir/Ritonavir/Dasabuvir and Ribavirin for 12 weeks; for genotype 1b-infected patients, treat with Ombitasvir/Paritaprevir/ Ritonavir/Dasabuvir for 12 weeks

Table 10d: Summary of recommended alternative regimens with treatment durations for patients with cirrhosis

	*	**		
Genotypes	**Daclatasvir/ Sofosbuvir**	**Simeprevir/ Sofosbuvir**	**Simeprevir/ Sofosbuvir/ Ribavirin**	**Sofosbuvir / Pegylated interferon/ Ribavirin**
1		24 weeks[a]	12 weeks[a]	
2	12 weeks			
3				12 weeks
4		24 weeks	12 weeks[a]	
5				12 weeks
6				12 weeks

[*] Can be prescribed to persons with compensated or decompensated cirrhosis

[**] These regimens should be prescribed only to persons with compensated cirrhosis because they can cause liver failure and death when prescribed to persons with decompensated cirrhosis. Therefore, they shoud be used only in settings where specialized care is available and where the degree of cirrhosis (compensated vs decompensated) can accurately be assessed

[a] If genotype 1a-infected patient is positive for the Q80K variant, a Simeprevir/Sofosbuvir regimen should not be chosen. For genotype 1a-infected patients, treat with Ombitasvir/ Paritaprevir/Ritonavir/Dasabuvir and Ribavirin for 24 weeks; for genotype 1b-infected patients, treat with Ombitasvir/Paritaprevir/ Ritonavir/Dasabuvir for 12 weeks

5.3.6 Contraindications for Treatment of Chronic Hepatitis C

Contra-indications for Interferon Therapy

- Hypersensitivity to Interferon alpha or any active ingredients
- Severe psychiatric disturbances e.g. depression, psychosis
- Auto-immune hepatitis
- Decompensated cirrhosis e.g. ascites, encephalopathy
- Cardiac failure
- Uncontrolled seizure disorders
- Pregnancy
- Pre-existing uncontrolled thyroid disorders

Contraindications to therapy with Ribavirin

The following are absolute contraindications for Ribavirin therapy:

- Pregnancy or unwillingness to use contraception
- Breast feeding women
- Severe concurrent medical disease, including severe infections
- Poorly controlled cardiac failure
- Chronic obstructive pulmonary disease
- Previous ribavirin hypersensitivity
- Co-administration of didanosine

The following are relative contraindications for Ribavirin therapy:

- Abnormal haematological indices: 1) Hb <10 g/dL, 2) Neutrophil count $<1.5x10^9$/L, 3) Platelet count $<90x10^9$/L
- Serum creatinine >1.5 mg/dL
- Haemoglobinopathies (sickle cell disease or thalassaemia)
- Significant coronary artery disease

5.3.6 Co-Infections

HBV, HIV, HCV and HDV share similar transmission routes. Concurrent infection with these viruses usually results in more severe and progressive liver disease, and a higher incidence of cirrhosis, HCC and mortality.

Co-infected persons are therefore more likely to need treatment. In general, the dominant virus responsible for liver disease should be identified and initial treatment targeted toward this virus. For example, if HCV is dominant, treatment should first be given to achieve HCV clearance and cure, followed by determination of whether treatment for hepatitis B is warranted based on ALT and HBV viral load.

HIV/HCV Co-Infection

In 2015, WHO updated its HIV treatment recommendations to recommend treatment for all persons living with HIV regardless of WHO clinical stage or CD4 cell count. The choice of ART for persons with co-infection is the same as for those with HIV alone. However, persons co-infected with HIV are at higher risk of developing side-effects of HCV therapy, and should be monitored more closely. Before starting HCV therapy, careful consideration of drug-drug interactions (DDIs) is essential.

It is important for clinicians to consider potential DDIs in choosing regimens, as DDIs vary both in number and clinical significance, depending on the medicines prescribed.

Where DDIs are likely, ARV drug substitutions should be made before commencement of HCV therapy. It is particularly important to be aware of HIV infection when considering ritonavir-based therapies (i.e. paritaprevir) in order to avoid single drug therapy of HIV infection, which could lead to drug resistance to ARVs. Table 11 summarizes the first-line ART regimens. It is advisable to first initiate treatment for HIV and achieve HIV suppression before starting HCV treatment, although there are some circumstances where it may make sense to treat HCV infection first and then initiate therapy for HIV. This could include persons with moderate-to-severe fibrosis at risk of rapid liver disease progression if the HIV infection is not associated with significant immunosuppression at the time of treatment.

Table 11: Summary of first-line ART regimens for adults, adolescents, pregnant and breastfeeding women and children for HIV/HCV Co-infection

Category of patients	Preferred first line regimens	Alternative first-line regimens
Adults	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + DTG[a] TDF + 3TC (or FTC) + EFV 400[a] TDF + 3TC (or FTC) + NVP
Pregnant/ breast feeding women	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + NVP
Adolescents	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF (or ABC) + 3TC (or FTC) + DTG[a] TDF (or ABC) + 3TC (or FTC) + EFV400[a] TDF (or ABC) + 3TC (or FTC) + NVP
Children aged 3 to 10 years of age	ABC + 3TC + EFV	ABC + 3TC + NVP AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + EFV (or NVP)
Children younger than 3 years of age	ABC or AZT + 3TC + LPV/r	ABC or AZT + 3TC + NVP

Source: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. WHO, 2015

3TC-lamivudine; ABC: abacavir; AZT: zidovudine; DTG: dolutegravir; EFV: efavirenz; EFV400: EFV at lower dose (400mg/day); FTC: emtricitabine; LPV: lopinavir; NVP: nevirapine; r: ritonavir; TDF: tenofovir

[a] Safety and efficacy data on use of DTG and EFV400 in pregnant women, people with HIV/TB coinfection, and children and adolecents younger than 12 years of age are not yet available

HBV/HCV Co-Infection

It is important to check for the presence of HBV infection before starting HCV treatment. HBV and HCV co-infection may result in an accelerated disease course; HCV is considered to be the main driver of disease and should be treated first.

