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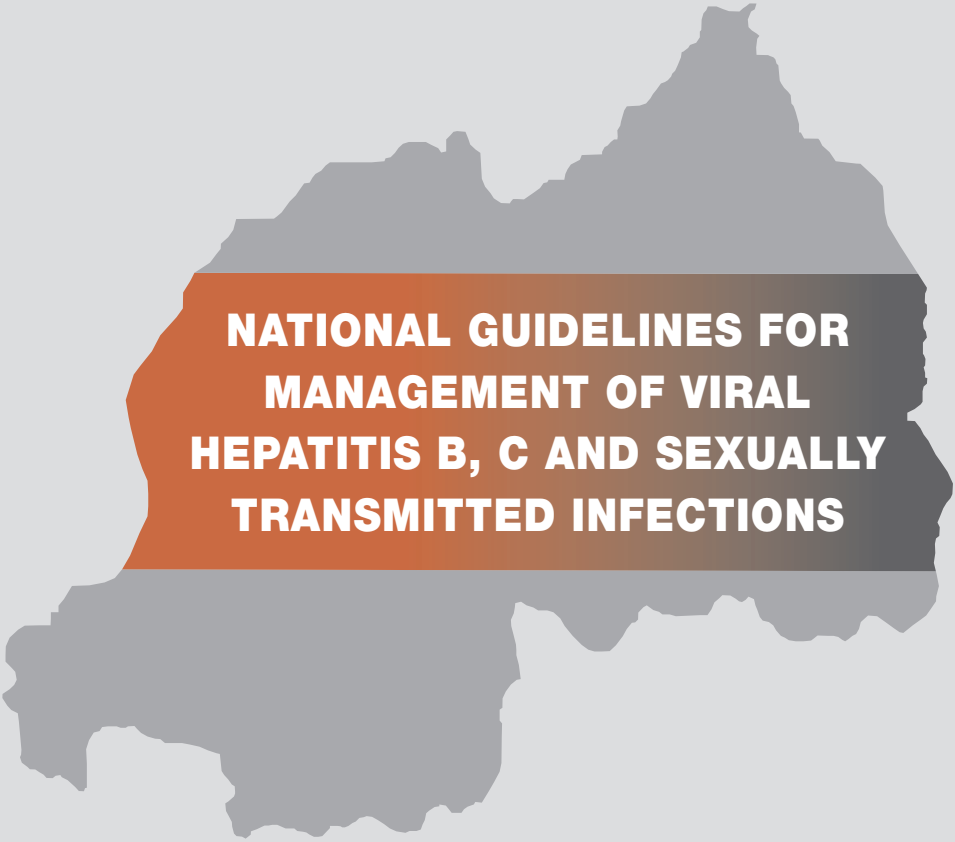

NATIONAL GUIDELINES FOR MANAGEMENT OF VIRAL HEPATITIS B, C AND SEXUALLY TRANSMITTED INFECTIONS

July 2024

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List of Acronyms and Abbreviation

AFP	:	Alpha Feto-Protein
AIDS	:	Acquired Immuno - Deficiency Syndrome
ALT	:	Alanine aminotransferase
Anti-HBe	:	Antibody to Hepatitis B e antigen
Anti-HBs	:	Antibody to the Hepatitis B surface antigen
Anti-HCV	:	Antibody to the Hepatitis C Virus
APRI	:	Aminotransferase to Platelet Ratio Index
ART	:	Antiretroviral Therapy
AST	:	Aspartate aminotransferase
BID	:	Two times a day
CBC	:	Complete Blood Count
CD4	:	Cluster of Differentiation 4
CHB	:	Chronic Hepatitis B
CHC	:	Chronic Hepatitis C
CHW	:	Community Health Workers
CKD	:	Chronic Kidney Disease
CLD	:	Chronic Liver Disease
CrCl	:	Creatinine Clearance
DAA	:	Direct Acting Antiviral
DCV	:	Daclatasvir
DDI	:	Drug-Drug Interaction
DNA	:	Deoxyribonucleic acid
eGFR	:	Glomerular Filtration Rate
EMTCT	:	Elimination of Mother to Child Transmission
ETV	:	Entecavir

FBC	:	Full Blood Count
GFR	:	Glomerular Filtration Rate
GP	:	General Practitioner
Hb	:	Hemoglobin
HBeAg	:	Hepatitis B Virus Early Antigen
HBIg	:	Hepatitis B Immunoglobulin
HBsAg	:	Hepatitis B surface Antigen
HBV	:	Hepatitis B Virus
HCC	:	Hepatocellular Carcinoma
HCV	:	Hepatitis C Virus
HDV	:	Hepatitis D Virus
HIV	:	Human Immunodeficiency Virus
IFN	:	Interferon
LDV	:	Ledipasvir
MoH	:	Ministry of Health
MSM	:	Men who have Sex with Men
MTCT	:	Mother To Child Transmission
NA	:	Nucleos(t)ide Analogue
N/A	:	Not Applicable
NAAT	:	Nucleic Acid Amplification Technology
NIT	:	Non-Invasive Tests
NRL	:	National Reference Laboratory
OD	:	Once daily
QID	:	Four times a day
RBC	:	Rwanda Biomedical Centre
RBV	:	Ribavirin
RDT	:	Rapid Diagnostic Test
RMS	:	Rwanda Medical Supply

RNA	:	Ribonucleic Acid
RT-PCR	:	Reverse Transcription Polymerase Chain Reaction
RVR	:	Rapid Virological Response
SOF	:	Sofosbuvir
STIs	:	Sexually Transmitted Infections
SVR	:	Sustained Virological Response
TAF	:	Tenofovir Alafenamide Fumurate
TB	:	Tuberculosis
TDF	:	Tenofovir Disoproxil Fumarate
TID	:	Three times a day
VEL	:	Velpatasvir
VL	:	Viral Load
VOX	:	Voxilaprevir
WHO	:	World Health Organization

Preface

Viral Hepatitis B (HBV) and C (HCV) infections are characterized by the inflammation of liver cells and may cause hepatocellular carcinoma (HCC) and cirrhosis if not treated. HBV and HCV infections can be either acute or chronic, and the associated illness ranges in severity from asymptomatic to symptomatic and progressive disease.

According to recent World Health Organization (WHO) statistics, worldwide, it is estimated that 296 million people are chronically infected with HBV, particularly in low and middle income countries[1]. Between 20% and 30% of those who become chronically infected will develop advanced complications and an estimated 820,000 people will die annually due to chronic HBV[2]. More than 58 million people around the world have chronic HCV infection and an estimated 290,000 people will die annually due to HCV-related complications[3]. The majority of people are unaware of their HBV and HCV infection. Among those who are diagnosed, treatment remains inaccessible and with the current HIV pandemic, the viral hepatitis and HIV co-infection remains critical. In Rwanda, HBV diagnosis is based on HBsAg rapid test followed by a confirmatory DNA molecular test.

Antiviral agents, active against HBV are available and have been shown to suppress HBV replication, prevent progression to cirrhosis, and reduce the risk of HCC and liver-related deaths. Current HBV treatments fail to eradicate the virus in most of treated cases, necessitating potentially lifelong treatment[4]. In Rwanda the available HBV antivirals include Tenofovir and Entecavir. However, universal hepatitis B immunization programs that target infants, with the first dose at birth, have been highly effective in reducing the incidence and prevalence of hepatitis B in many endemic countries.

Hepatitis C infection differs from other chronic viral infections such as HIV and HBV as it can now be cured using antiviral active treatments. In Rwanda, HCV diagnosis is based on HCVAb rapid test followed by confirmatory HCV RNA molecular test. Regarding treatment, several medicines are available to treat persons infected with HCV, and the cure rate has steadily improved with the introduction of newer medicines since 2012[5]. These new direct acting antivirals (DAAs) can cure more than 95% of persons with HCV infection and are effective against genotypes that were previously difficult to treat. In Rwanda the available HCV DAAs include but not limited to Sofosbuvir-Daclatasvir, Sofosbuvir-Velpatasvir and Sofosbuvir-Velpatasvir-Voxilaprevir.

In regards to sexually transmitted infections (STIs), more than a million STIs are acquired every day around the world [6]. STIs can have serious consequences such as increasing the risk of HIV acquisition, cervical cancer, and pelvic inflammatory diseases and in case of mother-to- child transmission, increase risk of adverse birth outcomes.

The current national guidelines for the management of HBV, HCV and STIs have been developed in line with the WHO guidelines. It thus responds to the Ministry of Health needs to improve the skills of health care providers as well as the quality of care and treatment offered in both public and private health facilities countrywide. to improve the quality of life of people infected with HBV, HCV and STIs.

These guidelines would not have been finalized without the usual support of all the stakeholders who are involved in the domain of STIs and other blood borne infections control in Rwanda.

We give our sincere thanks and appreciation to hepatitis technical working group members and other respective organizations that contributed to the development of these guidelines.

Dr. Sabin Nsanzimana
Minister of Health

Acknowledgment

The Rwanda Biomedical Centre is aware of the global burden of viral hepatitis and sexually transmitted infections and is committed to prioritize their prevention and control and ensure that healthcare providers are fully skilled in order to help all patients in need with a goal of having a healthy people and a wealthy nation.

We recognize the support of the Ministry of Health, RBC staff, stakeholders and health care providers who contributed to the elaboration and revision of the 2023 national guidelines for management of viral hepatitis B, C and sexually transmitted infections.

Furthermore, we give our sincere gratitude to the organizations that provided the technical and financial support. We also appreciate everyone's effort that contributed to the revision of these guidelines; accept our heartfelt gratitude.

We strongly encourage all the healthcare professionals to ensure that viral hepatitis and STIs services are being provided to the population in line with these guidelines. We commit to provide continuous mentorships, trainings and refresher courses for the proper implementation of these guidelines.

Prof Claude Mambo Muvunyi
Director General
Rwanda Biomedical Centre

PART I

MANAGEMENT OF HEPATITIS B INFECTION

Chapter I: Generalities on hepatitis B infection

Summary: Generalities on hepatitis B infection

Hepatitis B virus (HBV) infection is an inflammation of the liver caused by hepatitis B virus. It can present in acute or chronic form depending on the duration of the infection. Acute infection is characterized by the presence of Hepatitis B surface Antigens (HBsAg) within six months of acquiring infection and the infection is self- limited to six months and cleared. Recovery is accompanied by clearance of HBsAg with seroconversion to anti-HBs (antibodies to hepatitis B surface antigen), usually within 3 to 6 months. HBV infection is self- limiting and the virus can be cleared within 6 months of infection for 90-95% of adults while only 5-10% progress to chronic infection.

Chronic infection is defined as the persistence of HBsAg for more than 6 months after acute infection with HBV, it can be prevented by a vaccine but cannot be cured once confirmed chronic, thus a lifelong treatment is recommended Over time, the chronic infection can cause liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC).

HBV shares the same mode of transmission as HIV, but it is highly contagious: 10 times more contagious than HCV and 100 times more contagious than HIV. It is mainly transmitted through blood and sexual fluids.

1.1. Definitions

Hepatitis B virus infection: Inflammation of the liver caused by hepatitis B virus. It can present in acute or chronic form depending on the duration of the infection.

Acute HBV infection: Presence of HBsAg within six months of acquiring infection. Recovery is accompanied by clearance of HBsAg with seroconversion to anti-HBs, usually within 3 to 6 months.

Chronic HBV infection: Defined as the persistence of HBsAg for 6 months or more after acute infection with HBV.

Immune-tolerant phase: High replicative phase of infection seen in the early stage of chronic HBV among people infected at birth or in early childhood.

Immune-active phase: Phase of hepatitis B e antigen (HBeAg)-positive characterized by fluctuating aminotransferases and high HBV DNA concentrations. It may result in seroconversion from HBeAg to antibody to hepatitis B e antigen (anti-HBe).

Inactive phase (or immune-control phase): Low replicative phase of chronic hepatitis B characterized by HBeAg negativity, anti-HBe positivity, normal alanine aminotransferase (ALT), and HBV DNA concentration below 2000 IU/mL.

HBeAg seroconversion: Loss of HBeAg and seroconversion to anti-HBe.

HBsAg seroconversion: Loss of HBsAg and development of anti-HBs.

HBeAg reversion: Reappearance of HBeAg in a person who was previously HBeAg negative and usually associated with increased HBV replication.

Cirrhosis: An advanced stage of liver disease characterized by extensive hepatic fibrosis, nodularity of the liver, alteration of liver architecture, and disrupted hepatic circulation.

Decompensated cirrhosis: Clinical complications of cirrhosis become manifest, including jaundice, ascites, spontaneous bacterial peritonitis, esophageal varices and bleeding, hepatic encephalopathy, sepsis, and renal failure.

Hepatocellular carcinoma (HCC): Primary cancer of the liver arising in hepatocytes.

Treatment interruption: For the application of these guidelines, treatment interruption refers to stopping medications at any point of the treatment course.

Lost to follow-up: the patient is said to be lost to follow-up when he/she missed an appointment at a treating health facility for 3 months.

Persistently normal/abnormal ALT: Three ALT determinations below or above the upper limit of normal, made at unspecified intervals during 6-12 months period or predefined intervals during a 12-month period.

1.2. Transmission of HBV

HBV shares the same mode of transmission as HIV, but it is highly contagious: 10 times more contagious than HCV and 100 times more contagious than HIV[24, 25]. It is transmitted through the following modes:

- Blood and biological fluids contact (including needle stick injury);
- Unsafe blood transfusion and blood product transfusion;
- Unprotected sexual contact (heterosexual and homosexual);
- Vertical transmission (mother to child): perinatal transmission (at the time of, or shortly after birth, and rarely in the second or third trimester of pregnancy);
- Horizontal transmission: household contact, intra-familiar, child-to-child;
- Shared syringe use (for health facilities or intravenous drug users);
- Other unhygienic medical practice (razors, inadequate sterilization, dental and surgical procedures);

- Unhygienic practice of non-medical risk associated activities, such as manicures/pedicures, tattoos, toothbrush sharing, traditional surgical and scarification practice, haircuts etc.

Groups at high risk of hepatitis B infection

- Health care workers;
- People who are exposed to unsafe blood or blood products;
- Individuals infected with HIV or HCV;
- Inmates of correctional facilities;
- Persons who have ever injected drugs;
- Pregnant women;
- Children born to HBV positive mothers;
- Household and sexual contacts of HBs Ag-positive person;
- Patients undergoing renal dialysis and other invasive medical procedures;
- Sex workers;
- Men having sex with men (MSM);
- History of multiple sexual partners or STIs;
- Refugees;
- Individuals practicing body piercing or tattooing;
- People with immunosuppressive conditions.

High risk groups have been encouraged to create networks. This strategy has been highly effective allowing health care providers (HCPs) to reach them easily through their networks or their gathering locations (e.g., MSM, FSW, PLHIV, prisoners, refugees). This also allows high risk groups to access HBV services easily including targeted vaccination, screening, care, and treatment. Mass screening campaigns and routine hepatitis care provided in health facilities are also used to reach them.

Chapter II: Hepatitis B prevention

Summary: Hepatitis B prevention

Hepatitis B prevention consists of primary, secondary, and tertiary prevention. Primary prevention consists of all measures put in place before the onset of infection while secondary and tertiary preventions aim at preventing complications of the disease after its onset. The most critical primary prevention measure is vaccination against HBV.

This chapter details recommended vaccination schedule in Rwanda. Hepatitis B can be transmitted from HBV-infected pregnant mother to her child during pregnancy or perinatal period. The most important strategy to prevent mother-to-child transmission of HBV is the administration of the **birth dose vaccine** to the child within 24 hours after birth alongside with Hepatitis B Immune Globulin (HBIG) if available. To avoid infection, all potential sources of contact with infected individuals should be avoided.

Secondary, and tertiary prevention measures are also necessary for early detection and treatment but also reduction of transmission and prevention of disease complications.

Most people infected with HBV are unaware of their chronic infection. They are at high risk of developing severe chronic liver diseases and can unknowingly transmit the infection to other people.

2.1. Primary prevention of hepatitis B infection

The primary prevention of hepatitis B infection consists of activities aiming at reducing or eliminating potential risk for HBV transmission such as increasing awareness and knowledge on HBV transmission and prevention among general and high-risk population. Reaching high-risk groups has been done generally through their networks or mass screening. The following are specific areas of HBV primary prevention:

2.1.1. Communication for behavior change

- Increase awareness, knowledge and behavior change on HBV transmission, and prevention among the general population and high-risk groups;
- Train health care providers on HBV transmission, prevention, and behavior change.

2.1.2. Infection control precautions in community settings

- Avoid unsafe practices: cosmetic procedures, scarification, tattoos, circumcision practice and tooth extraction out of medical settings, etc;
- Harm reduction practices for injecting drug users to prevent HBV transmission;
- Safe household practice (avoid handling or sharing sharp objects, sharing toothbrushes, blood contact, unprotected sexual contact with carriers etc.);
- Promote correct and consistent condom use;
- Avoid multiple partners, seek regular screening and treatment for STIs;
- Routine screening of sex workers and provision of HBV immunization;
- Vaccinate HBsAg negative individuals;
- Put in place integrated actions to increase access to medical and social services to victims of gender violence.

2.1.3. Prevention of HBV infection in health-care settings

Put in place occupational safety measures to prevent transmission of viral hepatitis to health care workers or patients through:

- Hand hygiene including surgical hand preparation, hand washing and use of gloves;
- Safe handling and disposal of sharps and waste;
- Safe cleaning of equipment;
- Testing of donated blood and blood products;
- Improved access to safe blood and blood products;
- Training of health care personnel;
- Follow standard universal precautions with open cuts or bleeding;
- Safe injections in medical facilities;
- Management of HBV infected patients including health care providers;
- Precaution is needed in health settings such as: dialysis, maternity, etc.

2.1.4. HBV vaccination

2.1.4.1. HBV infant vaccination

HBV birth dose vaccine consists of a single dose monovalent vaccination administered within 24 hours of birth to all babies when it is universal and those born from HBV infected mothers when it is targeted. We recommend the administration of a universal HBV birth dose if possible and a targeted HBV birth dose if the universal cannot be implemented. The targeted HBV birth dose is mandatory for all babies born to infected mothers, and if possible, it should be co-administered with HBV Immune Globulin (HBIG). The HBV birth dose is followed by three routine doses of HBV vaccine as per the current Hepatitis B vaccination schedule. The subsequent three doses are administered at week 6, 10 and 14 of life and are co-administered with diphtheria, tetanus, whopping cough and haemophilus influenza

type B as part of the pentavalent vaccine [3]. All infants born to infected mothers must be followed up for HBsAg testing at 24 months to determine HBV infection status and further HBV treatment from 2 years of age if infected.

All older children who did not get all the recommended doses of hepatitis B vaccine as an infant should complete their vaccine series as soon as possible. Adolescents and adults who were not vaccinated in their young age are at increased risk of acquiring HBV infection, and they should also be vaccinated.

2.1.4.2. Routine adult vaccination for HBV

In Rwanda, HBV vaccination program for infants started in 2002. Catch-up vaccination is needed for people who were not targeted by infants' vaccination and for anyone who desires protection from hepatitis B. Blood testing before vaccination is recommended for children and adults. HBsAg negative people should receive HBV vaccine for their protection but HBsAg positive people should not be vaccinated, rather, they are referred to care and treatment (*See algorithm in Figure 2*). Vaccinating a person already immune to or infected with HBV will not bring any benefits or harm (*See Table 1 for vaccine schedule*).

In case of interruption of vaccine schedule, vaccine series should be continued rather than restarted. When possible, HBV antibody titer can be measured at least 2 months after last dose of vaccine to assess the level of the immune response. Present and past household and sexual contacts of HBsAg positive individuals are recommended to be followed up, get tested and receive HBV vaccination if they screen negative for HBsAg or be linked to care and treatment if HBsAg positive. National Guidelines for HBV, HCV and STIs management.

Table 1: Hepatitis B vaccination schedule in Rwanda [7]

Hepatitis B Vaccination Schedule Recommended in Rwanda					
No	**Group**	**Dose 1**	**Dose 2**	**Dose 3**	**Dose 4**
1.	Newborn	< 24 Hours	Week 6	Week 10	Week 14
2.	Children/Adult	M0	M1	M6	N/A
3.	HIV+ Adult	M0	M1	M2	M6

Recommendations

It is recommended to vaccinate babies within 24 hours after birth to prevent mother to child transmission and prevent HBV infection before week 6 of life when they start pentavalent vaccines:

- Adult dose is 1ml and 0.5ml for newborns.
- The dose is doubled (2 ml) in HIV-positive adult people.
- Pre-and post-counseling for screening of HBsAg is required priorto vaccination.
- When vaccine schedule is interrupted, vaccination series should be continued rather than restarted.