Persons co-infected with HBV and HCV can be treated with antiviral therapy for HCV; SVR rates are likely to be similar to those in HCV-monoinfected persons. During treatment and after HCV clearance, there is a risk of reactivation of HBV, and this may require treatment with concurrent anti-HBV antiviral therapy. DDIs must be checked before initiating treatment.

TB/HCV Co-Infection

People at increased risk of infection with HCV are also often at increased risk of infection with TB. Therefore, screening for active TB should be part of the clinical evaluation of patients being considered for HCV treatment. WHO recommends a four-symptom screening algorithm to rule out active TB. If the patient does not have any one of the following symptoms – current cough, fever, weight loss or night sweats – TB can be reasonably excluded; otherwise, the patient should undergo further investigations for TB or other diseases.

Most of the DAAs interact with metabolic pathways in the liver, which increases and/or decreases the drug level of DAAs when co-administered with antimicrobial medicines such as rifabutin, rifampin and rifapentin. Therefore, concurrent treatment of HCV infection and TB should be avoided. Active TB should generally be treated before commencing therapy for HCV.

Furthermore, in persons with HCV infection being treated for TB, it is important to monitor liver function tests, as the risk of antimycobacterial-induced hepatotoxicity is higher in patients with TB/HCV co-infection than in those with TB monoinfection, although the risk of severe hepatotoxicity is rare. Concurrent treatment of HCV infection and multidrug-resistant TB is particularly complicated because of many DDIs between DAAs and second-line antimicrobials.

There are limited data on the management of persons coinfected with HCV, HIV and TB, but such cases need sound clinical judgement in order to reduce the additive side-effects, pill burden and DDIs.

Clinicians need to be aware of the risk of reactivation of TB if the person, particularly if HIV co-infected, receives interferon-based therapy, as interferon-based therapy could increase the incidence of active TB.

5.3.6 Special Considerations for specific conditions

Cirrhosis

The spectrum of disease in those infected with HCV extends from mild fibrosis to compensated, then decompensated cirrhosis and HCC. Between 15% and 30% of persons infected with HCV will go on to develop cirrhosis of the liver within 20 years and a proportion of these will progress to HCC. The risk is markedly increased in those who consume excess alcohol and in those co-infected with HBV and/or HIV, particularly those who do not have access to ART.

Persons with cirrhosis have the least time available for treatment, the most to lose and much to gain from achieving SVR.

Treatment of HCV infection should be commenced before the onset of decompensated disease because medical management is more complicated and some HCV medicines can precipitate liver failure and death if administered at this stage.

Regular clinical examination and monitoring of serum bilirubin, albumin and coagulation profile are necessary in persons with cirrhosis on interferon based treatment in order to detect decompensated disease. The treatment of such persons with interferon-containing regimens carries a higher risk of serious side-effects, and the use of haemopoietic factors is recommended in settings where these are available.

Use of certain DAA regimens among persons with cirrhosis has been shown to be efficacious, especially in those with compensated disease. The addition of ribavirin to treatment increases the risk of serious adverse effects (SAEs), most notably those related to anaemia, and requires additional monitoring.

Simeprevir and mbitasvir/paritaprevir/ritonavir/dasabuvir are not approved for use in patients with decompensated liver disease. Daclatasvir, ledipasvir and sofosbuvir have been studied in persons with decompensated cirrhosis and their use has been demonstrated to be both feasible and effective (see above HCV treatment).

However, a proportion of patients with decompensated liver disease will deteriorate on treatment and currently there are no pretreatment predictors to identify these patients. Therefore, treatment of patients with decompensated liver cirrhosis should be considered only in centres with the expertise to manage complications and ideally where access to liver transplantation is available.

Assessment and follow up for the progression of disease and for evidence of HCC is an essential part of the care of persons with HCV-related cirrhosis. Compensated cirrhosis may also progress over time to decompensated cirrhosis associated with ascites, oesophageal and gastric varices, and eventually to liver failure, renal failure and sepsis, all of which are life threatening. The diagnosis of decompensated liver disease is based on both laboratory and clinical assessment, and therefore a careful medical examination of patients must be made before starting treatment. Persons with cirrhosis (including those who have achieved an SVR) should be screened for HCC with six-monthly ultrasound examination and α-fetoprotein estimation, and should have endoscopy every 1–2 years to exclude oesophageal varices.

Chronic Kidney Disease

There is an unmet need for DAA treatment in patients with severe renal disease (eGFR <30 mL/min/1.73 m^2) and those requiring haemodialysis. Sofosbuvir, which is used in many approved regimens, does not have the safety and efficacy data to support its use in these situations. Preliminary pharmacokinetic and clinical study data suggest that the use of ombitasvir/paritaprevir/ritonavir and dasabuvir is feasible and the early results suggest possible efficacy.

Both ribavirin and pegylated interferon require dose adjustment in persons with renal failure. Pegylated interferon α2a is cleared by the liver and pegylated interferon α2b via the kidneys. While a theoretical accumulation of pegylated interferon α2b could occur in persons on haemodialysis, no differences have been reported clinically. In persons with severe renal disease (eGFR <30 mL/min/1.73 m^2), including those on haemodialysis, a reduced dose of pegylated interferon α2a 135 μg once a week is recommended.

The dose of ribavirin must also be decreased as the risk of anaemia-related adverse events is high. In persons with renal impairment receiving chronic haemodialysis, ribavirin may be administered at a dose of 200 mg daily or 200 mg every other day. Plasma ribavirin is removed by haemodialysis with an extraction ratio of approximately 50%.

Patients receiving ARV drugs in combination with tenofovir and sofosbuvir may require enhanced renal monitoring (see section 9.2).

Women of Child Bearing Age

None of the DAAs have been evaluated among pregnant women. Thus, women with childbearing potential should be counseled that they require effective contraception during treatment and for six months after completion of therapy. Interferon can induce pregnancy termination and ribavirin is associated with fetal abnormalities. These two medicines are thus contraindicated in pregnant women and those with childbearing potential unless effective contraception (i.e. two forms of contraception) can be guaranteed during treatment and, for women taking ribavirin, for 6 months after completing therapy. Ombitasvir/paritaprevir/ritonavir-based regimens have DDIs with certain hormonal contraceptives and should be used with caution. Pre-treatment pregnancy tests should be conducted prior to treatment initiation.

Children And Adolescents

None of the DAAs have been approved for use among children; thus, the only approved treatment for children remains pegylated interferon/ ribavirin, which is recommended for children older than 2 years. The product literature for pegylated interferon reports that paediatric subjects treated with ribavirin combination therapy had a delay in weight and height increases after 48 weeks of therapy compared with baseline.

However, by the end of 2 years of follow up, most subjects had returned to baseline normative growth curve percentiles for weight and height (mean weight-for-age percentile was 64% at baseline and 60% at 2 years' post-treatment; mean height percentile was 54% at baseline and 56% at 2 years' post-treatment).

People Who Inject Drugs

Injecting drug use is prevalent in many countries around the world, affecting people in low-, middle- and high-income countries. Globally, approximately 67% of PWID have evidence of HCV infection (i.e. anti-HCV antibodies); 10 million of 16 million people in 148 countries. PWID are at increased risk of HCV-related and mortality, and therefore require specialized care and should be considered as a priority for HCV treatment.

In reality, many PWID with HCV infection are unaware that they are infected and HCV treatment rates among them are very low. This is due to a number of reasons, including the criminalization of drug use, as well as discrimination and stigma in healthcare settings. When caring for PWID, the central tenets of respect and non-discrimination should be followed, and additional adherence and psychological support given as required.

Extrahepatic Manifestations

Some patients with chronic HCV infection may suffer from extrahepatitic illnesses, with a symptomatic spectrum vary from fatigue to permanent organ damage such as renal disease, peripheral neuropathy, arthropathy, cryoglobulinaemia, lymphoproliferative disorders and peripheral and central nervous system vasculitis. These illnesses resolve following SVR by antiviral treatment. Interferon free treatment appear safe and effective in HCV patients with extrahepatic manifestations.

6. SUPERVISION, MONITORING AND EVALUATION

Supervision of Viral Hepatitis programme activities will be conducted at all levels of the health system namely; health facilities, sub-district, district and regional level. This will be done by trained supervisors every quarter.

The key indicators to be monitored monthly and evaluated annually are (Table 12):

1. Prevalence of Chronic HBV infection and Chronic HCV infection
2. Testing Infrastructure for HAV, HBV, HDV, HCV and HEV
3. Vaccine coverage: Timely Hepatitis B vaccination at birth dose Third-dose Hepatitis B vaccination of infants
4. Harm reduction: Needle–syringe distribution
5. Injection safety: Facility-level injection safety
6. People living with HBV and/or HCV diagnosed
7. Treatment coverage/ initiation
    a. Treatment coverage for HBV patients
    b. Treatment initiation for HCV patients Treated
8. Treatment effectiveness
    a. Viral suppression for chronic HBV patients treated
    b. Cure for chronic HCV patients treated
9. Incidence Rate
    a. Cumulated incidence of HBV infection in children 5 years of age
    b. Incidence of HCV infection
10. Deaths attributable to HBV and HCV infection

Table 12: Viral Hepatitis Indicators and Targets

Indicator	Indicator Definition	Numerator	Denominator	Source of data	Target
1a: Prevalence of Chronic HBV infection	Number and proportion of people living with chronic HBV infection (hepatitis B surface antigen [HBsAg] positive)	Number of persons with chronic HBV infection defined by HBsAg-positive serological status	Number of persons (total population)	Surveys, Hepatitis programme data	Reduce new cases of chronic viral hepatitis B infections
1b: Prevalence of Chronic HCV infection	Number and proportion of people living with chronic HCV infection (HCV RNA positive or HCV antigen [Ag] positive)	Number of persons with chronic HCV infection defined as positive for HCV RNA or positive for HCV Ag	Number of persons (total population)	Surveys, Hepatitis programme data	Reduce new cases of chronic viral hepatitis C infections
2. Testing Infrastructure for HAV, HBV, HDV, HCV and HEV	Ratio of facilities with capacity to test individuals for chronic hepatitis HBV and/or HCV per 100 000 population according to the following testing methods: - molecular methods (HCV	Number of facilities with capacity to test for chronic hepatitis - Tests to be used depend on national recommendations based on WHO guidelines. - Facilities include health workers using point-of-care (POC) testing, health facilities,	Number of persons (total population)	Hepatitis programme data	80%