2.1.5. HBV post-exposure prophylaxis

2.1.5.1. General measures

After exposure to blood or other body fluids, the following is recommended as soon as possible:

- Wash the wound site with soap and water;
- If eyes are contaminated, gently and thoroughly rinse eyes while open, with water or normal saline;
- If blood or other body substances are consumed in mouth, spit substances and rinse mouth with water several times;
- If clothing is contaminated, remove clothing and shower with soap;
- When water is unavailable, wash cuts or skin punctures with non-water cleanser or antiseptic.

2.1.5.2. Specific measures

Hepatitis B exposure management depends on the following:

- The HBV immuno-status of the exposed person;
- Level of protection of exposed individual (fully or partially immunized and/or immune);
- If fully vaccinated, anti-HBs test is recommended and if found negative (<10 IU/mL), re-start the vaccination courses.

Exposed individuals with no immunity to HBV should ideally be administered first dose of HBV vaccine within 24 hours of exposure as an active immunization. Passive immunization against hepatitis B with Hepatitis B Immunoglobulin (HBIg) given within 24 hours and up to 14 days of exposure is also recommended when available [4]. In case HBIg is not available, the active immunization (HBV vaccine alone) is recommended (*Fig. 1*).

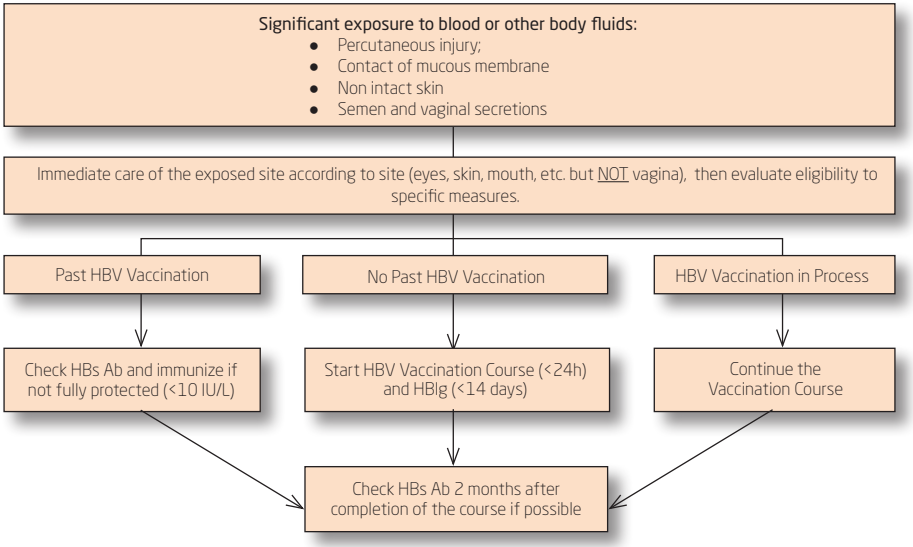


Figure 1: HBV Post Exposure Prophylaxis

An exposed individual should be followed up and tested for HBsAg after three months of exposure to exclude the infection and guided accordingly.

2.1.6. Prevention of mother to child transmission (PMTCT) of HBV

All pregnant women should be systematically screened for HBsAg at the first contact, and delivery and be followed up for treatment eligibility. All newborns should receive HBV birth dose vaccine within 24 hours after birth to prevent mother to child transmission but also to prevent HBV infection before they are enrolled in national child immunization program. Given the fact that HBV is mainly transmissible to newborn during delivery, HBV vaccine within 24 hours after birth, combined with HBIg (when available) should be administered to newborn from HBV infected mothers.[3].

All newborns should receive HBV birth dose vaccine within 24 hours after birth to prevent mother to child transmission

All infants born from HBV infected mothers should be followed up during the vaccination period and tested for HBV at two years. When the screening is positive, HBV DNA test will be done to assess the treatment eligibility.

Hepatitis B elimination plan is part of WHO global goals and the national plan for the triple Elimination of Mother to Child Transmission (eMTCT) of HBV, HIV, and syphilis. Thus every pregnant woman should be tested for HBV at first ANC visit and delivery, in addition to HIV and syphilis and managed accordingly.

Thus every pregnant woman should be tested for HBV at first ANC visit and delivery, in addition to HIV and syphilis and managed accordingly

In HBV infected pregnant women, eligibility criteria and indications for treatment are the same as for other adults, and treatment with tenofovir is recommended. All HBsAg positive pregnant women who are eligible for treatment based on the algorithm should start long term HBV treatment during pregnancy to prevent the transmission to their babies. In case of non-eligible pregnant women, a prophylaxis is provided, i.e. a woman is given TDF from the second trimester until completion of

infant HBV vaccination series. When a pregnant woman was on entecavir or any other regimen before pregnancy, it is recommended to switch to tenofovir based regimen except if contraindicated. For HBV/HIV coinfected adults and adolescents (with at least 30 kg of body weight), tenofovir + lamivudine (or emtricitabine)+ Dolutegravir (DTG) as a fixed-dose combination is recommended as the preferred option to initiate Antiretroviral Treatment (ART) [3, 10]. For children aged 2 to 11 years, Abacavir + Lamivudine (or emtricitabine) + Dolutegravir (DTG) + Entecavir is recommended.

2.2. Secondary and tertiary prevention of hepatitis B infection

This prevention aims at early detection of HBV infection for timely treatment and follow-up before any advanced liver disease and also reduces HBV transmission.

Early diagnosis helps infected people to take precautions to protect the liver from additional harm by abstaining from alcohol and tobacco consumption, avoiding certain toxic drugs, and adopting appropriate diet [8]. It is therefore advised to screen asymptomatic individuals with focus on high- risk groups to provide appropriate and timely counseling and close follow-up to those who screen HBsAg positive.

Chapter III: Screening and diagnosis of hepatitis B infection

Summary: Screening and Diagnosis of Hepatitis B Infection

Early detection of HBV infection helps prevent advanced liver diseases. ***It is thus recommended that everyone should be screened for Hepatitis B infection every 12 months although priority is given to high-risk populations where the screening is done every 6 months.*** Screening for hepatitis B infection is done by assessing the presence of HBsAg using rapid diagnostic tests (RDTs). In the general population, the presence of a single positive HBsAg using the RDT test calls for further evaluation of treatment eligibility. In person with HbsAg positive, diagnosis of HDV infection is recommended using a serological assay to detect total anti-HDV followed by a nucleic acid test (if anti-HDV is positive) to detect HDV RNA and active (viraemic) infection. In HIV-infected populations, cirrhotic persons, and patients with APRI score above 0.5 the presence of a single positive HBsAg is indicative of chronicity and calls for direct HBV treatment initiation[2].

3.1. Early detection for prevention of advanced liver diseases

Viral hepatitis B is a silent epidemic. Most acute HBV infections are asymptomatic or cause mild symptoms, which are often unrecognized [3].

Acute infection may cause nonspecific symptoms and clinical signs, such as: Jaundice, weakness, fatigue, malaise, anorexia, nausea, vomiting, myalgia, arthralgia, abdominal pain, hepatomegaly and splenomegaly, dark urine, and low-grade fever. Around 5-10% of adults acutely infected with hepatitis B virus progress to chronic

infection and stay in preclinical phase for decades [4]. In case of HDV co-infection, there is an accelerated progression to liver cirrhosis or liver cancer compared with CHB mono-infection. Early diagnosis of both HBV and HDV helps infected people to be treated and take precautions to protect the liver from additional harm by abstaining from alcohol, tobacco consumption, avoiding certain toxic drugs, or adopting appropriate diet. It is therefore advised to screen asymptomatic individuals with focus on high-risk groups to provide appropriate diagnosis pre- and post-counseling and close follow-up to those who screen HBsAg positive.

Hepatitis management services have been decentralized to the lowest level health facilities and the following diagnosis process is observed:

- The screening of asymptomatic individuals is done through routine care in health facilities including hospitals and health centers across the country in an integrated manner with other services;
- The recommended diagnosis of hepatitis B virus infection is the evaluation of the patient's blood for hepatitis B surface antigen (HBsAg). The viral load test comes in for eligibility to treatment;
- The presence of HBsAg confirms infection (acute or chronic);
- When available, other markers as detailed in the table below (HBsAg, Anti-HBs, Anti-HBc, IgM Anti-HBc) can help confirm chronicity of infection.

3.2. Interpretation of HBV serologic markers

Table 2: Interpretation of hepatitis B serologic test results

Interpretation of hepatitis B serologic test results		
Tests	**Results**	**Interpretation**
HBsAg	Negative	Susceptible to infection
Anti-HBc	Negative	
Anti-HBs	Negative	
HBsAg	Negative	Immune due to natural infection
Anti-HBc	Positive	
Anti-HBs	Positive	
HBsAg	Negative	Immune due to Hepatitis B vaccination
Anti-HBc	Negative	
Anti-HBs	Positive	
HBsAg	Positive	Acutely infected
Anti-HBc	Positive	
IgM anti-HBc	Positive	
Anti-HBs	Negative	
HBsAg	Positive	Chronically infected
Anti-HBc	Positive	
IgM anti-HBc	Negative	
Anti-HBs	Negative	

3.3. Hepatitis B infection screening criteria

General population should be screened for HBsAg with priority for high-risk groups.

The screening of hepatitis B should be done by assessing the presence of HBsAg using RDTs *(Figure 2)*. Following to a positive HBsAg, a viral load test is done as a confirmatory test. This can be achieved either through laboratory-based reflex NAT testing using a sample already held in laboratory, or clinic-based reflex testing in a health facility through immediate sample collection following a positive RDT HBsAg test.

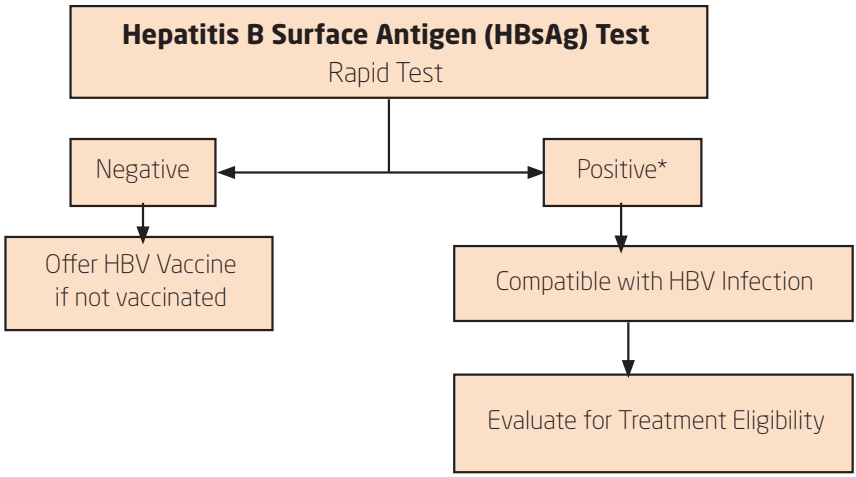


Figure 2: Algorithm for screening and diagnosis of chronic HBV infection

3.3.1. Hepatitis B screening schedules

Table 3: Hepatitis B screening schedules

Group	Initial	Results	Intervention
High risk groups	Systematic screening every 6 months	HBsAg-	Provide vaccine and check HBs Ab, 2 months after end of vaccine series, booster dose if not protected
		HBsAg+	Refer to care and treatment
Pregnant woman	Systematic screening at first contact and delivery	HBsAg-	Provide vaccine and check HBs Ab, 2 months after end of vaccine series, booster dose if not protected
		HBsAg+	Refer to care and treatment
Symptomatic people	Systematic screening at first contact	HBsAg-	Provide vaccine and check HBs Ab, 2 months after end of vaccine series, booster dose if not protected
		HBsAg+	Refer to care and treatment
General population	Screening once a year	HBsAg-	Provide vaccine and check HBs Ab, 2 months after end of vaccine series, booster dose if not protected
		HBsAg+	Refer to care and treatment

Chapter IV: The management of people with hepatitis B infection

Summary: treatment eligibility

After chronicity of hepatitis B infection is confirmed, an initial evaluation considers factors such as **liver function, age, liver fibrosis, and HBV DNA level. APRI score** should be calculated for all patients.

Patients **eligible** for treatment includes any of the following coupled with HBsAg positive result:

1. Co-infection with HIV, HCV and HDV;
2. Cirrhotic (compensated or decompensated);
3. Patients with APRI score > 0.5;
4. HBV DNA >2,000 UI/mL and /or persistent ALT level ULN (at least two occasions in a 6 to 12 months' period);
5. Patients with comorbidities (Diabetes mellitus, metabolism associated steatotic liver diseases;
6. Patients with immunosuppression (Chronic use of steroids, on immunosuppressant);
7. Family history of liver cancers or cirrhosis;
8. Extrahepatic manifestations of HBV (Gromerulonephritis or vasculitis).

Note: *The specialist review is mandatory for number 5, 6, 7 and 8 cases before treatment initiation.*

Regular follow-up of patients initiated on treatment is crucial to ensuring treatment adherence, monitoring potential side effects, and monitoring the development of HCC among patients with cirrhosis. The following assessment should be done during follow-up: creatinine levels, AST, ALT, side effects and adherence. For cirrhotic patients, AFP and liver ultrasound should be performed in addition to the above listed tests.

4.1. Evaluation of patients with chronic HBV infection

4.1.1. The Initial Evaluation

The baseline evaluation includes:

- History and physical examination;
- Family history of liver disease, and hepatocellular carcinoma (HCC);
- Lifestyle assessment with focus on alcohol consumption, over the counter medicine, traditional medicine, and diet;
- Laboratory tests to assess liver fibrosis (AST, ALT, Platelets) and HBV DNA;
- Ultrasound modalities to assess liver fibrosis such as transient elastography (Fibroscan or Fibrotest) or ultrasound scan;
- Tests to rule out viral co-infections: HIV, HCV and HDV;
- Tests to screen for HCC include Alpha fetoprotein (AFP), Ultrasound at baseline, CT scan or MRI and Liver biopsy (When possible).

4.1.2. Liver fibrosis assessment by non-invasive tests

APRI (Aspartate aminotransferase to Platelet Ratio Index) and transient elastography (FibroScan) are recommended as the preferred non-invasive tests to assess the presence of fibrosis or cirrhosis in people with viral hepatitis.

Aspartate aminotransferase (AST) to **P**latelet **R**atio **I**ndex **(APRI)** is a simple index for estimating liver fibrosis based on a formula derived from AST and platelet concentrations. For the purpose of early initiation of patients on therapy, the cutoff of > 0.5 should be considered as a significant fibrosis and the cutoff of > 1 as cirrhosis. Below is the formula to be used for APRI Score:

$$\textbf{APRI} = \frac{\dfrac{\text{AST Level}}{\text{AST (Upper Limit of Normal)}}}{\text{Platelet Count } (10^9/\text{L})} \times \mathbf{100}$$

APRI Score and liver fibrosis assessment formula[3]

In settings where Transient Elastography is available, the value of >7Kpa should be interpreted as a significant fibrosis and the value of >12.5 Kpa as evidence of Cirrhosis.

Table 4: Interpretation of Aminotransferase Platelet Ratio Index (APRI)[4]

APRI score	Interpretation	Action
> 0.5	High probability of fibrosis	Prioritize for treatment
>1	High probability of Cirrhosis	Prioritize for treatment
≤ 0.5	No potential risk of advanced Fibrosis	- Treatment is not recommended if no other eligibility criteria - Consider for treatment if persistently high transaminases without any other explanations (ex. No drug or alcohol-abuse etc.)

Assessment of HBV treatment eligibility

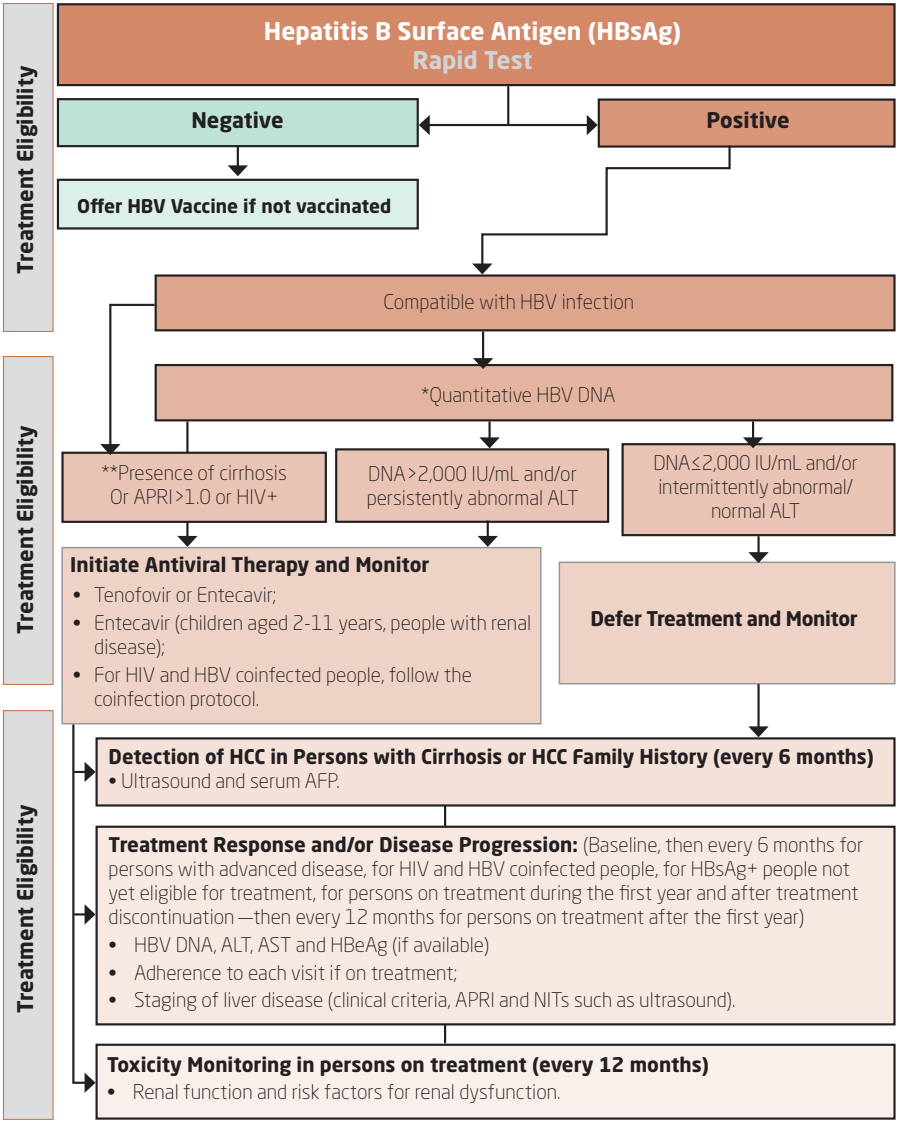


Figure 3: Diagnosis of HBV and Treatment Eligibility Criteria[3]

$$CrCl = \frac{(140 - Age) \times Weight\ (in\ Kg)}{\mathbf{72} \times Creatinine\ (mg/dL)}$$

4.1.3. Calculation of creatinine clearance

The Cockcroft Formula is used to calculate the glomerular filtration rate (GFR), or Creatinine Clearance expressed in **mL/min** as follow:

- If Creatinine Machine reports in mg/dL:

$$CrCl = \frac{(140 - Age) \times Weight\ (in\ Kg)}{\mathbf{72} \times Creatinine\ (mg/dL)}$$

Normal blood creatinine ranges [0.5 -1.4]

- If Creatinine Machine reports in µmol/L:

$$CrCl = \frac{(140 - Age) \times Weight\ (in\ Kg)}{\mathbf{0.8172} \times Creatinine\ (\mu mol/L)}$$

Normal blood creatinine ranges [>or =90]

N.B: The formulas are multiplied by **0.85** if a woman and **1** if a man

Table 5: Interpretation of renal creatinine clearance

Interpretation of renal creatinine clearance	
Value	**Interpretation**
≥ 90 mL/min	Normal
60-89 mL/min	Mild Renal Insufficiency
30-59 mL/min	Moderate Renal Insufficiency
≤ 29 mL/min	Severe Renal Insufficiency

4.2. Monitoring of patients not eligible to treatment

People who are not eligible to treatment need biannual (every 6 months) monitoring of HBV DNA levels, serum ALT, AST and liver ultrasound to determine the progress of the disease.

4.3. Education, counselling, and preparation for HBV treatment

4.3.1. Introduction

Decades can pass between the time of HBV infection and when patients develop fibrosis and cirrhosis. During that time, there are health conditions and behaviors that can accelerate the progression of liver damage, including alcohol consumption, substances abuse, obesity, etc. Therefore, any patient with HBV should receive clinical guidance on the following topics:

- Avoid alcohol consumption;
- Avoid smoking and substance abuse;
- Pre- and post-testing counseling as well as pre-treatment counseling about the lifestyle of the HBV-infected patient, indications of treatment and adherence to treatment, possible side effects, the risk of acute liver failure upon abrupt cessation of treatment, and risk of drug resistance in case of poor adherence.