Table 12: Viral Hepatitis Indicators and Targets (Continued)

Indicator	Indicator Definition	Numerator	Denominator	Source of data	Target
	RNA, HBV DNA) - serological methods (HBsAg, anti-HBc, anti-HCV)	laboratories.			
3a. Hepatitis B vaccination at birth dose	Proportion of newborns who have benefited from timely birth dose of hepatitis vaccine (within 24 hours) or from other interventions to prevent mother-to-child transmission of HBV (percentage)	Number of newborns receiving timely birth dose of hepatitis vaccine within 24 hours (HepB_BD) or benefiting from other interventions to prevent mother-to-child transmission of HBV (e.g. testing of the mother followed by immunoprophylaxis, or in the future, treatment)	Number of live births	EPI	90%
3b Third-dose Hepatitis B vaccination of infants	Proportion of infants (<12 months of age) who received the third dose of hepatitis B vaccine (HepB3) (percentage)	Number of infants (<12 months of age) who received the third dose of hepatitis B vaccine (HepB3)	Number of infants (<12 months of age in a year) surviving to age 1 year	EPI	90%

Table 12: Viral Hepatitis Indicators and Targets (Continued)

Indicator	Indicator Definition	Numerator	Denominator	Source of data	Target
4. Harm reduction: Needle–syringe distribution	Number of needles–syringes distributed per person who injects drugs	Number of sterile needles–syringes distributed in the past 12 months by needle–syringe programmes (NSPs)	Number of people who inject drugs	Numerator: programme records, e.g. NSP logbooks Denominator: population size estimation exercises	50%
5. Injection safety: Facility-level injection safety	Proportion of health-care facilities where all therapeutic injections are given with new, disposable, single-use injection equipment	Number of sampled health-care facilities where all therapeutic injections are given with new, disposable, single-use injection equipment	Number of facilities sampled	Health facility surveys (facility data).	90%
6. People living with HBV and/or HCV diagnosed	Proportion of people living with chronic HBV and/or HCV infection who have been diagnosed with HBV and/or HCV	Number of persons with chronic HBV and/or HCV infection who have been diagnosed	Estimated number of persons with chronic HBV and/or HCV infection	Counting persons reported with chronic infection and dividing this number by the estimated size of the population infected	80%

Table 12: Viral Hepatitis Indicators and Targets (Continued)

Indicator	Indicator Definition	Numerator	Denominator	Source of data	Target
7a. Treatment coverage for Hepatitis B	Proportion of HBV-infected persons who are currently on treatment	Number of persons with chronic HBV infection (defined by HBsAg-positive serological status) who are currently receiving treatment	Number of persons with chronic HBV infection	Numerator: programme records (clinical records of health-care facilities providing hepatitis treatment and care) Denominator: modelling estimates of the number of HBV-infected persons	80%
7b. Treatment initiation for Hepatitis C	Proportion of persons diagnosed with chronic HCV infection started on treatment during a specified time frame (e.g. 12 months)	Number of persons already diagnosed with chronic HCV infection (defined as positive for HCV RNA or positive for HCV Ag) who initiated treatment during a specified time frame (e.g. 12 months)	Number of persons already diagnosed with chronic HCV infection (defined as positive for HCV RNA or positive for HCV Ag) for the specified time period (12 months)	Numerator: programme records (clinical records of health-care facilities providing hepatitis treatment and care) Denominator: programme records and/or	80%

Table 12: Viral Hepatitis Indicators and Targets (Continued)

Indicator	Indicator Definition	Numerator	Denominator	Source of data	Target
			Note: All those already diagnosed to date but treated and cured would be excluded	modelling estimates	
8a. Viral suppression for chronic HBV patients treated	Proportion of patients with chronic HBV infection on treatment in whom HBV viral load (VL) is suppressed	Number of patients with chronic HBV infection on treatment who have a suppressed VL (HBV DNA not detectable), based on VL measurement in the past 12 months	Number of patients with chronic HBV infection on treatment and assessed for VL in the past 12 months	Programme records, cohort studies, patient records, combined with best estimates for the population with no VL data	80%
8b. Cure for chronic Hepatitis C patients treated	Proportion of patients with chronic hepatitis C cured among those who completed treatment	Number of patients who completed hepatitis C treatment and had a sustained virological response (SVR) based on VL measurement 12– 24 weeks after the end of treatment (in the past 12 months)	Number of patients who completed hepatitis C treatment and were assessed for SVR 12– 24 weeks after the end of treatment (in the past 12 months)	Programme records, cohort studies, patient records, combined with best estimates for the population with no VL data	90%

Table 12: Viral Hepatitis Indicators and Targets (Continued)

)

Indicator	Indicator Definition	Numerator	Denominator	Source of data	Target
9a. Cumulated incidence of HBV infection in children 5 years of age	Proportion of children 5 years of age with serological evidence of past or present HBV infection (anti-HBc positive) and/or chronic infection (HBsAg positive)	Number of survey children 5 years of age living with biomarkers of past or present infection and/or chronic infection	Number of children aged 5 years of age in surveys (35)	HBsAg biomarker prevalence survey in children 5 years of age (immunization coverage surveys and administrative vaccination coverage data)	Reduce new cases of viral hepatitis B
9b. Incidence of HCV infection	Number and rate of new infections with HCV (anti-HCV positive)	Total number of new infections with HCV defined as anti-HCV positive per year	Total population minus people living with hepatitis C	Modelled with inputs from repeated surveys of HCV infection: - general population (in selected countries with a high prevalence) at least every 10 years - people who inject drugs (PWID), at least every 3 years -	Reduce new cases of viral hepatitis C infections

Table 12: Viral Hepatitis Indicators and Targets (Continued)

Indicator	Indicator Definition	Numerator	Denominator	Source of data	Target
				antenatal care (ANC), at least every 3 years	
10. Mortality attributable to HBV and HCV infection	Deaths from hepatocellular carcinoma (HCC), cirrhosis and chronic liver diseases attributable to HBV and HCV infections	Deaths from hepatocellular carcinoma (HCC), cirrhosis and chronic liver diseases attributable to HBV and HCV infections	Not applicable	Country cancer registry	Reduce deaths due to viral hepatitis B and C

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8. Annexes

Annex 1: Post-exposure management of healthcare workers after occupational exposure to Hepatitis B infection

*HCW status	Post-exposure testing		Post-exposure prophylaxis		Post-vaccination anti-HBs
	Source patient	*HCW anti-HBs	§HBIG	HBV vaccination	
Documented responder(antibody titres ›10IU and › 3 doses received)	No action required				
Documented non-responder (after ›6 doses)	Positive	-	§HBIG twice (I month apart)	-	No
	Negative	-	No action required		
Response unknown (after ›3 doses)	Positive/ Unknown	‹10 mIU/mL	§HBIG once	Revaccinate	Yes
	Negative	‹10 mIU/mL	None	Revaccinate	Yes
	Any result	›10 mIU/mL	No action required		
Unvaccinated/ incomplete vaccination	Positive/ Unknown	-	HBIG once	Complete vaccination	Yes
	Negative	-	None	Complete vaccination	Yes

*HCW: Healthcare worker

§HBIG: Hepatitis B Immunoglobulin as soon as possible when indicated (0.06mL/Kg IM) or consult product literature

Anti-HBs titre should be performed 1-2 months after last dose of HBV vaccination series but ~ 4-6 months after HBIG to avoid detection of passively administered anti-HBs

Responder: person with anti-HBs > 10 mIU/mL after 3 or more HBV vaccination doses

Non-responder: person with anti-HBs < 10 mIU/mL after 6 or more HBV vaccination doses

N.B. All HCWs who have anti-HBs < 10 mIU/mL, unvaccinated or incomplete vaccination and sustain exposure to a source patient who is HBsAg-positive/ unknown HBsAg status should undergo HBsAg screening as soon as possible after exposure and follow up testing ~ 6 months later (HBsAg + anti-HBc).

Annex 2a: Hepatitis B and C (HBV and HCV) Viral Markers and their significance

Virus	Markers	Significance
HBV	HBV DNA	Markers of HBV replication. Present in acute and chronic infections, and for both wild type and pre-core mutant* HBV infections
	HBsAg	First serological marker to appear. Persistence for at least 6 months indicates chronic infection
	Anti-HBs	Detectable after HBsAg clearance and indicates complete recovery or immunity after immunisation with vaccine
	Anti-HBcIgM	Serological marker for acute infections. Single distinctive marker for recent infection
	Anti-HBcIgG	Indicates previous infection; not associated with recovery of immunity
	HBeAg	Serological marker for both acute and chronic infection. Remains positive during active viral replication but may be negative during mutant viral replication.
	Anti-HBe	Signals a cessation or minimal HBV replication. Prognostic marker for eventual improvement in hepatic pathology
HCV	Anti-HCV	Indicates active or past HCV infection
	HCV RNA	Marker for active HCV infection

*HBV DNA-Hepatitis B virus genomic DNA;

Annex 2b: Hepatitis B and C Viral Markers and Their Meaning

- HBsAg-Hepatitis B surface antigen
- Anti HBs-Antibody to hepatitis B surface antigen
- Anti HBcIgM-Early antibodies to hepatitis B core antigen
- Anti HBcIgG-Late antibodies to hepatitis B core antigen
- HBeAg-Hepatitis B e antigen
- Anti HBc-Antibodies to hepatitis B c antigen
- Anti HCV - Antibody to hepatitis C virus
- HCV RNA-Hepatitis C genomic RNA.
- In acute HBV infections, markers present are HBsAg, HBeAg and antiHBcIgM with or without HBV DNA.
- In chronic HBV infections, HBeAg is present with anti HBcIgG.
- Fully resolved HBV infection has no antigens present, but with all antibodies except anti HBcIgM.
- Pathogenicity of pre-core mutants are similar to wild type and can replicate in the presence of anti Hbe.