- Discussion on the willingness to commit to lifelong treatment, its cost implications, education on its benefits and side-effects, and follow-up monitoring both on and off therapy (possibility of HBV infection clearance)
- Advice on lifestyle and physical activity.

4.4. HBV Treatment options in Rwanda

4.4.1. Treatment for HBV mono-infection

All people eligible to treatment can take the nucleos(t)ide analogues that have a high genetic barrier to drug resistance as follows:

- Tenofovir Disoproxil Fumarate (TDF) or Entecavir (ETV) are recommended as preferred regimens;
- Tenofovir Disoproxil Fumarate (TDF) is indicated for people **aged 12 years and above with normal renal function;**
- Entecavir should be considered for **children aged 2-11 years and adults with established osteoporosis and/ or impaired kidney function;**
- Otherwise, Tenofovir Alafenamide Fumarate (TAF), if available, can be considered for people **aged 12 years and above with normal kidney function or established osteoporosis and/ or impaired kidney function.**

Chronic HBV is generally asymptomatic in children under 2 years of age who are generally immune-tolerant. A conservative approach to treatment is generally indicated. In exceptional cases of cirrhosis or necro-inflammatory disease, refer to a specialist for care and treatment.

Patients with any abnormal laboratory or imaging findings or complicated cases should be referred to a specialist for further evaluation and management.

Table 6: Treatment options for hepatitis B infection in Rwanda

Age	Drug	Dosage	Duration
≥ 12 years	Tenofovir (TDF or TAF)	300mg 1x/day for TDF 25 mg 1x /day for TAF	Lifelong treatment recommended (Exceptionally, see treatment endpoint)
*2 - 11 years or adult people with intolerance to Tenofovir (People with impaired renal function or on hemodialysis or with osteoporosis)	Entecavir	Children: Dependent on weight and age**	
		Adult: 1mg 1x /day	
	TAF	25mg 1x/day	

***** Entecavir is a therapy option for adults who cannot take Tenofovir such as people with renal failure and preferred therapy for children aged 2-11 years based on weight and age

****** Entecavir doses in treatment-naive children older than 2 and at least 10 kg are: 0.15 mg (10-11 kg), 0.2 mg (>11-14 kg), 0.25 mg (>14-17 kg), 0.3 mg (>17-20 kg), 0.35 mg (>20-23 kg), 0.4 mg (>23-26 kg), 0.45 mg (>26-30 kg), and 0.5 mg (>30 kg). For treat- ment-experienced children older than 2 and at least 10 kg, the entecavir doses are: 0.30 mg (10-11 kg), 0.4 mg (>11-14 kg), 0.5 mg (>14-17 kg), 0.6 mg (>17-20 kg), 0.7 mg (>20-23 kg), 0.8 mg (>23-26 kg), 0.9 mg (>26-30 kg), and 1.0 mg (>30 kg)[11]

4.4.2. Treatment of HIV-HBV co-infected people

The diagnosis of HBV infection is based on the presence of HBsAg which confirms the chronicity if the person is already HIV positive. Those who screen HBs Ag negative should directly start the HBV vaccine series. All HIV and HBV infected patients should start treatment for both infections as per new HIV "treat all" guidelines. HIV treatment must include an HBV active agent such as TDF/TAF or Entecavir, and the recommended treatment is for life.

Recommendations

HIV and HBV co-infected patients on ART regimen which does not contain TDF/TAF should take additional Tenofovir or Entecavir incase of TDF contraindication.

4.4.3. HBV treatment in special patient groups

4.4.3.1. HIV-HBV infection and pregnancy

The treatment criteria for HBV in pregnancy are the same as in the adult population. HIV positive pregnant women should receive ART regimen containing TDF/ TAF[12]. TDF/TAF is the preferred antiviral, because it has a better resistance profile and more extensive safety data in pregnant HBV positive women.

Breastfeeding is not contraindicated in HBsAg untreated women or on TDF based regimen, except when the mother has cracked, damaged, or bleeding nipples [18].

4.4.3.2. Hepatitis B in children

Children usually display an immune tolerant course of their HBV infection. Treatment decision should be taken in consultation with specialist. **Entecavir** is preferred in children aged 2-11 years.

Healthcare workers need special consideration for HBV screening and HBV vaccination. Those who are HBsAg-positive and undertake exposure-prone procedures, such as surgeons, gynecologists, nurses, phlebotomists, personal care attendants and dentists, should be considered for antiviral therapy to reduce direct transmission to persons. They should receive a potent antiviral agent with a high barrier to resistance (i.e., **Tenofovir** or **Entecavir**) to reduce levels of HBV DNA ideally to undetectable or at least to <2,000 IU/ mL, preferably before resuming exposure-prone procedures.

4.4.3.3. Chronic HBV infection with persistently normal transaminases

Chronic HBV infection may be present with high level of serum HBV DNA, but persistently normal transaminases. It is recommended to prioritize them for HBV treatment if HBV DNA >or = 2,000 IU/mL otherwise, a regular monitoring of ALT, and signs of cirrhosis (clinical signs and APRI) every 12 months is recommended.

4.4.3.4. Treatment of patients with compensated cirrhosis

Treatment should be prioritized in patients with cirrhosis and detectable HBV DNA at any level. The diagnosis of HBV infection is based on the presence of HBs Ag and there is no need to wait for other tests if the person is already cirrhotic. Cirrhosis can be diagnosed with characteristic findings on ultrasound (nodularity, splenomegaly)

or with APRI> 0.5. Life-long TDF/TAF therapy should be directly started after a single HBs Ag test, and regular monitoring of HBV DNA levels is essential.

4.4.3.5. Treatment of decompensated cirrhosis

Management of patients with decompensated cirrhosis who are infected with HBV is complex. Such patients should be referred to a specialist. All patients with decompensated cirrhosis should be considered for urgent treatment. Lifelong treatment with **Tenofovir** or **Entecavir** is indicated even if the HBV DNA level is low or undetectable in order to improve clinical outcomes and to prevent flares/ reactivation. For this category of patients as well, a single HBs Ag test is enough to initiate treatment.

4.4.3.6. Treatment of drug-resistant hepatitis B

HBV DNA monitoring is critical to detect treatment failure as follows:

- Undetectable HBV DNA levels by real-time PCR (level of detection < 20 IU/mL) should be expected to be achieved after one year of treatment in adherent patients to prevent resistance.
- If HBV DNA levels are still detectable, but declining at one year on Tenofovir or Entecavir, measures to improve adherence should be taken.
- If HBV DNA is still detectable without declining while on treatment, check the causes like poor adherence and reinforce counselling.

4.4.3.7. HBV and immunosuppressive therapy or cancer chemotherapy

Approximately 20-50% of HBV carriers undergoing immunosuppressive therapy or cancer chemotherapy develop reactivation of HBV replication, presenting with hepatitis flare and rarely hepatic decompensation. This may occur even in those with occult HBV infection. Administration of Tenofovir prior to these treatments is recommended and it is associated with reduced frequency and severity of hepatitis B flare and improved survival in these patients [4].

4.4.3.8. Treatment in patients with renal failure

TDF should **not** be given to patients with renal failure. For HBV patients with renal

failure, the preferred drug is **Entecavir** with renal adjustments. **TAF** can also be considered in the absence of **Entecavir**.

4.5. Follow-up of patients on HBV treatment

4.5.1. Patient follow-up on treatment

The aim of monitoring during (and after treatment if applicable) is to evaluate the effectiveness of treatment response, treatment adherence, adverse effects of treatment, progression of liver disease and development of HCC, the potential for treatment discontinuation, and early identification of reactivation in case of treatment discontinuation. Regarding drug pick-up schedules, the patients who are newly initiated on HBV treatment will start with three months' drug pick up during the first year of treatment and 6 months pick up from the second year of treatment, provided that there is a good adherence and viral load suppression.

4.5.2. Treatment adherence

Non-adherent patients: Adherence to treatment for this group will be assessed using standard procedures. This means, health care providers will assess if patients have taken all prescribed drugs. Poorly adherent patients encompass the following conditions:

- Missing one or more prescribed doses
- Treatment interruption: For the application of these guidelines, treatment interruption refers to stopping medications at any point of the treatment course.
- Lost to follow-up: For the application of these guidelines, patients are considered lost to follow-up if:
    - ◊ They missed the last pharmacy visit and Health care providers were not able to reach them by any communication mean (telephone call and home visit) within three months from the time they were expected to attend the clinic.

4.5.3. Treatment endpoint

4.5.3.1. Background

Although nucleos(t)ide analogues (NAs) are potent inhibitors of HBV DNA replication, they do not result in cure, because NA therapy does not eliminate the replicative template covalently closed circular DNA in the nucleus or integrated viral genome. Therefore, although there are considerable advantages of finite NA therapy, both for patients and policymakers, long-term maintenance suppressive therapy is generally required. Exceptionally, a finite duration of treatment may be possible in those rare patients who achieve HBsAg loss, some HBeAg-positive persons who achieve anti-HBe seroconversion, a sustained undetectable HBV DNA viral load and some other additional criteria as described later in this part of the chapter.

Discontinuation of HBV treatment is associated with high risk of reactivation and relapse of the disease. However, may be considered carefully and exceptionally if the following criteria are met:

- Persons without clinical evidence of cirrhosis (or based on APRI score <0.5 in adults);
- and in association with persistently undetectable HBV DNA levels, normal ALT levels and persistent HBsAg loss within 24 months of treatment initiation. Where HBV DNA testing is not available, discontinuation of therapy may be considered in persons who have evidence of persistent HBsAg loss within 24 months of treatment initiation;
- and if there is evidence of HBeAg loss and seroconversion to anti-HBe (in persons initially HBeAg positive) within 24 months of treatment initiation (optional, only valid if HBeAg test is available);
- Patient willing to discontinue.

Recommendations

- Any discontinuation of HBV therapy should involve the RBC program to provide appropriate guidance;
- The patient should be followed up carefully on a long-term basis for reactivation.

HBV treatment endpoint evaluation

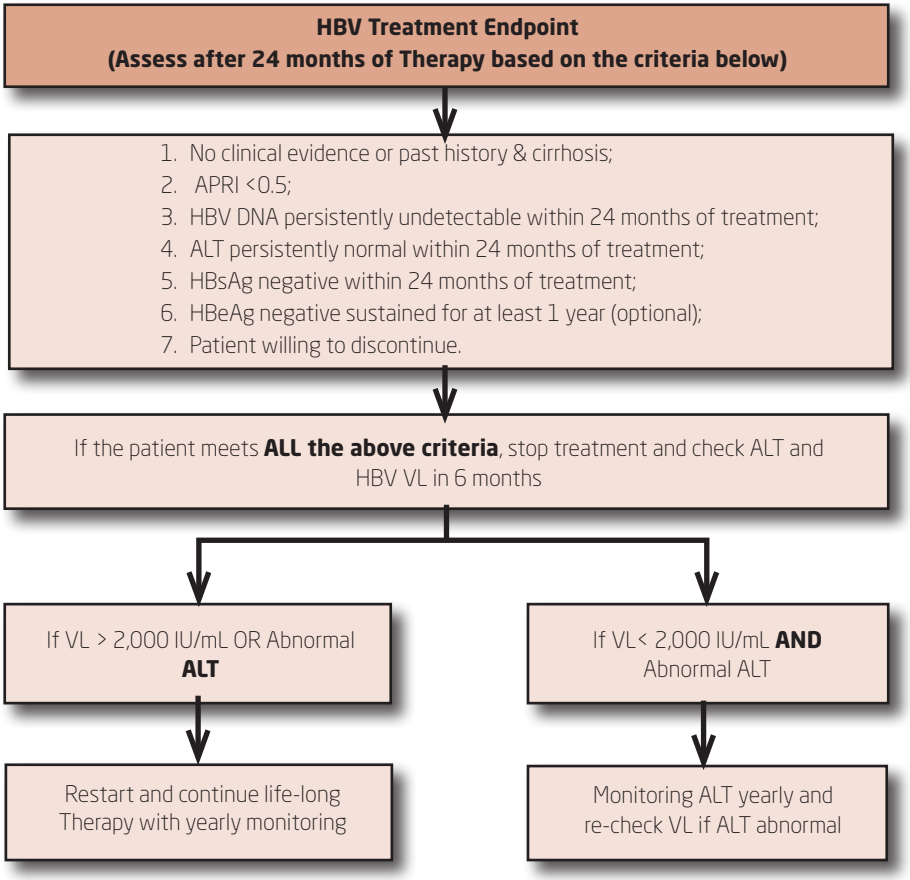


Figure 4: HBV treatment Endpoint Evaluation

4.6.3.2. Retreatment

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

Key messages for HBV management

- HBV is diagnosed using a single HBs Ag rapid test;
- Acute HBV is characterized by acute presence / absence of clinical symptoms, abnormal liver tests and disappearance of HBs Ag within 6 months;
- Chronic HBV is recognized by persistence of HBs Ag beyond 6 months;
- Immunization against HBV infection for all non-immune individuals is the best strategy for HBV prevention. Other prevention measures consist of avoiding all risk contacts with potential HBV infection sources;
- All pregnant women should be systematically screened for HBV. To prevent MTCT, positive pregnant women eligible to treatment should start HBV treatment. In addition, all babies should be vaccinated within 24 hours after birth and receive hepatitis B immunoglobulin (if available) to prevent MTCT;
- It is recommended that all newborns receive their first dose of hepatitis B vaccine within 24 hours after birth, and that the birth dose be followed by three doses of hepatitis B vaccine at week 6, 10, and 14;
- In HIV infected patients, cirrhotic patients, or patients with APRI score > 0.5, the presence of a single HBsAg automatically refers to the chronicity of HBV and further treatment;
- Treatment eligibility criteria in chronic HBV include:
    - ◊ Co-infection with HIV, HCV and HDV;
    - ◊ Cirrhotic (compensated or decompensated);
    - ◊ Patients with APRI score > 0.5;
    - ◊ HBV DNA >2,000 UI/mL and /or persistent ALT level (at least two occasions in a 6 to 12 months period);

- ◊ HBV treatment is also indicated in children and should be provided to children aged 2 -11 years, and in this case, the drug of choice is Entecavir;
- ◊ HBV treatment for pregnant women is the same as for other adult persons and the drug of choice is TDF or TAF. Entecavir is not indicated during pregnancy and breastfeeding;
- ◊ Treatment monitoring for both those on treatment and those who are initially ineligible for treatment should be done to optimize adherence to treatment, detect signs of treatment success /failure (e.g. HBV VL, Liver function tests), reassess treatment eligibility, and manage treatment related side effects;
- ◊ Specialist review is mandatory for the following cases:
  - Patients with comorbidities (Diabetes mellitus, metabolism associated steatotic liver diseases, etc);
  - Patients with immunosuppression (Chronic use of steroids or other immunosuppressive drugs);
  - Family history of liver cancers or cirrhosis;
  - Extrahepatic manifestations of HBV (Gromerulonephritis or vasculitis).

PART II

HEPATITIS C INFECTION MANAGEMENT

Chapter I: Generalities on HCV infection

Summary: Generalities on HCV infection

Hepatitis C virus (HCV) causes both acute and chronic infection. Acute HCV infections are usually asymptomatic, and most do not lead to a life-threatening disease. Around 30% (15-45%) of infected persons spontaneously clear the virus within 6 months of infection without treatment. The remaining 70% (55-85%) of persons will develop chronic HCV infection. Of those with chronic HCV infection, the risk of cirrhosis ranges from 15% to 30% within 20 years.

1.1. Definitions

Hepatitis C infection: Inflammation of liver caused by Hepatitis C Virus (HCV). HCV is a small, positive-stranded RNA-enveloped virus which can cause both acute and chronic infection.

Acute HCV: Presence of HCV within six months of acquiring infection.

Chronic HCV: Continued presence of anti-HCV and HCV RNA six months or more after acquiring infection.

Sustained virological response 12 (SVR12): Undetectable HCV RNA 12 weeks after the end of treatment.

Non-response: Detectable HCV RNA throughout treatment

Rapid Virological Response (RVR): Undetectable HCV RNA 4 weeks after the start of treatment

Relapse: Undetectable HCV RNA at the end of treatment but detectable HCV RNA 12 weeks after completing treatment.

Viral breakthrough: Undetectable HCV RNA during treatment followed by detectable HCV RNA.

1.2. HCV Transmission

Hepatitis C virus (HCV) is mostly transmitted through exposure to infectious blood. This may happen through transfusions of HCV-infected blood and blood products, contaminated injections during medical procedures, and sharing of needles and syringes among injecting drug users. Sexual or interfamilial transmission is also possible, but is much less common[13]. HCV is 10 times less contagious than HBV and 10 times more contagious than HIV. High risk groups are reached through their associations and can easily access HCV services through targeted screening, care, and treatment. Mass screening campaigns and routine hepatitis care provided in health facilities can also reach them.

1.2.1. HCV high risk groups

- Household members of positive HCV patients;
- Persons who have received medical or dental interventions in health-care settings where infection control practices are substandard;
- Patients who received blood products or organ transplants prior to the introduction of anti-HCV screening (HCV screening started in 1999 in Rwanda);
- Injecting Drugs Users (IDU);
- Persons who have had tattoos, body piercing, scarification, traditional surgical procedures, or unsafe injection;

- Children born to mothers infected with HCV;
- Persons with HIV infection;
- Prisoners, rehabilitation centers and previously incarcerated persons;
- Men having Sex with Men;
- Female Sex Workers;
- Victims of sexual violence;
- Recipients of organs (Transplant) and patients who chronically receive blood products and patients on chronic hemodialysis;
- Health care workers.

Chapter II: Prevention of HCV infection and disease progression

Summary: Prevention of HCV infection and disease progression

The prevention of HCV infection aims at reducing or eliminating potential risk of exposure to the virus. Most people who are infected with HCV are unaware of their status, they are therefore, at high risk of developing severe chronic liver disease and can unknowingly transmit the infection to other people. The population should be educated on how to prevent the acquisition and transmission of HCV infection. Education is provided through sensitization during mass gathering, mostly through healthcare and community health workers.

2.1. Prevention of hepatitis C infection

The primary prevention of hepatitis C infection consists of activities aiming at reducing or eliminating potential risk for HCV transmission such as increasing awareness and knowledge among the general and high-risk population. The following are specific areas of HCV primary prevention:

2.1.1. HCV prevention in community settings

There should be increased awareness and knowledge of HCV transmission, prevention, and control among the general population using the following approaches delivered through direct health education and media:

- Targeted education among high-risk groups: Provide specific messages to increase awareness and knowledge of HCV transmission, prevention, and control among the high-risk groups;

- Harm reduction practices for injecting drug users;
- Avoid unsafe practices around non-medical or traditional practices (pedicure and manicure, scarification, tattoos, circumcision procedures, traditional medical practice);
- Avoid unsafe household practices (handling or sharing of sharp objects, sharing toothbrushes) and promote hand washing and safe blood contact;
- Safe injections for injection drug users;
- Promotion of correct and consistent condom use;
- Avoid multiple partners, seek regular screening and treatment for STIs;
- Routine screening of high-risk groups;
- Integrated action to eliminate discrimination and gender violence and increase access to medical and social services for vulnerable persons.

2.1.2. Prevention of HCV transmission in health-care settings

Occupational safety measures to prevent transmission of viral hepatitis to health care workers are enhanced through:

- Training of healthcare providers and community health workers on good clinical practices;
- Hand hygiene including surgical hand preparation, hand washing and use of gloves;
- Safe handling and disposal of sharp objects and waste;
- Safe cleaning of equipment;
- Testing of donated blood and blood products;
- Follow standard safety precautions while managing open cuts or bleeding;
- Ensure safe injections in health facilities.

2.1.3. Implementation of HCV post exposure prophylaxis measures

2.1.3.1. Immediate care of the exposed person

After exposure to blood or other body substances, the following is recommended as soon as possible:

- Wash the wound site with soap and water;
- If eyes are contaminated, rinse them gently but thoroughly while they are open with water or normal saline;
- If blood or other body substances get in the mouth, spit them out and then rinse the mouth with water several times;
- If clothing is contaminated remove them and shower with soap;
- When water is not available use a non-water cleanser;
- Antiseptic should replace the use of soap and water for washing cuts or punctures of the skin or intact skin.

2.1.4.2. Secondary care of the exposed person

At present there is no prophylaxis proven to be effective following exposure to HCV. The aim of follow-up is to detect hepatitis C so that appropriate management can be instituted:

- The person should be informed and advised on the risk of transmission to secondary contacts, especially during the first 6 months following the incident;
- The exposed person should have baseline testing for HCV antibody. If negative, the person should be retested for HCV 6 months post-exposure as well as for other blood borne viruses;
- If HCV antibody is positive, the person should be referred for HCV PCR testing and follow-up if necessary;
- No HCV infection vaccine is yet available.