Annex 3: Tests for Assessment and Monitoring of Hepatitis B Infection

Test	Definition
Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)	Intracellular enzymes which, as they are released after cell injury or death, reflect liver cell injury
HBV DNA	HBV viral genomes that can be detected and quantified in serum. HBV DNA correlates with levels of circulating viral particles. HBV DNA is measured as IU/mL or copies/mL. 1 IU/mL ~ 5.3 copies/mL, and so values given as copies/mL can be converted to IU/mL by dividing by a factor of 5. (i.e. 10 000 copies/mL = 2000 IU/mL; 100 000 copies/mL = 20 000 IU/mL; 1 million copies/mL = 200 000 IU/mL). All HBV DNA values in the recommendations in these guidelines are reported in IU/mL. An undetectable viral load is an HBV DNA level below the level of sensitivity of the laboratory assay. For sensitive polymerase chain reaction assays, this is generally a concentration below 15 IU/ml.
AFP (alpha-fetoprotein)	A host cellular protein. High levels can occur in persons with hepatocellular carcinoma.
Persistently abnormal or normal ALT level	ALT levels fluctuate in persons with chronic hepatitis B and require longitudinal monitoring to determine the trend. Upper limits for normal ALT have been defined as below 30 U/L for men and 19 U/L for women, although local laboratory normal ranges should be applied. Persistently abnormal or normal may be defined as three ALT determinations above or below the upper limit of normal, made at unspecified intervals during a 6–12-month period or predefined intervals during a 12-month period.

Annex 4: Assessment of Liver Fibrosis by Non-Invasive 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 (10^9/L x [ALT (IU/L)1/2]).
FibroTest (FibroSure)	Commercial biomarker test that uses the results of six blood markers to estimate hepatic fibrosis
Transient elastography (FibroScan)	A technique to measure liver stiffness (as a surrogate for fibrosis) and is based on the propagation of a shear wave through the liver

Annex 5: Viral Hepatitis Summary Reporting Form

Region	District	Sub-district	Year	Month

Officially Expected Number of Reports_____Number of Reports received_____ Number of Reports received on time_____

C–cases; D– Deaths; LC– Lab. Confirmed; HAV–Hepatitis A; HBV–Hepatitis B; HCV–Hepatitis C; HDV–Hepatitis D; HEV–Hepatitis E

Reporting Sub-District/ Health Facility	Suspected Viral Hepatitis			Acute Viral Hepatitis										Chronic Hepatitis				Others*	
				HAV		HBV		HCV		HDV		HEV		Chronic Hepatitis B		Chronic Hepatitis C			
	C	D	LC	C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D
Total																			

Name of Person Reporting: _____ Telephone No.: _____ E-mail:

Date Report sent to next level: / / Name of Person Receiving:_____

Date Report Received at next level: / / Telephone No.: E-mail

*Lab test negative for Viral Hepatitis A, B, C, D and E

Annex 6A: Acute or Chronic Viral Hepatitis Case Investigation Form

Acute or Chronic Viral Hepatitis Case Investigation Form		
No.	**Variable/Description**	**Answer**
General characteristics – identification		
1	Epid. Number (e.g. GHA-RRR-DDD-YY-NNN)	GHA- _ _ _ - _ _ _ - _ _ - _ _ _
2	GPS coordinates: Latitude; Longitude	
3	Reporting Region	
4	Reporting District	
5	Reporting health facility	
6	Patient Health Facility Identification Number	
7	Date seen at health facility (dd/mm/yyyy)	/__ __/__ __/__ __ __ __/
8	Date health facility notified district (dd/mm/yyyy)	/__ __/__ __/__ __ __ __/
9	Patient Surname	
10	Patient Other Names	
11	Name of mother/father/ Care taker if child ≤ 12 years	
12	Date of birth (dd/mm/yyyy)	/__ __/__ __/__ __ __ __/
13	Country of Birth	
14	Age (Completed Years, Months, Days)	☐ Years ☐ Months ☐ Days
15	Sex: M=Male F=Female	
16a	Patient's residential Address: (House Number, Location, Community of residence)	
16b	Telephone number	
16c	Occupation	
16d	Place of work	
17	Urban/Rural	
18	Sub-district of Residence	
19	District of Residence	
20	Region of Residence	
21	Country of Residence	
Clinical characteristics and testing circumstances		
22	Clinical diagnosis	Acute ☐ Chronic ☐
23	Acute Onset	Yes ☐ No ☐
24	If Acute, Onset Date (first symptoms) (dd/mm/yyyy)	/__ __/__ __/__ __ __ __/
25	Systematic testing (Screening)	Yes ☐ No ☐
26	History of chronic hepatitis	Yes ☐ No ☐
27	In-patient or Out-patient?	
28	If In-patient, date of admission (dd/mm/yyyy)	/__ __/__ __/__ __ __ __/
29	Clinical Signs and Symptoms	Jaundice: Yes ☐ No ☐ Others:

Acute or Chronic Viral Hepatitis Case Investigation Form		
Prior Diagnosis and Treatment History		
30	Previously identified with chronic HBV infection	Yes ☐ No ☐ Unknown ☐
31	Previously identified with chronic HCV infection	Yes ☐ No ☐ Unknown ☐
Hepatitis Vaccination History		
32	Has the person ever received at least one dose of hepatitis A vaccine?	Yes ☐ (____doses) No ☐
33	Has the person ever received at least one dose of hepatitis B vaccine?	Yes ☐ (____doses) No ☐
34	Has the person ever received at least one dose of hepatitis E vaccine?	Yes ☐ (____doses) No ☐
35	Date of last vaccination (dd/mm/yyyy)	/__ __/__ __/__ __ __ __/
General Exposures		
36	Is the person health-care worker exposed to blood through patient care?	Yes ☐ No ☐ Unknown ☐
37	Is the person a man who has sex with other men?	Yes ☐ No ☐ Unknown ☐
38	Does the person undergo chronic haemodialysis?	Yes ☐ No ☐ Unknown ☐
39	Does the person inject recreational drugs?	Yes ☐ No ☐ Unknown ☐
40	Is the person involved in a reported, identified outbreak?	Yes ☐ No ☐ Unknown ☐
Possible exposures in the 2–6 weeks before onset (acute hepatitis only)		
41	Was there contact with patient(s) with the same symptoms?	Yes ☐ No ☐ Unknown ☐
42	Did the person drink water from a well or other unsafe water source?	Yes ☐ No ☐ Unknown ☐
43	Did the person eat unwholesome food e.g. raw, uncooked shellfish?	Yes ☐ No ☐ Unknown ☐
44	Is the person a child or a staff member in a day-care centre?	Yes ☐ No ☐ Unknown ☐
45	Did the person travel to an area highly endemic for hepatitis A?	Yes ☐ No ☐ Unknown ☐
Possible exposures in the 1–6 months before onset (acute hepatitis only)		
46	Did the person receive injections in a health-care setting?	Yes ☐ No ☐ Unknown ☐
47	Was the person hospitalized?	Yes ☐ No ☐ Unknown ☐
48	Did the person undergo surgery?	Yes ☐ No ☐ Unknown ☐
49	Did the person receive a blood transfusion?	Yes ☐ No ☐ Unknown ☐
50	Did the person go to the dentist?	Yes ☐ No ☐ Unknown ☐
51	Was there sexual contact with someone with hepatitis B?	Yes ☐ No ☐ Unknown ☐
52	Was there household contact with someone with hepatitis B?	Yes ☐ No ☐ Unknown ☐
53	Was there unprotected sex with non-regular partner(s)?	Yes ☐ No ☐ Unknown ☐
54	Skin piecing and tattooing	Yes ☐ No ☐ Unknown ☐
55a	Outcome (1=Alive; 2=Dead; 3=Unknown)	
55b	If dead, Date of death (dd/mm/yyyy)	/__ __/__ __/__ __ __ __/
56	Final classification (1=Lab Confirmed; 2=Confirmed by Epidemiological linkage; 3=Discarded (lab negative); 4= Pending (Suspected with specimen lab results pending)	

Viral Hepatitis Laboratory Reporting Form		
Part I. Referring health worker to complete this form and send a copy to the lab with the specimen		
	Variable	**Answer**
1	Date sample collected (dd/mm/yyyy)	/__ __/__ __/__ __ __ __/
2	Date sample sent to Laboratory (dd/mm/yyyy)	/__ __/__ __/__ __ __ __/
3	Type of sample (specify)	
4	Date laboratory received sample (dd/mm/yyyy)	/__ __/__ __/__ __ __ __/
5	Epid Number (e.g. GHA-GAR-DDD-YY-NNN) *	GHA- _ _ _ - _ _ _ - _ _ - _ _ _
6	Patient name(s)	
7	Sex: (M= Male F= Female)	
8	Age (Completed Years, Months, Days)	☐ Years ☐ Months ☐ Days
9	Person sending sample: Name, Designation, Tel No., E-mail	
Part II. Laboratory Officer to complete this section and return the form to district and clinician		
	Laboratory Name and location	
10	Sample condition 1=adequate (good) 2=not adequate (not good)	
11	Lab Results: Hepatitis A: Anti-HAV IgM Hepatitis B: HBsAg or IgM anti-HBc Hepatitis C: Anti-HCV Hepatitis D: HBsAg or IgM anti-HBc plus anti-HDV Hepatitis E: IgM anti-HEV and/or IgG anti-HEV	Anti-HAV IgM Pos Neg Unknown Anti-HBc IgM Pos Neg Unknown HBsAg Pos Neg Unknown Anti-HCV Pos Neg Unknown HCV RNA Pos Neg Unknown HCV core Ag Pos Neg Unknown HCV genotype Anti-HEV IgM Pos Neg Unknown
12	Other lab results	
13	Date laboratory sent results to Clinician (dd/mm/yyyy)	/__ __/__ __/__ __ __ __/
14	Date laboratory sent results to District (dd/mm/yyyy)	/__ __/__ __/__ __ __ __/
15	Date district received laboratory results (dd/mm/yyyy)	/__ __/__ __/__ __ __ __/
16	Name of Lab Personnel completing form Phone number Signature E-mail address Date	

* The epid number should be the same as one in the acute or chronic viral hepatitis investigation form

ANNEX 6B: LINE LIST FOR REPORTING VIRAL HEPATITIS CASE-BASED INFORMATION

Line List for reporting Viral Hepatitis case-based information

Reporting: Health Facility: _____ **Sub-district:** _____ **District:** _____ **Region:** _____

Epid Number	Epid Week	(0)ut, (n) (S)creening	Name	Place of Residence				Age (completed sex: years, in M=Male moths, if F=Female <1year)	Telephone Number	Occupation	Place of Work	Date Seen at health facility	Date Seen at health facility (DD/MM/YY)	Hepatitis Vaccination History	
				Community/ Town	Subdistrict	District	Region							Vaccinated Yes/No	If Yes Which Vaccine