Chapter III: Screening and diagnosis of HCV infection

Summary: Screening and diagnosis of HCV infection

It is recommended that everyone should be screened for hepatitis at least every 12 months (general population) and at least every 6 months, or better, at any contact (high-risk populations such as healthcare providers, HIV-infected population, prisoners, key populations, and patients with unexplained abnormal liver function). Screening for hepatitis C is done through assessing the presence of anti-HCV antibody as well as the HCV viral load, using rapid diagnostic tests (RDTs) and a confirmatory HCV RNA test respectively. However, people who have ever been screened positive for HCV or treated (cured or not), will always be HCV antibody positive and will be assessed by HCV RNA test.

In case HCV self-test is available, it would be a good approach to enhance HCV testing. HCV self-test result should be confirmed by further testing using HCV antibody test and a viral load test.

3.1. Screening and diagnosis of HCV infection

In Rwanda, HCV infection screening is done using RDTs. If positive, a NAT for HCV RNA is used to confirm chronic HCV infection. Anti-HCV antibody is generally not detectable in patients with initial signs or symptoms of hepatitis C and generally develops between 2 and 8 weeks after evidence of liver injury [14-15]. A pre- and post-testing counseling service is provided to all clients consulting for HCV testing. People who have ever been screened positive for HCV or treated (cured or not), will always be HCV antibody positive and will be assessed by HCV RNA test. All HCV testing services are provided at no cost in the framework of HCV elimination.

Hepatitis C screening and treatment services are decentralized and integrated to the lowest health facility level and with a task sharing model, nurses can manage hepatitis in addition to medical Doctors.

All patients who screen positive for HCV antibody should also be screened for HBV infections. Hepatitis C viremia can be detected by RT-PCR within 4-8 days after infection [16].

In case HCV self-test is available, it would be a good approach to enhance HCV testing. HCV self-test result should be confirmed by further testing using HCV antibody test and a viral load test.

- If HCV self-test is positive, proceed with HCVAb rapid test;
- If HCV Self-test and rapid test are negative, there is no further action required.

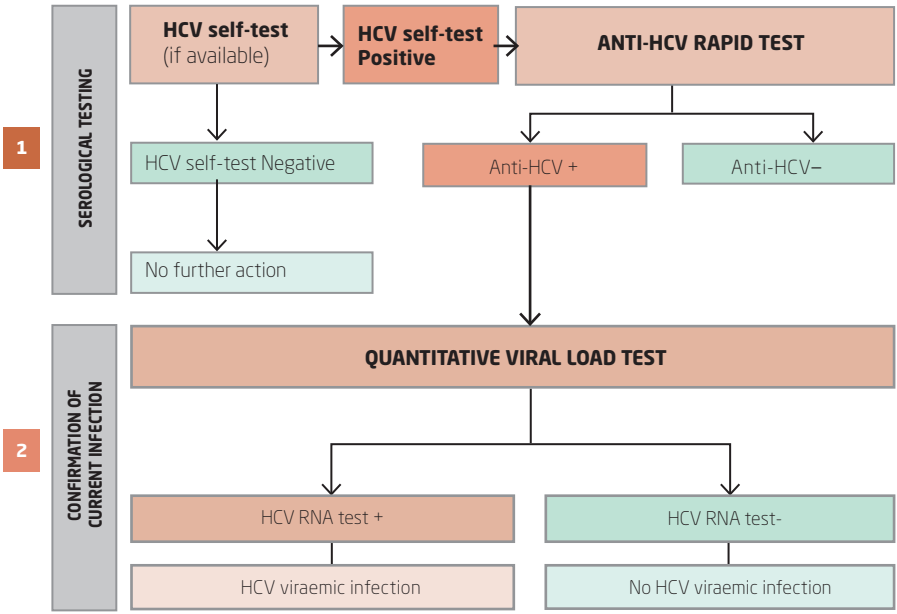


Figure 5: Algorithm for screening and diagnosis of HCV infection

3.1.1. Point of care

Point Of Care (POC) viral load testing is an additional diagnostic strategy where the test is performed immediately to promote linkage to care and treatment. It is particularly useful for marginalized communities with limited access to care and concern of loss to follow-up. Point Of Care viral load finally is the best option to enhance testing and treatment uptake. It can be used as alternative test for both confirmatory viremia and SVR12. Point Of Care testing is recommended for the implementation of these guidelines.

3.1.2. Reflex testing

Reflex testing is done when a patient is screened positive and a viral load sample is collected immediately while he/she is still at health facility or enough blood sample can be withdrawn and used for rapid testing and confirmatory VL test if the screening result turns positive. The reflex testing prevent unnecessary additional travel for a viral load test sample collection, shortens the results turnaround time and speed up the treatment initiation. Reflex testing is recommended for the implementation of these guidelines.

3.2. HCV Screening eligibility

Anybody seeking HCV screening should be offered the service. However, high risk groups cited in prevention section and patients with unexplained abnormal liver function are priority for HCV screening.

Chapter IV: Treatment of HCV infection

Summary: Treatment of HCV infection

The goal of the treatment is to eradicate the virus, prevent liver cirrhosis and its complications including hepatocellular carcinoma (HCC) [17]. The current HCV treatment can cure the virus after 12 weeks or 24 weeks of treatment depending on the severity of the disease. The real-world success rate is above 90%.

All patients, both adults and children aged 3 years and above weighing 14kg and above with detectable HCV RNA viral load should be initiated on treatment with Direct Acting Antivirals (DAAs). Current treatment with DAAs is contraindicated in pregnant women.

4.1. Initial evaluation of HCV-infected patients

Patients with chronic HCV infection should undergo thorough history and physical evaluation including risk factors, family history, extra-hepatic manifestations (ex. Skin rash, vasculitis) and co-morbidities. Tests to rule out viral co-infections such as HIV and HBV are mandatory.

Patient history and physical evaluation should be followed by complementary investigations for chronic HCV that include:

- Aminotransferase/platelet ratio index (APRI) score;
- ALT/ASAT;
- Full blood count (hemoglobin, platelets and leucocytes including differential count);
- Check for coinfection of HBV and HIV;

- Ultrasound to evaluate or assess the liver status (Size, echotexture, and intrahepatic lesions);
- Alpha-fetoprotein (AFP) when possible, in cirrhotic patients (APRI >0.5) with suspicion of HCC;
- Endoscopy for esophageal varices in cirrhotic patients with platelets <150x10^9/L when possible;
- In addition, when available, elastography (fibroscan) should be considered for evaluation of liver fibrosis/ cirrhosis instead of liver biopsy, which is an invasive method;
- Pregnancy test is mandatory for all women in reproductive age, and advise for family planning if negative until at least six months post treatment. If pregnancy test is positive, defer treatment until end of breastfeeding.

$$\textbf{APRI} = \frac{\dfrac{\text{AST Level}}{\text{AST (Upper Limit of Normal)}}}{\text{Platelet Count } (10^9/\text{L})} \times \mathbf{100}$$

APRI Score and liver fibrosis assessment formula

Note

- In this formula, 3 zeros in platelets count are chopped off.
  e.g: If you find 137,000 platelets, you consider 137.
- An online calculator can be found at: http://www.hepatitisc.uw.edu/page/clinical-calculators/apri

Table 7: Interpretation of Aminotransferase Platelet Ratio Index (APRI)

APRI Value	Interpretation	Action
>0.5	High Probability of advanced fibrosis / cirrhosis	Determine whether compensated or decompensated and referto care and treatment as appropriate
≤0.5	Low risk of advanced fibrosis	Treat all

HCV Diagnosis and Treatment Algorithm

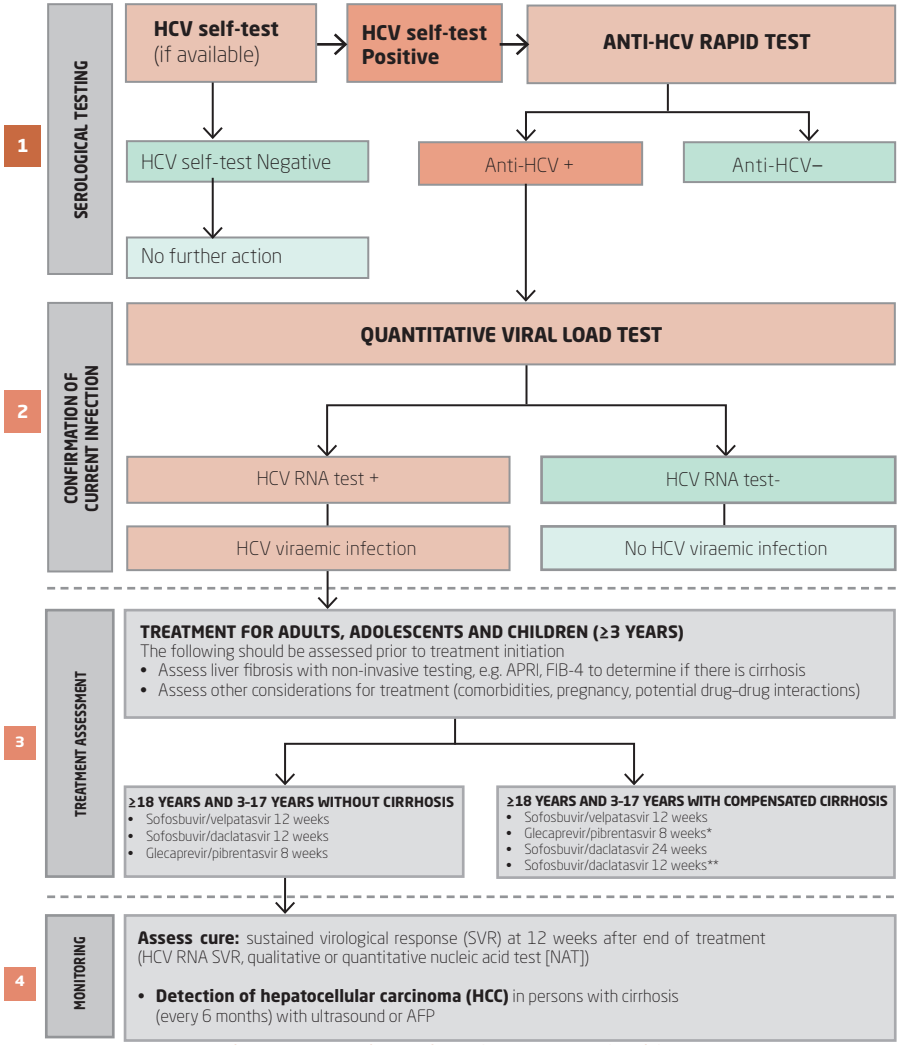


Figure 6: HCV Diagnosis and Treatment Algorithm

* Persons who failed prior therapy with interferon, ribavirin, and/or sofosbuvir with HCV genotype 1, 2, 4-6 with cirrhosis should be treated for 12 weeks, and with HCV genotype 3 with or without cirrhosis should be treated for 16 weeks.

4.2. Treatment of HCV mono-infection

4.2.1. Children aged 3 years and above

WHO recommends to treat all adults, adolescents, and children aged ≥3 years with chronic HCV infection, using pangenotypic DAA regimens, regardless of disease stage. These updated guidelines reaffirm the use of one of three highly effective pangenotypic DAA combinations in a simplified scheme. Duration and dose of DAA treatment based on weight categories is summarized below:

Table 8: Dose by weight*

Pangenotypic DAA regimens			Non-pangenotypic DAA (in settings with minimal GT3 infection) Sofosbuvir / Ledipasvir 12 weeks
Sofosbuvir/ daclatasvir 12 weeks	**Sofosbuvir/ Velpatasvir** 12 weeks	**Glecaprevir/ Pibrentasvir*** 12 weeks	
>26 kg 400/60 mg OD (film-coated tablets)	>30 kg 400/100 mg OD (FDC tablet)	>45 kg 300/120 mg OD (FDC tablet or 6 packets of oral pellets)	≥35kg 90/400 mg OD (FDC tablet)
14–25 kg 200 mg/30 mg OD (as single tablets, sofosbuvir preferred as smaller 100 mg tablet)	17–29 kg 200/50 mg OD (FDC tablet or granules)	30–<45 kg 250/100 mg OD (5 packets of oral pellets) 20–<30 kg 200/80 mg OD (4 packets of oral pellets)	17– 35kg 45/200 mg (tablet) OD
	<17 kg 150/37.5 mg OD (coated granules)	<20 kg 150/60mg OD (3 packets of oral pellets)	<17 kg 33.75/150 mg OD (FDC granules packets)

* For use in those with genotype 1, 4, 5, or 6 infection or where genotype 3 infection is uncommon. In the SHARED trial, (in adults) a sustained virological response (SVR) with sofosbuvir (400 mg) and ledipasvir (90 mg) was observed in 261 (87%) overall, but in only 56% of those infected with HCV genotype 4r, compared with 93% of those infected with genotype subtypes other than 4r. Realistically, these findings do not support the use of sofosbuvir–ledipasvir as the initial therapy for HCV infection without genotype subtyping in some regions and countries in sub-Saharan Africa.

Dosing based on population pharmacokinetic modelling studies

Available as tablets (FDC) 100/40 mg and oral pellets or granules 50/20 mg, depending on locally approved product information

** In those without cirrhosis. Treatment for 24 weeks is recommended in those who are treatment experienced or with compensated cirrhosis. May be considered in settings where genotype 3 is known to be highly prevalent (>10%).

*** For use in those with genotype 1, 4, 5, or 6 infections.

The duration of treatment of children aged 3 years and above is detailled as follows:

- Non cirrhotic and treatment naïve patients:
  - ◊ Sofosbuvir +Daclatasvir for 12 weeks
  - ◊ Sofosbuvir +Velpatasvir for 12 weeks
  - ◊ Glecaprevir /Pibrentasvir for 8 weeks
  - ◊ Sofosbuvir + Ledipasvir for 12 weeks in genotypes 1,4,5 and 6

  (N.B: To be ONLY used when pangenotypic regimens are not available)

- Cirrhotic, treatment experienced and patients with viral load > 600,000 copies / ml based on weight dosing.
  - ◊ Sofosbuvir +Daclatasvir for 24 weeks
  - ◊ Sofosbuvir +Velpatasvir for 24 weeks
  - ◊ Glecaprevir /Pibrentasvir for 12 weeks
  - ◊ Sofosbuvir + Ledipasvir for 24 weeks in genotypes 1,4,5,6

  (N.B: To be ONLY used when pangenotypic regimens are not available).

Note

The recommended second line treatment for experienced patients who failed 1st line treatment is SOF/VEL/VOX.

***In case of HCV-HIV co-infected patients on treatment with Efavirenz based regimen, Daclatasvir dosing should be increased to 90mg daily and in case of co-administration with Protease inhibitor boosted with Ritonavir, Daclatasvir should be reduced to 30mg daily.*

4.2.2. Patients with decompensated cirrhosis

Diagnosis of decompensated liver disease is based on both laboratory and clinical assessment. A proportion of persons with decompensated liver disease will deteriorate on treatment and currently, there are no predictor to identify these

people. Patients with decompensated cirrhosis are clinically complex and require close monitoring and long-term follow-up. These patients should be managed by specialists and trained general practitioners (GPs).

Sofosbuvir + Daclatasvir and Sofosbuvir + Velpatasvir have been studied in persons with decompensated cirrhosis and their use has been demonstrated to be generally safe and effective. In contrast, regimens that contain an HCV protease inhibitor (e.g., Glecaprevir + Pibrentasvir) are not approved for use in persons with decompensated cirrhosis. The following treatment may be prescribed [18, 23]:

- Patients who are ribavirin-eligible (Hb>10g/dL): 24 weeks of either SOF+DCV or SOF+VEL or SOF+LDV + weight-based ribavirin depending on regimens. Patients who are ribavirin-ineligible (Hb<10g/dL): 24 weeks of SOF+LDV, SOF+DCV or SOF+VEL.
- Option for liver transplantation may be considered when possible.

Table 9: Administration of weight-based Ribavirin in adults

Adult weight	Ribavirin dose
≤75 kg	1000mg divided doses: 600mg (am) and 400mg (pm)
>75 kg	1200mg divided doses: 600mg (am and pm)

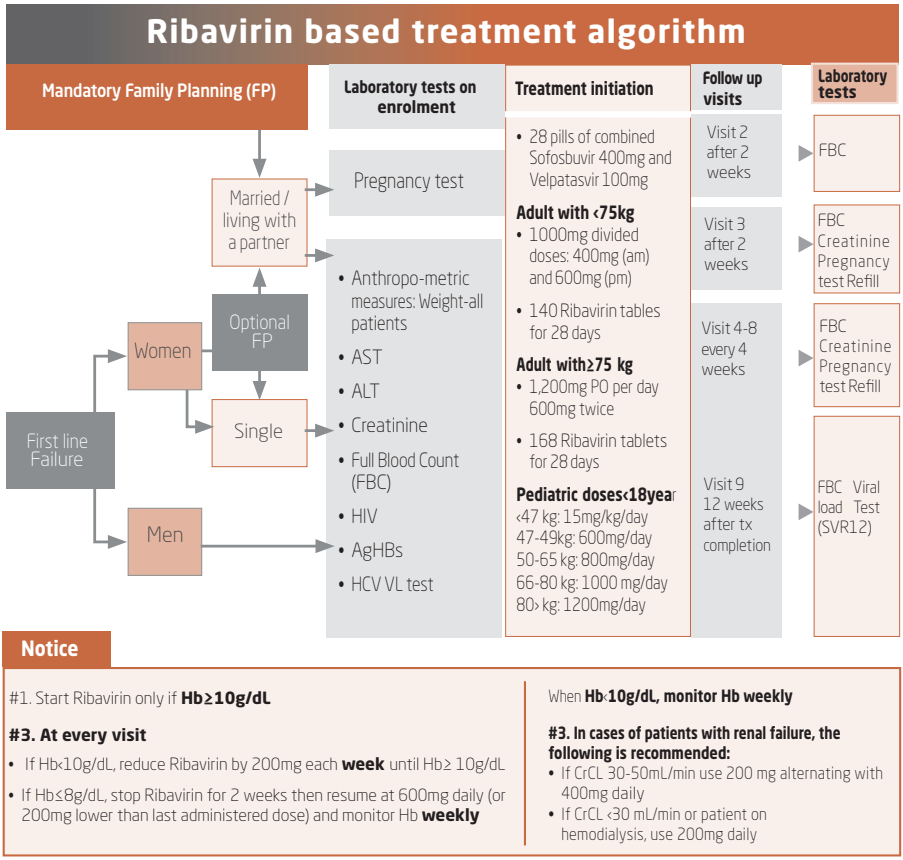


Figure 7: Alternative Second line Treatment Algorithm

4.3. Education, counselling and preparation for HCV treatment

Lifestyle of patients is critical to the success of patient management. Patients should receive guidance on the following:

- Length of treatment and potential side effects;
- The importance of treatment adherence for cure;

- Importance of SVR 12 to determine cure;
- Risk factors that can accelerate progression of liver damage including alcohol, substance abuse, obesity, etc;
- Advice on balanced diet and physical activity;
- Potential for re-infection after successful cure;
- Family planning.

4.4. Common side effects of hepatitis C antiviral agents

Although DAAs are generally well-tolerated, the following side-effects detailed in Table 10 have been reported:

Table 10: DAAs and commonly reported side-effects

Molecule	Side Effects
Sofosbuvir	Fatigue and headache
Ledipasvir	Fatigue, headache, insomnia, and nausea
Daclatasvir	Nausea, headache, fatigue
Velpatasvir	More common side effects include fatigue and headache, less common side effects include nausea, insomnia, diarrhea, rash, and anemia
Ribavirin	Dose-dependent hemolytic anemia, headache, nausea insomnia and may cause dyspepsia and rash. Birth defects have been produced in animal experiments and contraception should be used during treatment and until 6 months after end of treatment, for females on ribavirin treatment, but also for partners of HCV- infected men who are taking ribavirin therapy.[23]
Voxilaprevir	Right-sided upper stomach pain. nausea, vomiting, loss of appetite and dark

4.5. Patient follow-up

4.5.1. Patient follow-up during treatment on first line

Patients will receive preferably the complete dose of DAAs for the entire period of treatment to avoid any possible stock-out and consecutive interruption of treatment. However, if there is a need for a close follow-up, patients should be seen more frequently as needed by healthcare provider for an effective treatment monitoring. After treatment, patients should be seen at week 12 after end of treatment for SVR12. In special cases, nurses can choose to refer patients to general practitioners as needed.

HIV-HCV co-infected patients will be followed-up by HIV nurses per HIV protocol. For patients on retreatment for 24 weeks, they should be seen at 12 weeks interval for general physical check-up as well as the assessment of adherence and side effects. No laboratory monitoring is required unless the patient is prescribed ribavirin, in cases of cirrhosis, or re-treatment after treatment failure. Ribavirin use requires more intensive monitoring for side- effects.

On the day of the visit for (last) DAA pick-up as applicable, patients should be given an appointment for VL testing to evaluate treatment response, 12 weeks after completing treatment course *(SVR12)* [20] .

SVR12 results should be returned to prescribers for result interpretation. Patients should return to prescribing healthcare provider to be informed of the results and the way forward.

Undetectable HCV RNA levels 12 weeks or longer after end of treatment indicates treatment success.

4.5.2. Follow-up of patients on Ribavirin-second line treatment

Severe hemolytic anemia may occur in patients using Ribavirin-based regimens. When using Ribavirin, careful monitoring of hemoglobin (Hb) should be done. Hb

levels need to be assessed before starting therapy and then at 2 and 4 weeks after therapy initiation as follows:

- Start Ribavirin only if Hb>10g/dL;
- If Hb<10g/dL, reduce Ribavirin by 200mg each week until Hb ≥ 10g/dL;
- If Hb ≤ 8g/dL, stop Ribavirin for 2weeks then resume at 600mg daily (or 200mg lower than last administered dose) and monitor Hb weekly;
- When Hb <10g/dL, monitor Hb weekly.

In cases of renal failure in patients using Ribavirin, the following is recommended:

- If Creatinine Clearance (CrCl) 30-50 mL/min use 200mg alternating with 400mg daily;
- If Creatinine Clearance (CrCl) <30 mL/min or on hemodialysis, use 200mg daily.

4.5.3. Treatment adherence

Patient adherence to prescribed treatment regimen is crucial to successfully achieve a viral suppression. Prior to treatment initiation, treating healthcare providers should provide adherence counselling including basic information on the benefits and side effects of antiviral medications, how the medications should be taken and the importance of not missing any dose:

- Pre-treatment adherence counselling;
- Monitoring adherence during treatment;
- Managing side effects during treatment.

The following factors are known to improve adherence:

- Increased availability of treatment and reduced stock-outs;
- Patient cards where appointment dates are pre-specified, including SVR 12 appointment;
- Adherence counselling pre-treatment and during treatment;

- Managing side effects during treatment;
- Individual patients, family, and other treatment supporters.;
- Drug regimen simplicity or shorter duration of therapy when possible.

In cases of missed doses or treatment interruption, healthcare providers should provide enhanced adherence support till the end of treatment course. SVR12 should be assessed as usual, and the decision should be guided by the result. In complicated cases from non-adherence, refer to specialist.

4.5.4. Patient visit post-SVR 12

Upon availability of SVR12 results, patients should return to the healthcare provider to interpret SVR12 results and discuss the way forward.

4.5.4.1.Cured (VL suppressed) patients

It is important to remind patients that they can still be re-infected with HCV and review patient understanding of routes of HCV transmission while discussing the methods to avoid risky behavior and lifestyle. For cured patients with no evidence of fibrosis (APRI <0.5), the recommended follow-up is the same as if they were never infected with HCV. Patients with a high likelihood of fibrosis (APRI>0.5) should be assessed for ongoing risk of HCC with every 6-month Alpha-fetoprotein (AFP) and liver ultrasound.

Assessment of reinfection is recommended only if the patient has ongoing risk for HCV infection. Quantitative HCV RNA assay is needed to assess reinfection rather than anti-HCV serology test.

Curing HCV infection in patients with cirrhosis does not cure patient's cirrhotic status. Patients who are cured with evidence of liver cirrhosis have a persistent risk of hepatocellular carcinoma. They should be followed up every six months with lab tests for liver enzymes, ultrasonography, and AFP for HCC monitoring. Monitoring for esophageal varices using endoscopy should be conducted at least once in a lifetime for patients with cirrhosis and platelets $<150 \times 10^{[9]}/L^{[5]}$. Further follow-up of patients found to have esophageal varices is to be done by the specialist.

4.5.4.2 Not Cured (VL not suppressed) Patients

If a patient is not cured (VL not suppressed), retreatment using highly effective drugs should be done and those patients should be refered to specialists for further evaluation as necessary. Follow-up assessments should be planned..

In case of detectable SVR12 post second line treatment, the patient should be referred to a specialist for further assessment and genotyping test is advised.

Liver disease progression should be assessed every 6 to 12 months through liver function panel and complete blood count (CBC). For patients with advanced fibrosis, HCC screening should be conducted every 6 months. Monitoring for esophageal varices should be conducted for patients with cirrhosis.

4.6. HCV treatment in special populations

4.6.1. HIV-HCV co-infection

4.6.1.1. Overview of HIV-HCV co-infection

Co-infection with HIV adversely affects the course of HCV infection. Co-infected persons have a risk of accelerated progression to compensated and decompensated cirrhosis and HCC compared to HCV-noninfected persons, especially those with advanced immunodeficiency (CD4 count <200 cells/ mm^3) [2].

However, indications for treatment in HCV-HIV co-infected patients are identical to HCV mono-infected patients and co-infected patients have the same likelihood of achieving SVR 12 as mono-infected patients. The following is recommended for patients co-infected with HIV-HCV:

- HIV-infected patients should be screened for hepatitis C virus (HCV) infection, preferably before starting antiretroviral therapy (ART);
- Treat all HIV-HCV co-infected patients for both HIV and HCV;
- When treatment for both HIV and HCV is indicated, consider drug-drug interactions and overlapping toxicity;

- In ART naive patients with CD4 counts >500 cells/mm^3, if there is concern of drug-drug interaction, consider completing HCV treatment prior to ART initiation;
- In patients with lower CD4 counts < 200 cells/mm^3 with no advanced liver disease, it is recommended to initiate ART and delay HCV therapy until CD4 counts increase;
- For patients with CD4 count between 200 – 500 cells/mm^3 the time to initiate treatment will be situational and judged by a specialist.

4.6.1.2. Drug combinations and /or interactions of ART and DAAs

Persons with HIV require special consideration in regard to the selection of a DAA regimen. Detailed recommendations on specific ART and DAA combinations can be found in Table 11.

Sofosbuvir

The safety profile in HCV-HIV co-infected subjects treated with Sofosbuvir is similar to that observed in HCV mono-infected subjects. However, sofosbuvir-based regimens should not be used with tipranavir/ritonavir. Elevated total bilirubin (grade 3 or 4) occurs extremely commonly in persons treated with Sofosbuvir and Atazanavir as part of the antiretroviral regimen.

Sofosbuvir (400mg) + Ledipasvir (90mg)

Renal function should be monitored when SOF+LDV is given with TDF/TAF because this combination increases plasma levels of TDF/TAF. SOF+LDV can be used in patients with eGFR >30 ml/min.

Daclatasvir

- Increase Daclatasvir dosage to 90mg per day when co-administered with NNRTI's Efavirenz, Nevirapine or Etravirine;
- Decrease Daclatasvir dosage to 30mg per day when co-administered with Atazanavir+Ritonavir;

- Do not co-administer Daclatasvir with Rifampin.

Sofosbuvir (400mg) + Velpatasvir(100mg)

Renal function should be monitored when SOF+VEL is used in combination with TDF/TAF because this combination increases plasma levels of TDF/ TAF. SOF+VEL can be used in patients with estimated Glomerular filtration rate (eGFR) >30ml/min. SOF+VEL should not be co-administered with EFV, Etravirine and Nevirapine.

Glecaprevir (100mg) + Pibrentasvir (40mg)

This treatment cannot be used in combination with ATZ/r (Atanazavir/ Ritonavir)

Summary of recommendations in HIV/HCV co-infected patients:

- Antiretroviral treatment should not be interrupted to allow HCV therapy;
- Sofosbuvir + Velpatasvir should not be used with Efavirenz, Etravirine, or Nevirapine;
- Sofosbuvir-based regimens should not be used with Tipranavir/Ritonavir;
- Ribavirin should not be used with Didanosine, Stavudine, or Zidovudine.

Table 11: Effect of drug combinations and recommended actions between ARTs and DAAs [18, 23].

DAAs / ARTs	ABC	ATZ/r	DRV/r	DTG	EFV	LPV/r	NVP	RAL	TDF	TAF	ZDV	XTC
Daclatasvir		Adjust dose			Adjust dose							
Glecaprevir/ Pibrentasvir												
Sofosbuvir												
Sofosbuvir/ Ledipasvir		Monitor renal toxicity when used with TDF	Monitor renal toxicity when used with TDF		Monitor renal toxicitywhen used with TDF	Monitor renal toxicity when used with TDF			Monitor renaltoxicity when used with TDF			
Sofosbuvir/ Velpatasvir		Monitor renal toxicity when used with TDF	Monitor renal toxicity when used with TDF			Monitor renal toxicity when used with TDF			Monitor for renal toxicity			

Red : Do not co-administer

Yellow : Possible toxicity/interaction/dose adjustment as specified

Green : No interaction, can be co-administered

ABC : Abacavir

ATZ/r : Atazanavir/Ritonavir

DRV/r : Darunavir/Ritonavir

DTG : Dolutegravir

EFV : Efavirenz

FTC/3TC : Emtricitabine/Lamivudine

LPV/r : Lopinavir/r

NVP : Nevirapine

RAL : Raltegravir

TAF : Tenofovir Alafenamide

TDF : Tenofovir Disoproxil Fumarate

ZDV : Zidovudine

4.6.1.3. Patients with HCV and Cirrhosis

Between 15% and 30% of persons infected with HCV will develop cirrhosis within 20 years and a proportion of these will progress to HCC[21].

Cirrhotic patients with liver failure (cirrhosis with jaundice, ascites, encephalopathy, esophageal varices bleeding) should be reviewed by a medical doctor for specific treatment.

4.6.2. Hepatitis C in pregnant women

Although there is a low risk of mother-to-child transmission (MTCT) of HCV, there are currently no interventions available to decrease MTCT of HCV. Women of child-bearing age already infected with HCV should be advised to delay pregnancy until treated and cured of HCV[18].

Pregnant women can be screened for HCV infection during antenatal visits, those who screen negative should be counselled of prevention strategies against hepatitis C infection during the antenatal period; for those who screen positive, a confirmatory viral load should be done. For confirmed positive cases, HCV treatment will be delayed until post-partum and post-breastfeeding due to incomplete drug safety data for DAAs in pregnancy. The best timing for initiation of HCV treatment after breastfeeding and early weaning should be based on case by case and balancing micro-nutrients needs for newborn and mother's treatment need. If cirrhotic, counselling should be done to inform on increased risk of adverse maternal and perinatal outcomes including preeclampsia, cesarean section, hemorrhagic complication, preterm delivery, low birth weight and mother or neonatal death[18]. Breastfeeding is not contraindicated in women with HCV infection, except when the mother has cracked, damaged, or bleeding nipples. [18]

4.7. Hepatitis C in children and adolescents

4.7.1. Diagnosis

Hepatitis C maternal antibodies can be present in the child till 18 months. Hepatitis C is diagnosed in children after 18 months. Upon positive lab tests, children will be assessed for progression of liver disease till 3 years of age and above to start treatment.

4.7.2. Treatment of children with compensated cirrhosis

4.7.2.1. Children aged 3 years and above

Treatment options for children depend on age and weight in addition to cirrhotic status and whether or not the child has previous treatment. Children confirmed with chronic HCV infection who are over 3 years of age and weigh over 14kg and do not have decompensated cirrhosis are eligible for treatment.

4.7.2.2. Children Aged < 3 years

Children under 3 years of age confirmed with chronic HCV infection are currently not eligible for DAAs. Children in this age category who are not cirrhotic should be followed up until they are 3 years of age and 14 kg of weight, to be initiated on DAAs.

4.7.3. Treatment of children with decompensated cirrhosis

Children confirmed with chronic HCV infection with decompensated cirrhosis are complicated cases which are difficult to manage. General practitioners/nurses must refer such cases to Pediatricians.

4.7.4. Additional considerations

Management of HCV in children and adolescents should involve their parents or caregivers. Parents should be counselled on HCV transmission to minimize stigmatization of the child and precautions should be taken to minimize HCV transmission.

4.8. HBV-HCV co-infection

HBV and HCV share similar modes of transmission with the possibility of co-infection.

HBV-HCV co-infected patients eligible to both HBV and HCV treatment, HBV treatment should be started before HCV treatment to avoid HBV reactivation leading to potentially severe acute/fulminant liver disease among co-infected patients.

In co-infected patients with a positive HBsAg (without any further consideration) and detectable HCV RNA, both HBV and HCV treatment should be initiated without delay. For HBV-HCV coinfection cases, HBV treatment is initiated 4 weeks before the initiation of HCV treatment to prevent HBV reactivation [19, 23].

HBV-HCV co-infected patients already on HBV treatment who are planning to initiate HCV treatment should continue HBV treatment and the treatment can be co-administered for HBV and HCV.

In co-infected patients with a positive HBsAg (without any further consideration) and detectable HCV RNA, both HBV and HCV treatment should be initiated without delay. For HBV-HCV coinfection cases, HBV treatment is initiated 4 weeks before the initiation of HCV treatment to prevent HBV reactivation.

4.9. Patients with renal impairment

Although all commonly used DAAs can be administered to patients with any level of renal impairment, caution should be taken when administering Ribavirin to patients with renal impairment. Ribavirin is predominantly excreted by the kidneys and the drug should normally be cautiously used in patients with a creatinine clearance <60mL/min[22]. On an individual basis, Ribavirin may be administered cautiously to patients with renal failure. This requires careful monitoring of hemoglobin and plasma Ribavirin levels, and this treatment should be centralized at referral centers.

Table 12: Dose adjustments and monitoring of DAA-use by stage of Chronic Kidney Disease (CKD)[18]

Chronic kidney disease stage (CKD)	Recommendations
CKD 1,2 &3 (eGFR>30ml/ min)	No dose adjustment is required when using: • Fixed-dose combination of Ledipasvir (90 mg) +Sofosbuvir (400 mg) • Fixed-dose combination of Sofosbuvir (400 mg) +Velpatasvir (100 mg) • Sofosbuvir (400 mg) • Daclatasvir (60 mg) Dose adjustment when using Ribavirin: • 400mg alternate with 200mg daily
CKD stage 4&5 (eGFR<30ml/ min)	• Limited data on the use of Sofosbuvir 400mg based regimen; use of Sofosbuvir based regimen requires close monitoring. • Dose adjustment when using Ribavirin: 200mg daily

4.10. TB and HCV co-infection

In patients co-infected with TB and HCV, it is recommended that TB should be treated before commencing therapy for HCV. In case of TB prevention, HCV treatment should be delayed until the end of TB prevention. If a patient is already on HCV treatment and is diagnosed to have TB, HCV treatment has to be stopped and TB treatment initiated. HCV treatment will be resumed after completion of TB treatment, The TB program has to work closely with the Hepatitis Clinic and share timely updates on the shared patients.

The following table documents drug indications for uses of HCV DAAs with commonly used TB drugs.

Table 13: Drug-drug interactions between commonly used TB drugs and DAAs

	SOF	SOF+LDV	SOF+DCV	SOF+VEL	SOF+VEL+VOX	RBV
INH						
Rifampicin						
Ethambutol						
Pyrazinamid						
Rifabutin						

Red: Do not co-administer

Yellow: Possible toxicity/interaction/dose adjustment as specified

Green: No interaction, can be co-administered

White: No data

There is limited data on the management of persons co-infected with HCV, HIV and TB. Clinical judgement is needed to reduce additive side- effects, pill burden and drug-drug interactions.

4.11. Drug-drug interactions (DDI)

Multiple drug use is at times common in patients initiating treatment on DAAs, so there is potential for drug-drug interaction. DAAs are metabolized by the Cytochrome P450 3A4 isoenzyme in the liver. Other drugs metabolized by this enzyme-particularly the Rifamycin, Rifampicin and Rifabutin can either raise or lower the level of DAAs or be increased or decreased themselves by these interactions and are thus contraindicated to be used together.

Co-administration of the following medicines with DAAs should be given special attention:

- ARTs;
- Amiodarone;
- Rifampin;
- Antacids;
- Anti-epileptics.

4.11.1. Warnings/ contraindications to therapy

- Sofosbuvir-based regimens (SOF+LDV, SOF+VEL) are contraindicated in patients receiving Amiodarone who cannot switch therapies;
- Sofosbuvir should be used with caution in patients with severe renal impairment (eGFR <30mL/min) as safety of Sofosbuvir-derived metabolites in patients with severe renal dysfunction is still being ascertained;
- DAAs are contraindicated in patients taking Rifampicin, Phenytoin, or Carbamazepine;
- Ribavirin is contraindicated in pregnant women, men whose partners are pregnant and patients with hemoglobinopathies.

Table 14: Drugs contraindications/ warnings

HCV Drugs	Drug Contraindications / warnings
Sofosbuvir	• Amiodarone co-administration ***(caution with beta-blockers)***
	• Renal failure ***(eGFR <30 mL/min/1.73 m2)***
Sofosbuvir +Ledipasvir	• Amiodarone co-administration
	• P-glycoprotein (gp) inducers
	• Renal failure ***(eGFR <30 mL/min/1.73 m2)***
Daclatasvir	• Drugs inducing or inhibiting CYP3A
Ribavirin	• Pregnant women or men whose partners are pregnant
	• Didanosine can result in life-threatening toxicity
	• Azathioprine can cause myelotoxicity
	• Caution with Stavudine, Zidovudine, Lamivudine ***(Decreased antiretroviral activity)***

In addition to the above contraindications and warnings:

- Antiepileptics of Carbamazepine, Phenytoin, Phenobarbital, and Oxcarbazepine cannot be used with DAAs;
- If SOF+LDV is used with Antacids, the two should be taken at least 4 hours apart;

- It is not recommended to co-administer SOF+VEL to patients taking antacids;
- Daclatasvir should be decreased to 30mg once daily when used with Atazanavir - Ritonavir, Clarithromycin, Itraconazole, Ketoconazole and Voriconazole.

An exhaustive list of DDIs can be found at http://www.hep-druginteractions. org. In doubt, please consult this database and a specialist.

4.11.2. Treatment failure

4.11.2.1. Reasons for treatment failure

Treatment failure, defined as detectable HCV RNA 12 weeks after end of treatment, can occur due to the following reasons:

- Patient non-adherence (taking medication, following a diet, and/or executing lifestyle changes as recommended by the healthcare provider);
- Administration of regimen that was not preferred especially when treating with non-pan-genotypic drugs;
- Drug-drug interactions decreasing efficacy of DAAs;
- Drug resistance.

4.11.2.2. Recommended actions for treatment failure

In case of treatment failure, the only highly effective and recommended drug for treatment failure **is SOF/VEL/VOX for 12 weeks**. When SOF/VEL/VOX is not available for retreatment/second line treatment, health care providers should reevaluate patient with relevant lab tests and can use the following treatment guiding principles:

- Addition of Ribavirin to failed treatment and possible extension of treatment duration to 24 weeks;
- Keep the same period of treatment as 12 weeks when using SOF/VEL/VOX;
- SOF/VEL /VOX cannot be used in cirrhotic patients with Child-Pugh Class B or C cirrhosis or with renal failure;

- Glecaprevir/ Pibrentasvir combination is effective for retreatment of patients that failed SOF based regimens and those who have failed treatment with either a protease inhibitor or an NS5A inhibitor (but not both). Treatment duration is 16 weeks.

Table 15: DAA regimens and durations for re-treatment of patients who are non-cirrhotic or have compensated cirrhosis [18]

Regimen 1st line	Duration 1st line	Regimen 2nd line	Duration 2nd line
Sofosbuvir 400mg OD + Ledipasvir 90mg OD	12 weeks	SOF + VEL + VOX	12 weeks
		SOF + VEL + Ribavirin SOF + LDV + Ribavirin SOF + DCV + Ribavirin	24 weeks
Sofosbuvir 400mg OD + Daclatasvir 60/30mg OD	12 weeks	SOF + VEL + VOX	12 weeks
		SOF + VEL + Ribavirin SOF + DCV+ Ribavirin	24 weeks
Sofosbuvir 400mg OD+ Velpatasvir 100mg OD	12 weeks	SOF + VEL + VOX	12 weeks
		SOF+V EL + Ribavirin	24 weeks
Glecaprevir 100mg OD + Pibrentasvir 40mg OD	8 weeks	Glecaprevir 100mg + Pibrentasvir 40 mg	16 weeks
		SOF + VEL + VOX	12 weeks

Recommendation

For SOF/ DAC first line treatment, patient should be initiated on 24 weeks if*:*

- Fibrotic/Cirrhotic or APRI score≥ 0.5
- VL: ≥600,000 copies/ml ≥ or 120,000 IU/ml
- Experienced patients

4.11.2.3. Drug resistance

- There is potential for drug resistance with DAAs. When healthcare providers have exhausted all other reasons for treatment failure, genetic sequencing for resistance testing can be done to select the most appropriate DAA for future therapy. This should be done in consultation with an expert specialist and the program.