LINE LIST FOR REPORTING VIRAL HEPATITIS CASE-BASED INFORMATION

Clinical Signs and Symptoms	Date of Onset (DD/MM /YY)	Date Sample Collected (DD/MM /YY)	Laboratory Test and Results		Final classification (1=Lab Confirmed; 2=Confirmed by Epidemiological linkage; 3=Not a case (lab (Suspected with specimen lab results pending)	Outcome (1=Alive 2=Dead 3=Uknown)	If Dead, Date of Death (DD/MM /YY)	Viral Hepatitis Vaccine Administration			Referred for Treatment Yes/No	If Yes Where?	Date Started Treatment	Treatment Outcome			Comments
			RDT e.g Hep. A,B,C,D & E	PCR				Type of Vaccine and Date (DD/MM /YY) 1st Dose	Type of Vaccine and Date (DD/MM /YY) 2nd Dose	Type of Vaccine and Date (DD/MM /YY) 3rd Dose				Cured? Yes/No	Viral Supression Yes/No	Lose to Follow-up Yes/NoS	

Name of Person Reporting: _____ **Phone Number:** _____ **E-mail address**_____ **Date:** ___/___/_____

Signature:_____

Annex 7: District/Health Facility Viral Hepatitis Blood Donors Screening Reporting Form

Region_____ District_____

Sub-District _____ Year _____ Month____

Officially Expected Number of Reports_____ Number of Reports received_____

Number of Reports received on time_____

HAV=Hepatitis A; HBV=Hepatitis B; HCV=Hepatitis C; HDV=Hepatitis D; HEV=Hepatitis E

Reporting Sub-District	**Number of Blood Donors Screened**	**Number of blood donors Positive for Viral Hepatitis**					**Number of Blood Donors Negative for Viral Hepatitis**
Name of Facility		**HAV**	**HBV**	**HCV**	**HDV**	**HEV**	

Name of Person Reporting: _____

Telephone No.: _____ E-mail_____

Date Received at next level: ____/____/_____

Name of Person Receiving: _____

Telephone No.: _____ _____ E-mail_____

4. How do you get viral hepatitis?

- You can get Hepatitis A and E virus by eating or drinking contaminated food or water
- You can get Hepatitis B, C and D viruses by;
    - Sharing drug needles with an infected person.
    - Sharing toothbrushes, razors or such personal care items with an infected person.
    - Getting pricked with a needle that has infected blood on it (especially for health workers).
    - Tattooing, body piercing

5. How can I protect myself from getting viral hepatitis B and C?

- Do not share personal care items such as razors, toothbrushes, needles etc.
- Consider the risk if you are thinking about tattooing or piercing any part of your body. Only use sterile instrument if you have to.
- If you have or had Hepatitis B or C, do not donate blood, organs or tissue.
- Practice safe sex using barrier methods such as latex condoms every time you have sex.
- Vaccination offers the best protection against Hepatitis B.
- There is no vaccine for Hepatitis C. Limit exposure to infection.
- If you are a health care or public safety worker, get vaccinated for Hepatitis B and always follow routine barrier precautions when handling needles and other sharp objects.
- If you are pregnant you should get a blood test for Hepatitis B and C. Knowing your status may help prevent your newborn baby from being infected. It will also inform management for you and your child.

Annex 8: Sample Messages on Viral Hepatitis

1. What is hepatitis?

- Hepatitis means inflammation of the Liver (injury to liver cells). Hepatitis can be caused by toxins, drugs, and heavy alcohol use, bacterial and viral infections. Hepatitis is most often caused by one of several viruses.

2. What is viral hepatitis?

- Viral Hepatitis is inflammation of the liver caused by the Hepatitis viruses A, B, C,D, E. It makes your liver swell and stops it from functioning properly.

3. What are the symptoms of viral hepatitis?

- Some people do not have any symptoms. However, it has been shown that if you are infected with Hepatitis B or C, liver damage continues regardless of the signs and symptoms.
- Early symptoms may be non-specific, including fever, a flu-like illness, and joint pains.
- You might:
    - Feel tired
    - Feel abdominal discomfort
    - Have a fever
    - Have poor appetite, Nausea and Vomiting
    - Have stomach pain
    - Have diarrhoea
- When symptoms appear the infected person who needs treatment and does not get treated could develop complications.
- If you have symptoms or think you might have viral hepatitis, visit the nearest hospital/clinic for care and support.

4. To prevent viral hepatitis A and E one needs to:

- Wash hands thoroughly with soap under safe running water before eating, or feeding a baby or handling food, after toilets or handling any suspected material
- Eat all foods warm/hot
- Avoid buying foods that are not covered or sold around dirty gutters or filthy environment
- Wash fruits and vegetables thoroughly with safe water before eating
- Use the toilet for defecation. Avoid open defecation; if toilets are not available bury your faeces after defaecation

5. Talk to your Healthcare Professional for advice on TESTING, VACCINATION & TREATMENT FOR HEPATITIS B & C

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NATIONAL GUIDELINES **FOR PREVENTION, CARE AND TREATMENT OF VIRAL**

Hepatitis

ABCDE

For furthter information contact:
National Viral Hepatitis
Control Programme
Ghana Health Service
nvhcp@ghsmail.org