4.11.2.4. Patient follow-up during treatment

Patients should be administered a 12- or 24-week treatment at a visit and particularly be seen every month if there is a need for a close follow-up. An HCV RNA test no-sooner than 12-weeks after completion of treatment course is necessary to assess treatment success, defined by undetectable HCV RNA 12-weeks post-treatment (SVR12). Patients on ribavirin involve more careful monitoring of hemoglobin levels (refer to Ribavirin based treatment algorithm). Treatment adherence is key to achieve a successful cure. Efforts such as adherence counselling prior to and during treatment and management of side effects of Anti- HCV drugs should be taken to improve adherence.

4.11.2.5. Patient follow-up post-treatment

There are no specific recommendations for long-term follow-up of non- cirrhotic patients who are cured from HCV infection. All patients with cirrhosis should be followed-up every 6 months for HCC monitoring regardless of whether they were cured or not. Patients who are not cured should be referred to a specialist.

4.11.2.6. Special cases for care and treatment

Special care (Referral to specialists) should be taken when managing and treating the following patient groups:

- Patients with decompensated cirrhosis are clinically complex and require close monitoring and long-term follow-up;
- Patients with renal impairment;
- Any other complicated case that may need a special attention.

Key Messages for HCV Management

1. HCV is screened by detecting the presence of HCVAb Rapid Test;
2. HCV self-test can be used to enhance testing uptake and early detection of HCV. Its result should be confirmed by further tests using a blood based rapid test and a confirmatory viral load if the rapid test is positive;
3. Confirmation of chronic HCV is defined as detectable HCV RNA viral load;
4. All patients diagnosed with chronic HCV should be initiated on treatment with DAAs unless they are part of special population groups requiring additional considerations or monitoring by specialists. Pregnant patients and those aged less than 3 years are currently the only patient's ineligible for treatment;
5. DAAs are generally well-tolerated with few side effects;
6. Patients should be followed up as needed by health facilities during therapy;
7. Patients who are cured with evidence of liver cirrhosis have a risk of HCC; they should be followed up every 6 months with lab tests for liver enzymes and ultrasound;
8. If a patient is not cured, he/she has to be retreated and a second line treatment should be initiated. Detectable SVR12 post second line treatment requires specialist assessment and possible genotyping test;
9. HIV-infected patients have increased risk of accelerated progression to compensated and decompensated cirrhosis and HCC;
10. Treatment for pregnant women confirmed HCV RNA positive will be delayed until post-breastfeeding;
11. HCV treatment with DAAs is recommended to children confirmed with chronic HCV infection who are 3 years and above with weight of at least 14kg and do not have decompensated cirrhosis. Children under 3 years, infected by chronic HCV are advised to wait until they have 3 years.

PART III

VIRAL HEPATITIS PROGRAM IMPLEMENTATION

Chapter I: Program implementation

1.1. Introduction

Successful implementation of the recommendations in these guidelines and establishment of affordable screening, treatment, and care programs in the public and private sectors for persons with chronic hepatitis B and C infections in Rwanda depends on a well-planned process of adaptation and integration into national strategies and guidelines. The implementation of the recommendations in these guidelines should be informed by local context, including national health systems, laboratory capacity, supply systems for drugs and other commodities, availability of financial resources, the organization and capacity of the health system and anticipated cost– effectiveness of the various interventions. Given differences in health facilities capacity (personnel and laboratory), viral hepatitis program will continue to be implemented following the minimum package of services per level of implementation.

In general, viral hepatitis services are composed of prevention including all sensitization methods to raise awareness and hepatitis related skills, screening and diagnosis of both HBV and HCV based on capacity but also care, treatment and patient follow-up including specific counseling and timely referral of complicated cases to higher level facilities according to the national guidelines.

The central level will continue to ensure the coordination of the guideline's implementation at all levels through medical procurement, training, and clinical

mentorship for health care providers, supervision and monitoring and evaluation of programs at national level.

The new guidelines will introduce task-shifting where general practitioners (GPs) and nurses are authorized to and trained to prescribe both HBV and HCV treatment medication. Specialists will be available to provide supervision and guidance as needed.

1.2. Minimum service package

Viral Hepatitis related services have been decentralized and integrated in the existing health care delivery systems. Below is a table with details on the minimum hepatitis service package provided at each health facility level.

Table 16: Minimum package for Viral Hepatitis B&C Services per Level of Health Facility

Minimum Package for Viral Hepatitis B&C services per level of health facility			
Lever/Provider	**Prevention**	**Laboratory/Imaging Service**	**Treatment**
Community - CHW	- Prevention message - Provide information to the community	- Provide information to the community	- Program adherence support - Provide information to the community
Health Center - Nurse - Laboratory Technician	- Prevention message - Vaccination of newborn - Adults' vaccination - Post exposure prophylaxis - Capacity building of CHWs	- Rapid test for screening - Liver function tests - Renal function tests - Hematology - Provide Ultrasound service - HBV and HCV viral load test and monitoring	- Clinical assessment for cirrhosis - Assess eligibility criteria for HBV using available capacities - Counseling (adherence, lifestyle) - Initiate HBV and HCV treatment for simple cases - Follow up of patients on HBV and HCV treatment - Refer complicated cases to the next level as appropriate
District Hospital - Specialist - General Practitioner - Nurse - Laboratory Technician - Medical imaging Technician - Counsellor - Nutritionist	- Prevention message - Vaccination of newborn - Adults' vaccination - Post exposure prophylaxis - Supervision and clinical mentorship of health centers	- Rapid test for screenning - Liver function tests - Renal function tests - Hematology - HBV and HCV viral load test and monitoring - Capacity building of Laboratory technicians at Health center level (Training, mentorship)	- Clinical assessment for cirrhosis - Assess eligibility criteria for HBV using available capacities - Counseling (adherence, lifestyle) - Initiate HBV and HCV treatment - Follow up of patients on HBV and HCV treatment - Provide Ultrasound service - Refer complicated cases to the next level as appropriate - Follow up of patients on HBV and HCV treatment - Capacity building of medical personnel at District Hospitals (Training, mentorship, supervision)
Provincial/Referral Hospital - Specialist - General Practitioner - Nurse - Laboratory Technician - Radiologist/ Medical imaging Technician - Counsellor - Nutritionist	- Prevention message - Vaccination of newborn - Adults' vaccination - Post exposure prophylaxis - Supervision and clinical mentorship of health centers	- Rapid test for screening - Liver function tests - Renal function tests - Hematology - HBV and HCV viral load test and monitoring - Capacity building of Laboratory technicians at Health center level (Training, mentorship)	- Clinical assessment for cirrhosis - Assess eligibility criteria for HBV using available capacities - Counseling (adherence, lifestyle) - Initiate HBV and HCV treatment - Follow up of patients on HBV and HCV treatment - Refer complicated cases to the next level as appropriate - Follow up of patients on HBV and HCV treatment - Capacity building of medical personnel at District Hospitals (Training, mentorship. supervision)

For a better coordination and increased access to hepatitis services, the following minimum package of services to be offered to the population was defined based on the available resources and capacity of each level of health facility. At the health center level, all cases are managed by trained nurses, at the district hospital, hepatitis is managed by doctors and/or nurses with a possibility of referring complicated cases to the next level (referral and provincial hospitals to be managed by specialists.

1.3. Diagnosis and Supply chain

The national hepatitis program works closely with other entities under the Rwanda Biomedical Centre including the National Reference Laboratory, the Rwanda Medical Supply and the Blood Transfusion Division to ensure integration of hepatitis services within the health system. The National Reference Laboratory supervises all diagnostic activities and ensures laboratory quality management systems implementation across the country including hepatitis diagnosis. There are hubs in country offering viral load services that include hospitals and health centres. The hepatitis program also leverages the national sample transportation to move samples from the health centres to the nearest viral load testing hubs and results are shared electronically through the Viral Load Sample Management (VLSMS) and (LIS) platforms.

Hepatitis and HIV commodities supply chain is integrated. An annual national quantification exercise is conducted, and a procurement plan is developed. The program ensures commodities are purchased and once received in the country, they are stored and distributed through a decentralized national distribution system up to the health centre level. A national electronic system is used to request commodities from health centres and hospitals to RMS branches and from RMS branches to the RMS central level.

Additionally, the program works with the Blood Transfusion Division (BTD) to ensure timely linkage to care and follow up of all hepatitis patients identified through the blood transfusion program. The BTD ensure safety and security and distribution of blood across facilities and contributes greatly to the hepatitis program's case finding strategy.

1.4. Monitoring and Evaluation

A monitoring and evaluation system has been developed to help the program monitor the progress towards hepatitis elimination and inform program decisions and initiatives. Hepatitis program is progressively moving from a paper-based data system to a digital system in the framework of the health systems digitalization. Currently, viral hepatitis data is routinely collected in HMIS and DHIS2 tracker electronic systems. The HMIS collects and stores aggregated data while the DHIS2 tracker collects and stores individual data. Both HBV and HCV data are routinely collected. The program monitoring is conducted through programmatic and impact indicators. Programmatic indicators are collected using the DHIS2 tracker, ensuring that every patient enrolled in care completes all involved steps. The impact indicators are monitored through surveys and other national systems such as the death and cancer registries.

The table below shows the relationships between different data collection systems:

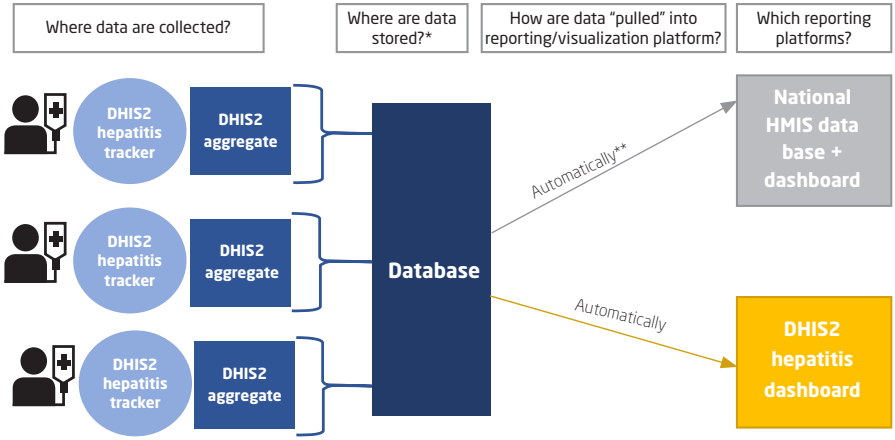


Figure 8: Data collection and aggregation from hepatitis tracker to other systems

**MOH server, tracker and aggregate are separate databases,*
***Aggregation of data from health facility> HMIS will be eventually all automated. Currently, there is a parallel process where data managers taking aggregate data from facility registers (e.g, total # of patients screened in January) and manually enter them into HMIS database*

1.4.1. Routine sources for viral hepatitis program data

- DHIS2-based hepatitis tracker;
- Facility-based registration books (in process of being phased out);
- National facility-based health management information systems (HMIS);
- Laboratory Information system (LIS);
- VLSMS data system (viral load testing database system, operational in all hubs except national laboratory).

1.4.2. Surveillance data

Rwanda is on the journey towards Hepatitis elimination. Hepatitis surveillance plays an important role to ensure hepatitis present cases are treated and new cases are identified at an early stage. The different sources of surveillance data for the program include:

1.4.2.1. Routine care

The DHIS2 trackers is used to monitor programmatic indicators using the pathway below:

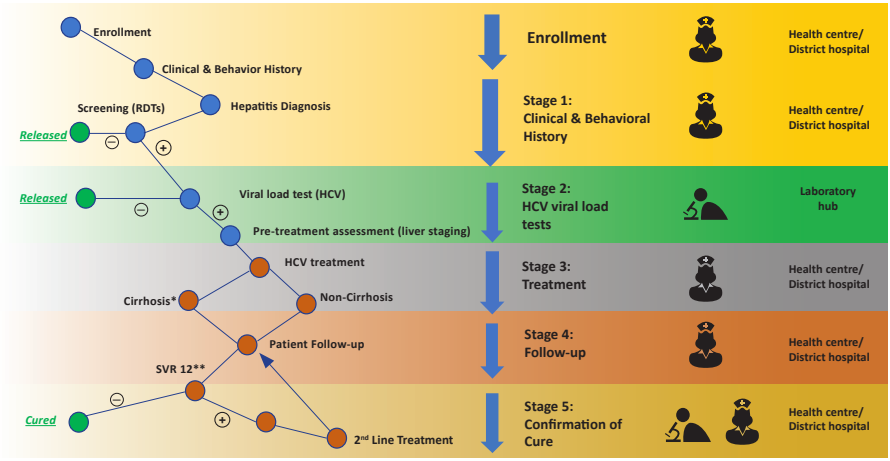


Figure 9: Hepatitis C cascade of care

In addition to the routine surveillance, the program will leverage HIV sentinel sites to track acute hepatitis cases.

Table 17: M&E roles and responsibilities

Level	Healthcare provider	Role in hepatitis management	DHIS2-related responsibilities
Health facility, district level	Nurses	• Screening • Treatment • Patients follow up	• Enter patient data at the clinic. • Track individual patients along the cascade of care; follow-up as necessary.
	Data Managers	• Not directly involved in provision of care • Data aggregation	• Provide real-time support on issues related to DHIS2. • Conduct data quality review. • Aggregate HMIS data • Provide mentorship to nurses on data management systems.

1.4.2.2. Death registry (Civil registration and vital statistics (CRVS) system)

Rwanda has already established civil registration and vital statistics (CRVS) to monitor vital events including deaths. The program will use CRVS data to monitor mortality caused by hepatitis. Hepatitis-caused deaths are captured in the following ICD10 codes:

- Hepatocellular carcinoma (HCC; ICD-9 code: C22.0);
- Cirrhosis (ICD-K74.6);
- Chronic liver diseases (ICD-9 code: K72-K75).

1.4.2.3. Cancer registry

The national cancer registry will be used to understand the attributable/ etiologic fraction of deaths from the causes directly attributed to hepatitis infection. Digital cancer registries in selected referral hospitals will be used to estimate the attributable fraction from HCV and HBV.

Table 18: Frequency of data collection by data source

Data source	Frequency that data is collected/reported	Frequency of data review
DHIS2	Continuous	Monthly dashboard review by data managers. Quarterly dashboard review at the central level.
LIMS	Continuous	Monthly dashboard review by data managers. Quarterly dashboard review at the central level.
Death registry	Continuous	Annual review at the central level.
Cancer registry	Continuous	Annual review at the central level.
Incidence study	Upon study completion	Upon study completion
DHS	Every ~5 years	Upon study completion

PART IV

GOVERNANCE, COMMUNITY ENGANGEMENT, HEPATITIS ELIMINATION, HUMAN RIGHTS, EQUITY AND GENDER EQUALITY

Chapter I: Governance and community engagement

1.1. Governance

Rwanda Government through the Ministry of Health (MoH) and Rwanda Biomedical Centre (RBC) provides a strong support to the hepatitis program and support all initiatives towards hepatitis elimination. In this regard, hepatitis services including vaccination, testing and treatment are provided at no cost to all Rwandans in need and refugees residing in Rwanda. All STIs services are covered under the national Community-Based Health Insurance (CBHI) that covers over 97% of Rwandans. This ensures universal access to hepatitis and STIs services especially the lowest social categories of the population.

Viral hepatitis and STIs program form a unit under HIV, STIs, Viral Hepatitis and Other Viral Disease Control Division within RBC. This unit has been created by the MoH in 2011 within RBC, a public institution operating under the supervision of the Ministry of Health.

The viral hepatitis and STIs have a Technical Working Group (TWG) that decides on testing and treatment options including new technologies and new plans. The TWG is composed of members from different institutions including the MoH, RBC, hospitals, partners, health insurances, NGOs, private sector, civil societies, representatives of communities of hepatitis patients.

1.2. Community engagement

The population is continuously educated on hepatitis prevention and treatment and they respond positively to the program's case finding strategies including mass screening health facility based routine screening and treatment. The program works with the local governance and association of hepatitis patients to continually identify high-risk groups and family members of positive patients. Screening can be voluntary and is available to all or can be provider-initiated in case of suspicion of hepatitis infection. Hepatitis diagnosis and treatment services have been decentralized up to health centers, and healthcare providers are trained to diagnose, treat and follow up hepatitis patients.

1.3. Human rights

All Rwandans have the same right to access all health services including hepatitis B, C and STIs management services from testing to treatment and follow-up. There is no discrimination of any kind to access healthcare services including hepatitis B, C and STIs. There is no discrimination based on gender, age, region, employment, education, housing, social benefits, sexual orientation, incarceration experience, immigration status or profession as a criterion for exclusion from hepatitis management services.

Persons infected with HBV, HCV and STIs are informed on their status and counselled accordingly for testing and treatment. Persons infected with hepatitis B and/or C, high-risk groups (e.g., FSW, MSM, IDU, PLHIV, Prisoners etc.), key populations and people who belong to vulnerable groups such as refugees have the same rights to access healthcare services as any other Rwandans as human beings.

1.4. Equity and gender equality

The national hepatitis program ensures every person residing in Rwanda receives quality and timely hepatitis services. Availing services free of charge and leveraging the national health insurance for advanced testing has ensured equitable access to hepatitis services decentralization of hepatitis services to lowest facility level, the program has allowed access to all, especially marginalized populations that could

not access services due to long distances. Women in particular have benefited from hepatitis services decentralization to the health center where they receive other services including antenatal care (attended at 98%) delivery (attended at 93%) and children vaccination (attended at 97%)[1]. These different initiatives have ensured equity and equality in matter of accessing hepatitis and STIs management services.

There is no preference given to men or women in matter of provision of hepatitis and STIs management services. Men and women living with hepatitis infection are followed up for adequate care and treatment and counselled to live their life without stigma. People who are infected with hepatitis B or C and STIs are counselled before, during and after provision of services to avoid any stigma which may arise from their life conditions.

Generally, there is no observed stigma around the patients consulting for hepatitis management services as well as all people living with hepatitis.

1.5. Viral Hepatitis elimination

Hepatitis elimination was launched in 2016 by the publication of the WHO Health Sector Strategy which aimed at eliminating HBV and HCV by 2030. The following targets have been set by WHO for HBV and HCV elimination:

Table 19: HBV and HCV elimination impact and programmatic indicators

Elimination targets	Elimination of chronic HCV as a public health problem		Elimination of chronic HBV infection Infection as a public health problem	
2030 GHSS relative reduction reference targets (compared to 2015)	**Incidence** 95% reduction	**Mortality** 65% reduction	**Incidence** 80% reduction	**Mortality** 65% reduction
HBV- and HCV-specific absolute prevalence, incidence and mortality targets	HBV EMTCT ≤0.1% HBsAg prevalence in ≤5 year olds. Additonal target ≤2% MTCT rate (where use of targeted Hep8-BD)	Annual mortality(HBV) ≤4/100 000	Annual incidence (HCV) ≤5/100 000 ≤2/100 (PWID)	Annual mortality (HCV) ≤2/100 000
Programmatic targets	**Countries with universal HBV vaccine birth dose (BD)** ≥90% HepB3 vaccine coverage ≥90% HepB timely hepatitis B BD (HepB-BD) coverage **Countries with targeted HBV vaccine birth dose (BD**) ≥90% HepB3 vaccine coverage ≥90% coverage of those infants at risk with targeted HepB-BD ≥90% coverage of maternal antenatal HBsAg testing ≥90% coverage with antivirals for those eligible	**Testing and treatment** ≥90% of people with HBV diagnosed ≥80% of people diagnosed with HBV and eligible for treatment are treated[h] **Prevention** ≥90% HepB3 vaccine coverage ≥90% HepB-BD coverage	**Testing and treatment** ≥90% of peopie with HCV diagnosed ≥80% of people diagnosed with HCV are treated[g] **Prevention** 0% unsafe injections 100% blood safety 300 needles/syringes/ PWID/year	

Following the country's efforts in case finding, treatment availability and services decentralization, Rwanda decided to take a bigger stride. In December 2018, a national plan for hepatitis C elimination was launched aiming to screen 7 million people aged 15 years and above and treat all positive cases to eliminate HCV. Following the launch, the program has intensified case finding strategies and

ensured linkage to care of all confirmed cases. Currently, over 7,000,000 people have been screened and 60,000 have been treated. WHO allows countries to choose an elimination model that works for eliminating hepatitis B and C individually or elimination both hepatitis B and C at the same time. Rwanda has chosen the first option and started with hepatitis C elimination.

Table 30: Options for validation of HBV and HCV elimination as a public health threat

Option	Options for validation of elimination	Impact indicators	Programme indicators
Option A	HBV EMTCT (as part of triple elimination of HIV, syphilis and HBV, or HIV/HBV)[3]	Annual HBV incidence and MTCT rate (additional target) in countries with targeted timely HepB-birth dose (BD)	HBV birth dose and infant vaccination coverage for newborns and infants HBV antenatal testing and antiviral prophylaxis coverage
Option B	HCV as a public health problem	Annual HCV incidence and HCV mortality	Coverage of prevention, testing and treatment
Option C	HBV as a public health problem (including HBV EMTCT)	nnual HBV incidence (and MTCT rate) and HBV mortality	Coverage of prevention, testing and treatment
Option D	Elimination of both HBV and HCV as a public health problem (including HBV EMTCT)	A, B and C above	A, B and C above

In terms of hepatitis B elimination, the country has leveraged the same efforts deployed towards hepatitis C, to vaccinate, screen and treat adults infected with hepatitis B. The program has also initiated efforts to prevent mother to child transmission of hepatitis B, through systematic screening of pregnant women, provision of treatment to confirmed positive women and administration of hepatitis B birth dose to all newborns within 24 hours after birth.

PART V

SEXUALLY TRANSMITTED INFECTIONS MANAGEMENT

Chapter I: Generalities on Sexually Transmitted Infections

1.1. The management of STIs

The management of STIs is based on the following principles:

- Education about signs and symptoms of STIs, the modes of transmission, prevention, early consultation for diagnosis and treatment;
- Community sensitization / mobilization on uses of STIs services;
- Integration of STI control activities in the minimum activity package of health services;
- Availability and accessibility of STIs related commodities;
- Immunization of high risk groups;
- Post exposure prophylaxis;
- Systematic STIs risk assessment and categorization, screening, diagnostic and linkage to treatment if needed;
- Contact tracing and partner notification from the index client;
- Clients care and treatment, follow up, monitoring and evaluation;;
- Reporting on STIs management indicators.

1.2. Programmatic implementation

- Advocate for a better diagnosis and management;
- Contact tracing and screening of STIs patients;
- Provide friendly STIs complete care and treatment to avoid stigma;
- Routine and regular collection and management of STIs data through HMIS.

Note:

Complete care of STIs includes:

1. Information, education and communication (IEC)/ behaviour change communication (focus on risk factors, STIs and HIV relationship);
2. Systematic screening of syphilis, HIV, HBV and other STIs in pregnant women;
3. Systematic screening of STIs in newborns, adolescents and adults;
4. Screening and systematic treatment of FSW and MSM;
5. Carry out the syndromic/ etiologic diagnosis;
6. Provide correct antimicrobial treatment corresponding to the syndrome of STIs, corresponding to the clinical diagnostic of STIs or corresponding to the micro-organism of the STIs;
7. Explain the adherence of the treatment;
8. Demonstrate the correct condom use and to make them available and accessible;
9. Provide counselling on the treatment of partners and to give the patient an orientation form for the sexual partner so that he/she can send it to his/her partner (s);
10. Systematic HIV testing and counselling (HTC).

1.3. Definitions of terms and concepts

Sexually Transmitted Infections (STIs): Infections that are due to microbial agents (bacteria, virus, parasites, fungi), which are transmitted exclusively or mainly through sexual relations. Note that microbial agents are often associated among themselves and infections become mixed.

Index client (case): STI client treated in the health system from which we search for one or several partners.

Clients-contacts (or sexual partners): Persons who will have or had sexual relations with the Index client

Search for partners: Methodological investigation based on responses from the index client that enables the census and the treatment of contact- clients.

Sex worker: Any individual who engages in sexual activity that consists of satisfying sexual needs of another person in exchange of material or financial goods.

Paedophilia: Any sexual activity carried out on children by adults.

MSM (Pederast): Any male person who engages in sexual activities with other people of the same sex

Lesbian: Any female person who engages in sexual activities with other people of the same sex

Key population: Defined by UNAIDs as people who inject drugs, gay men (MSM) and other men who have sex with women (MSM, bisexual), transgender persons and sex workers.

Core group (group of the transmission): Group of people in a limited population who maintain and perpetuate the propagation of STI within the community (Ex. Sex workers).

Bridging population: People having sexual relations with the core group as well as the general population: i.e., the clients of sex workers.

Genital Tracts Infections (GTI): Infection of the genital organs including STIs and those not always transmitted by sexual means.

Table 21: STIs types and etiological agents

Name of the infection	Name of the micro-organism
STIs due to bacteria	
Gonococcus	Neisseria gonorrhoea
Syphilis	Treponema pallidum
Wet Chancre	Bacilli of Ducrey
Venereal Lymphogranulomatosis (VLG) or the disease of Nicolas Favre	Chlamydia trachomatis
Chlamydia	Chlamydia trachomatis
Mycoplasmosis	Ureaplasma urealyticum and Mycoplasma hominis
Donovanosis	Calymmatobacterium granulomatis
Bacterial Vaginosis	Anaerobic bacteria
STIs due to fungi (mycosis)	
Candida	Candida albicans
STIs due to other parasites	
Scabies	Sarcoptes scabiei hominis
Phtiriasis	Phtirius inguinalis
STIs due to Protozoa	
Trichomonas	Trichomonas vaginalis
STIs due to viruses	
HIV infection	Human Immuno-deficiency virus type 1 and 2
Genital Herpes	Herpes virus simplex type 2
Condyloma acuminata	Human Papillomavirus
Viral Hepatitis B	Hepatitis B Virus
Viral Hepatitis C	Hepatitis C Virus

1.4. Risk factors

1.4.1. Biological factors

- **Age:** Rates of STIs tend to peak between 15 to 49 years of age and then decline. Up until puberty, children do not suffer from STIs apart from congenital syphilis, neonatal conjunctivitis, HBV, HCV and HIV infection transmitted from mother to child.
- **Sex:** STIs are more frequent among women than men due to several factors:
    1) Precocity of sexual relations in girls where they are more likely to have sexual relations with older partners at higher risk for infection;
    2) Larger area of exposure of the vagina;
    3) Shorter length of female urethra compared to males.
- **Others:** Weak immunity (PLHIV, Diabetic, chemotherapy, etc.) status and non-circumcision in males are additional risk factors.

1.4.2. Socioeconomic, educational and occupational factors

- Poverty;
- Wars;
- Displacement of populations;
- Professions involving movement (long-distance truck drivers, army, police, seasonal workers, miners or gold diggers, itinerant traders, tourists);
- Ignorance of the mode of transmission of STIs;
- Marital situations including forced and premature marriage;
- Socio-economic dependence and lack of sexual control;
- Early debut of sexual intercourse;
- History of STIs in the same household.

1.4.3. Behavioral factors

- Unprotected sexual relations;
- Sexual intercourse with multiple partners;
- Unprotected sex with sex workers;
- Sexual relations with casual partners;
- High risk sexual practices (anal, oral, homosexuality, bisexuality etc.);
- Self-medication for an STI infection;
- Drug and alcohol abuse;
- Tattoos.

1.4.4. Cultural and religious factors

- Taboos linked to sex;
- Mutilation and cultural labial stretching in girls;
- Scarification.

1.5. Relationship between HIV and other STIs

Several epidemiological and biological studies provide evidence of a complex interaction between HIV and other STIs through the following mechanisms:

- STIs facilitate the transmission of HIV;
- The presence of HIV may make the persons more susceptible to STIs;
- The presence of HIV aggravates certain STIs and increases their resistance to treatment.

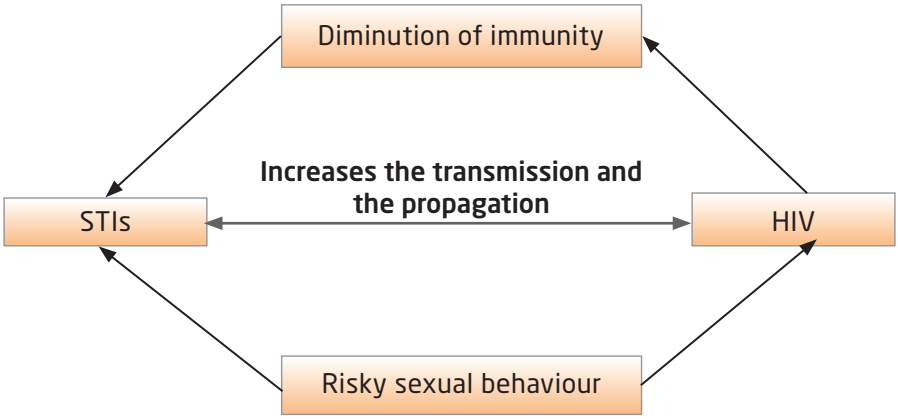


Figure 10: Relationship between STIs and HIV

1.6. Complications

Late, untreated or poorly treated STIs may lead to the following complications in women, men and newborns.

1.6.1. Complications in men

The following complications can be observed:

- Orchi-epididymitis;
- Prostatitis;
- Sterility;
- Urethral strictures.

1.6.2. Complications in women

The most frequent complications are the following:

- Pelvic Inflammatory Disease (PID) or Pelvic Inflammatory Syndrome (PIS);
- Sterility;

- Ectopic pregnancy;
- Cervical cancer;
- Complication during pregnancy: abortion, still birth, underweight newborn following premature childbirth or delay in delivery.

1.6.3. Complications in newborns

- Neonatal conjunctivitis due to ***Neisseria gonorrhea*** and/or due to ***Chlamydia trachomatis*** that may lead to blindness;
- A pulmonary infection due to ***Chlamydia trachomatis;***
- Congenital syphilis due to ***Treponema pallidum***;
- Premature childbirth;
- Underweight.

Chapter II: Prevention of STIs

2.1. Strategies

The prevention and the control of STIs are based especially on the following 5 major strategies:

1. Education and counselling of high-risk persons on changing their sexual behavior;
2. Identification of infected persons with clinical signs (symptomatic) or without clinical signs (asymptomatic) that should consult services in charge of diagnosis and treatment of STIs;
3. Efficient and early diagnosis and treatment of persons infected with STIs;
4. Evaluation, treatment, and counselling of partners of persons infected with STIs;
5. Vaccination of girls aged 11 to 15 years for HPV infection.

2.2. Primary prevention

Primary prevention involves activities that will reduce the risk of infection by reducing high risk sexual activities or interventions such as the following:

- Abstinence;
- Reduction of the number of partners (one faithful partner);
- Consistent and correct use of condoms;
- Male circumcision;
- Immunization.

2.3. Secondary Prevention

Secondary prevention involves activities to reduce STI complications for patients already infected by:

- Promoting treatment seeking;
- Provision of quality care services to treat STIs;
- Offering support and counseling services.

Chapter III: Diagnosis and treatment

In Rwanda, two approaches are used for the diagnosis and treatment of STIs. These include:

- Syndromic approach;
- Etiologic approach.

3.1. Syndromic approach

The syndromic approach is based on the identification and treatment of a set of symptoms communicated by the patient and signs observed during the history and physical examination.

The 6 syndromes which may be caused by one or several STI germs, are the following:

- Urethral discharge in men;
- Vaginal discharge;
- Genital or anorectal lesions;
- Anorectal discharge;
- Pelvic pain in women;
- Purulent conjunctivitis of the newborn.

Although etiologic approach is known to be more specific, in Rwanda the most used approach is syndromic, due to limited laboratory diagnostic capacity. The syndromic approach enables one to carry out rapid presumptive diagnosis and to administer immediate treatment beginning with the first consultation.

It enables the client to receive treatment without delay and increases the chances of healing. However, the syndromic approach does not identify the responsible pathogen, thus risk of over/under treatment which may lead to drug resistance.

In all cases of STIs warranting syndromic management, the following counselling and procedures should be provided:

- Tracing and treating the partner(s): Emphasize on the prevention of possible reinfection once the partner is not treated;
- Consistent and correct condom use;
- Advice for local care when applicable;
- HIV, HBV, HCV testing.

Below is a summary of the syndromic management of ano/genital discharge, lower abdominal pain and ano-genital lesion (syphilis), followed by specific treatment algorithms based on syndrome diagnosed.

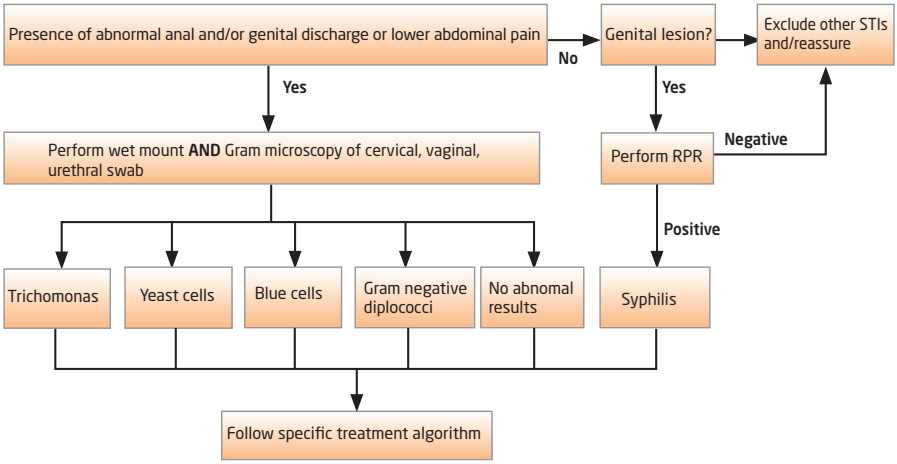


Figure 11: Management of abnormal anal and/or genital discharge

3.1.1. Syndromic management for urethral discharge

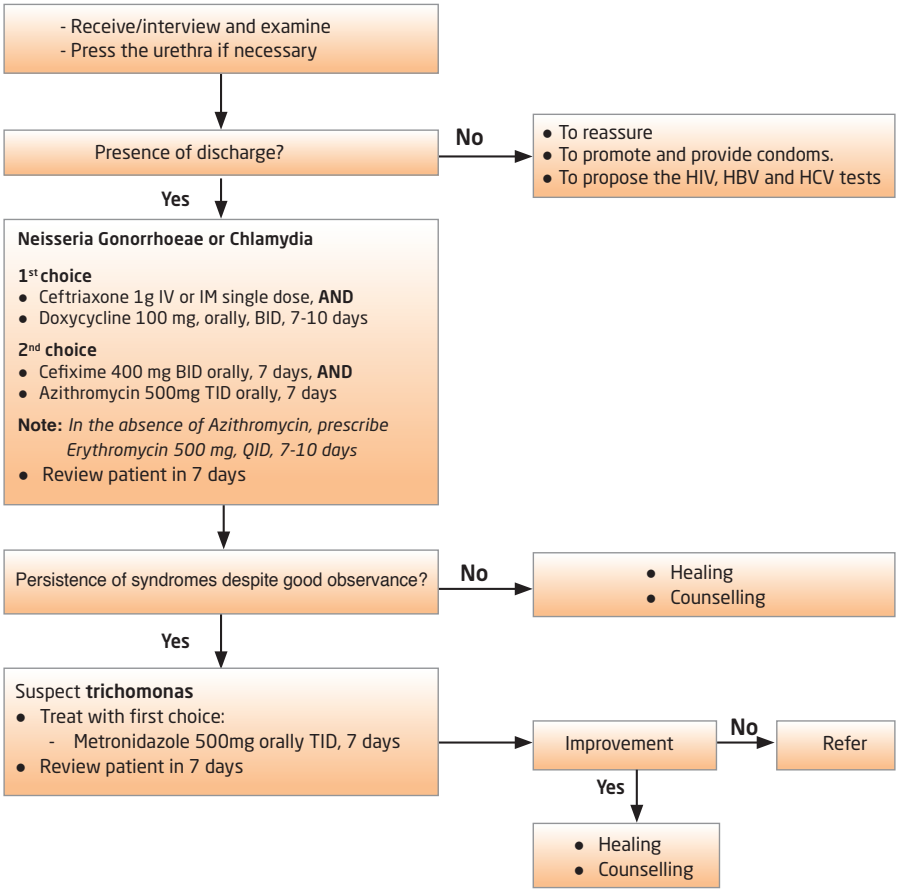


Figure 12: Algorithm of urethral discharge diagnosis and treatment

3.1.2. Syndromic management for vaginal discharge

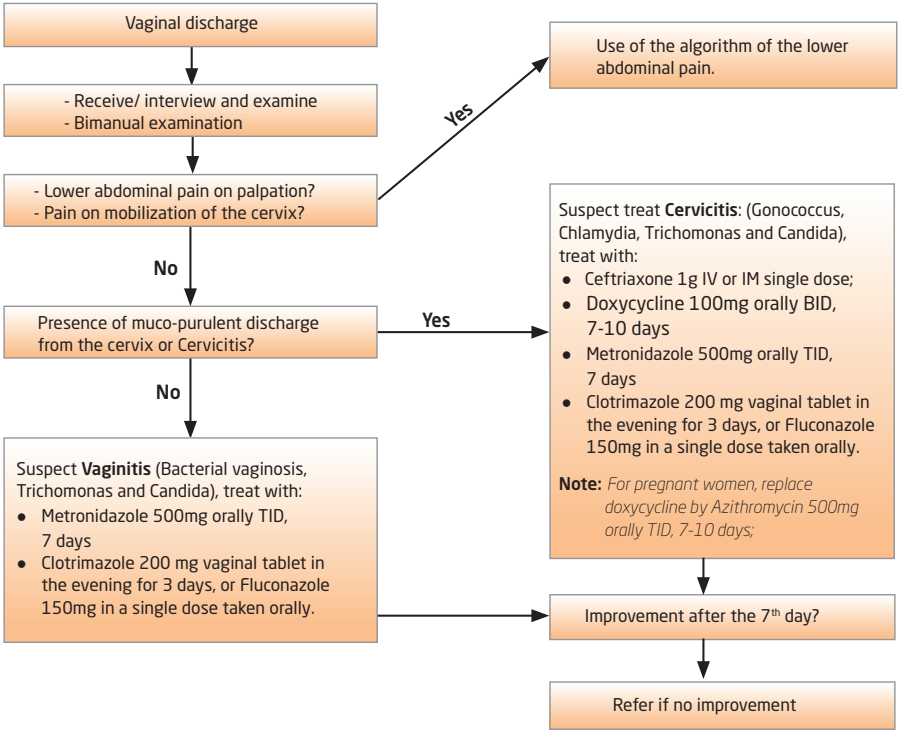


Figure 13: Algorithm of vaginal discharge diagnosis and treatment

3.1.3. Genital/anorectal lesions

Genital/anorectal lesions are defined as any wound (s) at the level of external genital organs and/or anorectal of a man or a woman. It may be accompanied by inguinal lymphadenopathy, losses of tegument substance at the level of genital organs, may be painful or painless, clean or dirty, fixed or mobile.

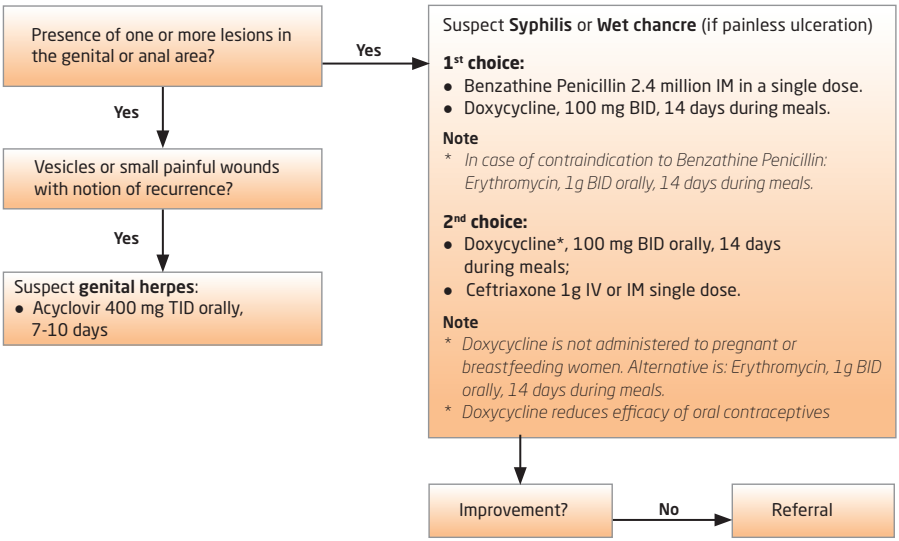


Figure 14: Algorithm of Genital/anorectal lesions diagnosis and treatment

3.1.4. Anorectal discharge

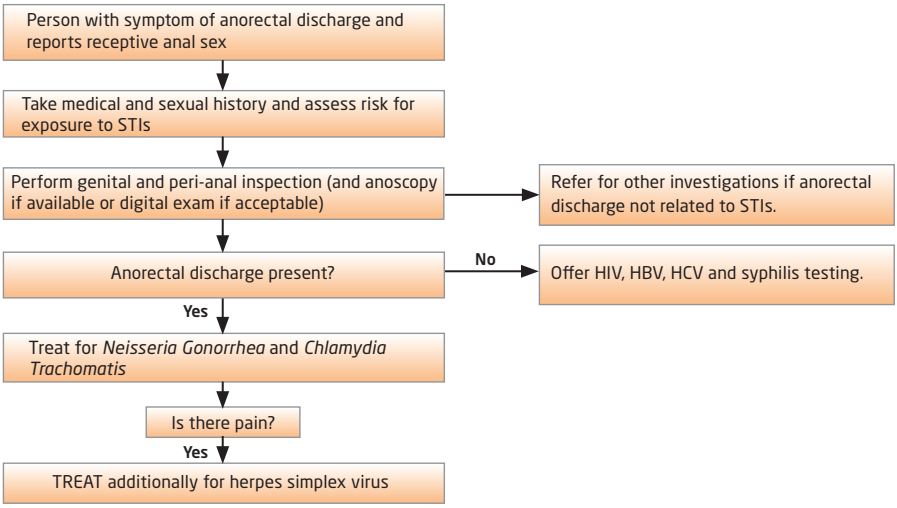


Figure 15: Algorithm of anorectal discharge diagnosis and treatment

3.1.5. Pelvic pain in women

Pelvic pain in women is defined as painful manifestations of the lower abdomen. Lower abdominal pain constitutes frequent reasons for consultations in emergency services. It is in most cases a manifestation of an evolving genital infection (cervicitis, endometritis, salpingitis, and ovaritis) that may be the cause of sterility and extra-uterine pregnancy.

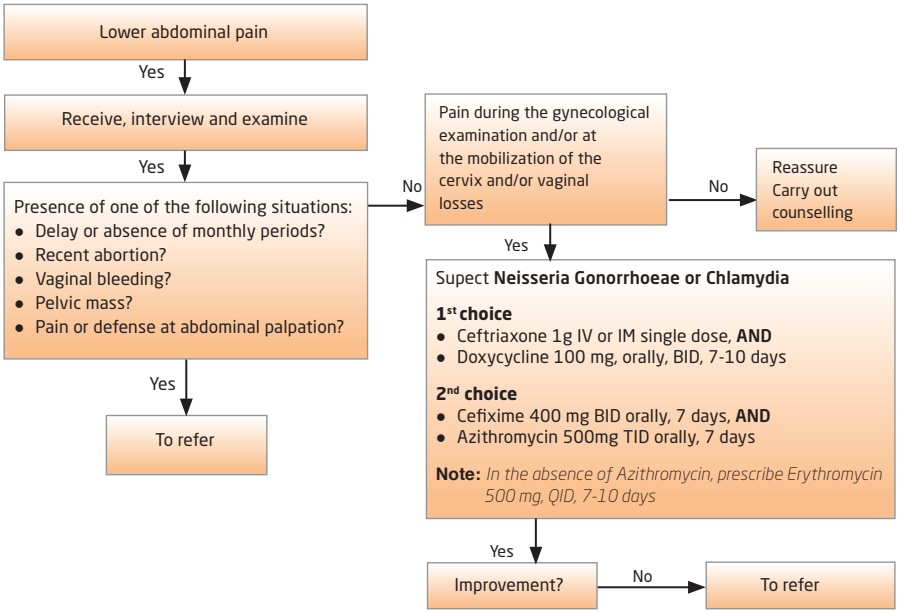


Figure 16: Algorithm of pelvic pain diagnosis and treatment

3.1.6. Purulent Conjunctivitis of the newborn

Purulent conjunctivitis of the newborn is an ocular infection of the baby aged less than one month marked by red eyes with purulent and sticky secretions. Purulent conjunctivitis of the newborn is contracted at birth through contact with infectious vaginal secretions of the mother. It may lead to blindness, especially when it is due to ***Neisseria Gonorrhoea***. In the case of an infection due to Chlamydia, the newborn may develop pneumonia and/or conjunctivitis.

The prophylaxis consists of meticulous cleaning of the eyes immediately after birth and the application of the 1% tetracycline ointment.

3.2. Etiological approach

The etiological approach uses laboratory tests with the support of data obtained from the interview and physical examination. It constitutes an ideal strategy in the care of STIs but it requires adequate laboratory and qualified personnel.

Table 22: Clinical presentation and treatment in adults of common bacterial STIs

Clinical signs and symptoms	Diagnosis	Etiology	Diagnosis method/ Lab	Treatment
• Urethral discharge • Cervicitis and lower abdominal pain in women	Gonorrhoea	*Neisseria gonorrhoea*	• Gram Staining • Culture • NAT	**1st choice** • Ceftriaxone 1g IV or IM single dose, **AND** • Doxycycline 100 mg, orally, BID, 7-10 days **2nd choice** • Cefixime 400 mg BID orally, 7 days, **AND** • Azithromycin 500mg TID orally, 7 days Note: *In the absence of Azithromycin, prescribe Erythromycin 500 mg, QID, 7-10 days*
• General symptoms: fever, polyarthritis, skin lesions • Usually no urogenital symptoms	Disseminated gonococcal infection	*Neisseria gonorrhoea*	• Gram Staining • Culture • NAT	• Ceftriaxone of 1g IV for every 24 hours until clinical improvement (at least 7 days) **AND** • Azithromycin 500mg TID orally, 7 days
• Urethral discharge • Cervicitis and lower abdominal pain in women	Chlamydiosis	*Chlamydia trachomatis*	• Culture • ELISA • Direct Immunofluorescence • NAT	• Doxycycline, 100 mg orally, BID, 14 days **OR** • Azithromycin, 500 mg orally, TID, 7 days
Cervicitis and lower abdominal pain	Chlamydial infection during pregnancy	*Chlamydia trachomatis*	• Culture • ELISA • Direct Immunofluorescence • NAT	• Azithromycin, 500 mg orally, TID, 7 days **OR** • Erythromycin, 500 mg orally, QID, 7 days
• Tender inguinal and/or femoral lymphadenopathy that is typically unilateral • Proctocolitis, including mucoid and/or hemorrhagic rectal discharges	Lymphogranuloma venereum	*Chlamydia trachomatis*	• Culture • ELISA • Direct Immunofluorescence • NAT	• Azithromycin, 500 mg orally, TID, 14 days **OR** • Doxycycline, 100 mg orally, BID, 21 days **OR** • Erythromycin, 500 mg orally, QID, 21 days

Clinical signs and symptoms	Diagnosis	Etiology	Diagnosis method/ Lab	Treatment
• Painless ano-genital ulcers (chancre) • Inguinal tumefaction • Painless mucocutaneous lesions • Cutaneous accidents (gums), cardio-vascular (aortitis) and neurological (neurosyphilis)	Syphilis (primary, secondary, latent syphilis, or late latent syphilis)	*Treponema pallidum*	• Screening: VDRL, RPR • Confirmation tests: Treponemal tests: TPHA, FTA. Dark field microscopy, Direct fluorescent antibody test and NAT	• Benzathine benzylpenicillin, 2.4 million IU IM, once weekly for 3 consecutive weeks **OR** • Procaine benzylpenicillin, 1.2 million IU IM, OD, 20 consecutive days **OR** • Erythromycin, 500 mg orally, QID, 30 days
Genital ulcers with inguinal tumefaction (bubo) in most of the cases	Wet Chancre	*Haemophilis ducreyi*	• Culture • NAAT	• Erythromycin base 500 mg orally TID, 7 days, **AND** • Ceftriaxone 1g IV or IM single dose, **OR** • Cefixime 400 mg BID orally, 7 days, **AND** • Azithromycin 500mg TID orally, 7 days
• Ulcerative vascular lesions on the genitals or perineum, subcutaneous, granulomas (pseudo oboes) • Hypertrophic, necrotic, or sclerotic variants • Extragenital infection can occur with extension of infection to the pelvis, intro-abdominal organs, bones, or the mouth.	Granuloma Inguinale (Donovanosis)	*Klebsiella granulomatis*	Microscopy with dark-staining Donovan bodies on tissue crush preparation or biopsy	• Azithromycin orally 500mg TID for at least 3 weeks and until all lesions have completely healed, **OR** • Erythromycin base 500 mg orally QID for at least 3 weeks and until all lesions have completely healed, **OR** • Doxycycline, 100 mg orally, BID for at least 3 weeks and until all lesions have completely healed

Table 23: Clinical presentation and treatment of viral STIs in adults

Clinical signs and symptoms	Diagnosis	Etiology	Diagnosis method/Lab	Treatment
Vesicular lesions and ano-genital ulcerations	Genital Herpes	*Herpes virus of the simplex type 2 (HSV-2)*	• Diagnosed clinically • Culture • NAAT	**1st choice** • Acyclovir 400 mg orally, TID, 7-10 days **OR** • Acyclovir 800mg orally, BID, 5 days **2nd choice** • Famciclovir 250 mg orally, TID, 7-10 days **OR** • Valacyclovir 1g orally, BID, 7-10 days
• Abnormal growth that is usually flat, popular, or pedunculated growths on the genital mucosa • Usually asymptomatic	Genital Warts	*HPV 6 or 11*	Clinical diagnosis	• Topical treatment with Podofilox 0.5% solution or gel, 3 times a week for up to 4 months until lesions disappears **OR** • Podophyllin resin 10%-25% solution a compound tincture of Benzoin, once a week up to 6 weeks **OR** • Cryotherapy with liquid nitrogen or Cryoprobe, 1-2 weeks until lesions disappears **OR** • Surgical removal
• Swollen ano-genital condylomas • Cervical condylomas	Genital Condylomas	*Human papilloma Virus (HPV)*	Clinical diagnosis	• Destruction of the condylomatous tissue by physical and clinical method (Cryotherapy, use of liquid nitrogen, silver nitrate crayon, curettage followed by the application of iodine dye). • Refer to a specialist

Table 24: Clinical presentation and treatment of parasitic STIs in adults

Clinical signs and symptoms	Diagnosis	Etiology	Diagnosis method/Lab	Treatment
Diffuse, malodorous, yellow-green vaginal discharge with vulvar irritation	Trichomoniasis	*Trichomonas vaginalis*	Direct wet-mount microscopy **OR** NAT (Test of choice)	• Metronidazole 500mg TID, 7days, orally **OR** • Tinidazole 500mg TID, 7 days, orally
Pruritus	Pediculosis Pubis	*Pubic lice*	Clinical diagnosis	• Personal hygiene
Cutaneous rash, itching	Scabies	*Sarcoptes scabiei*	Clinical diagnosis	• Permetrine 5% cream one application per day **OR** • Lindane 1% **OR** • Benzyl Benzoate

Table 25: Clinical presentation and treatment of yeast STIs in adults

Clinical signs and symptoms	Diagnosis	Etiology	Diagnosis method/Lab	Treatment
Pruritus, vaginal soreness, dyspareunia, external dysuria, and abnormal vaginal discharge	Vulvovaginal Candidiasis	Usually caused by C. albicans, but occasionally by other Candida species	Wet preparation or Gram stain of vaginal discharge culture	• Polygynax vaginal pill OD, 12 days **OR** • Fluconazole 200mg, OD, 5 days **OR** • Clotrimazole 2% cream 5g intravaginal, OD, 5 days **OR** • Miconazole 200 mg vaginal suppository, OD, 5 days

Chapter IV: STI management in special cases

4.1. Treatment of STIs in children and adolescents

Table 26: STIs in children and adolescents according to syndrome

Syndrome	Organisms/ Diagnoses	Treatment of adolescent	Treatment of infant/ child
Urethritis and cervicitis: - Cervicitis occur rarely in prepubertal girls (see Prepubertal vaginitis) - Conjunctivitis of the new born may be asymptomatic	***Neisseria gonorrhoea, Chlamydia trachomatis***, ***Mycoplasma genitalium***, possibly ***Ureaplasma urealyticum***, and sometimes ***Trichomonas vaginalis*** and Herpes simplex virus (HSV)	**Neisseria Gonorrhoeae or Chlamydia** **1st choice** • Ceftriaxone 1g IV or IM single dose, **AND** • Doxycycline 100mg, orally, BID, 7-10 days **2nd choice** • Cefixime 400mg BID orally, 7 days, **AND** • Azithromycin 500mg TID orally, 7 days **Note:** *In the absence of Azithromycin, prescribe Erythromycin 500mg, QID, 14 days* • Review patient in 7 days	***Children <45 kg:*** • Ceftriaxone, 250mg, IM, in a single dose **OR** • Cefixime, 8mg/kg (maximum 400 mg, orally, in a single dose) **AND** • Azithromycin, 1g, orally, in a single dose ***Children ≤45 kg and <8 years of age:*** • Erythromycin - Ethylsuccinate, 50mg/kg per day, orally, in 4 divided doses (maximum 2g/day) for 14 days ***Children ≥45 kg but <8 years of age:*** • Azithromycin, 1g, orally, in a single dose ***Children ≥45 kg and ≥8 years of age:*** • Azithromycin, 1g, orally, in a single dose **OR** • Doxycycline, 100mg, orally, BID, 7 days

Syndrome	Organisms/ Diagnoses	Treatment of adolescent	Treatment of infant/ child
Prepubertal vaginitis (STI related):	*Neisseria gonorrhoeae*	See adult treatment	***Children <45 kg:*** • Ceftriaxone, 250mg, in a single dose
	Chlamydia trachomatis	See adult treatment	***Children <45 kg and <8 years of age:*** • Erythromycin - Ethylsuccinate, 50mg/kg per day, orally, QID, (maximum 2g/day), 14 days ***Children ≥45 kg but <8 years of age:*** • Azithromycin, 1g, orally, in a single dose ***Children ≥45 kg and ≥8 years of age:*** • Azithromycin, 1g, orally, in a single dose **OR** • Doxycycline, 100mg, orally, BID, 7 days
	Trichomonas vaginalis	See adult treatment	***Children <45 kg:*** • Metronidazole, 15mg/kg per day, orally, TID, (maximum 2g/day), 7 days
	Bacterial vaginosis	See adult treatment	***Children <45 kg:*** • Metronidazole, 15mg/kg per day, orally, BID, (maximum 1g/day), 7 days
	HSV-primary infection	• Acyclovir, 400 mg, orally, TID, 7–10 days **OR** • Acyclovir, 200 mg, orally, 5 times/day, 7–10 days **OR** • Famciclovir (250 mg, orally, TID), 7–10 days **OR** • Valacyclovir (1 g, orally, BID), 7–10 days	***Children <45 kg:*** • Acyclovir, 80mg/kg per day, orally, in 3-4 divided doses (maximum 1.2 g/day), 7-10 days **OR** • Valacyclovir, 40mg/kg BID, orally, 7–10 days

Syndrome	Organisms/ Diagnoses	Treatment of adolescent	Treatment of infant/ child
Adolescent vulvovaginitis	*Trichomonas vaginalis*	• Metronidazole, 2g, orally, in a single dose **OR** • Tinidazole, 2g, orally, in a single dose	...
	Bacterial vaginosis	• Metronidazole, 500mg, orally, BID, 7 days **OR** • Metronidazole gel 0.75%, 1 full applicator (5 g), intravaginally, OD, 5 days **OR** • Clindamycin cream 2%, 1 full applicator (5g), intravaginally at bedtime, 7 days	...
	Candida species	See Table 4.4, Recommended Regimens for Vulvovaginal Candidiasis	...
	HSV—primary infection	• Acyclovir, 400mg, orally, TID, 7–10 days **OR** • Famcyclovir, 250mg, orally, TID, 7–10 days **OR** • Valcyclovir, 1g, orally BID, 7–10 days	...
Pelvic inflammatory disease (PID)	*Neisseria gonorrhoeae, Chlamydia trachomatis,* anaerobes, coliform bacteria, and ***Streptococcus*** species	See adult treatment	PID occurs rarely, if at all, in pre-pubertal girls
Syphilis	***Treponema pallidum***	See Syphilis	***Children <45 kg:*** Same as for congenital syphilis

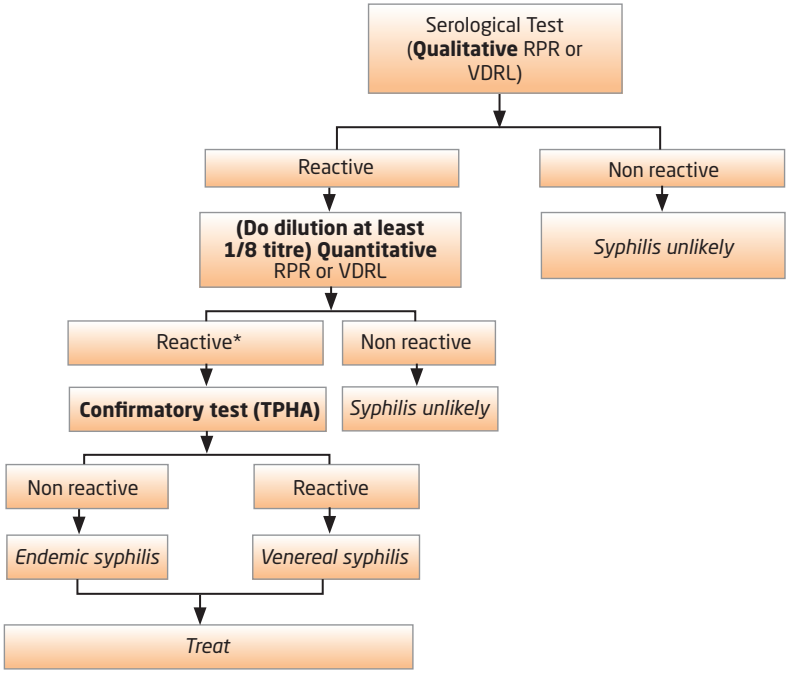
Syndrome	Organisms/ Diagnoses	Treatment of adolescent	Treatment of infant/ child
Sexually acquired epi- didymitis	*Chlamydia trachomatis*, *Neisseria gonorrhoeae*	• Ceftriaxone, 1g, IV/ IM, in a single dose **PLUS** • Doxycycline, 100 mg, orally, BID, 10 days	...
	Enteric organisms (for patients allergic to cepha- losporins and/or tetracycline)	• Levofloxacin, 500 mg, orally, OD, 10 days **OR** • Ofloxacin, 300 mg, orally, BID, 10 days	...
Gonococcal infections of the pharynx	*Neisseria gonorrhoeae*	• Ceftriaxone, 1g, IV/ IM, in a single dose **OR** • Cefixime oral 400mg single dose **AND** • Azithromycin 1g oral single dose	Ceftriaxone, 250 mg, IM, in a single dose
Anogenital warts	*Human papilloma- virus*	***Patient-applied:*** • Podofilox 0.5% solution or gel **OR** • Imiquimod 5% cream **OR** • Sinecatechins 15% ointment ***Provider- administered:*** • Cryotherapy **OR** • Podophyllin resin 10%–25%[c] **OR** • Trichloroacetic acid **OR** • Bichloroacetic acid **OR** Surgical removal	***Children <45 kg:*** Same as for adolescents Refer as needed

IM: Indicates Intramuscularly; **STI:** Sexually Transmitted Infection. For laboratory diagnosis refer to adult table

4.2. STIs management among pregnant women and neonates

4.2.1. Syphilis in pregnant women and exposed infants

In Rwanda, systematic screening for syphilis is conducted among pregnant women attending antenatal care services (ANC). This screening aims to detect disease and mitigate transmission from the syphilis-infected mother to the child, by counseling and treating them according to national guidelines. Although this program was implemented many years ago in Rwanda, the risk of syphilis transmission to the newborn was not considered a priority despite its magnitude, potential complications, and increased risk of HIV transmission, neonatal death, and stillbirth. In the current guidelines, measures to prevent syphilis and to treat pregnant women and children are emphasized.



***In the absence of TPHA test, patient is treated according to quantitative RPR/VDRL results**

Figure 17: Algorithm for Syphilis testing in pregnant women

Quantitative nontreponemal (lipoidal antigen) serologic tests (e.g., RPR or VDRL) are recommended for use in babies born to mothers with positive syphilis serologies during pregnancy. Nontreponemal (lipoidal antigen) serologic tests should be performed on serum and not cord blood. The same nontreponemal serologic test should be used in the infant that was used in the mother at delivery so titer levels can be compared. A four fold change in infant titers as compared to mother titers, (e.g., 1:32 and 1:8), is considered as an active infection in infant. Thus, the infant should be treated accordingly.

In infants with confirmed congenital syphilis or infants who are clinically normal, but whose mothers have had untreated syphilis, inadequately treated syphilis (including within 30 days of delivery) or syphilis treated with non-penicillin regimens, treat the infant with aqueous benzylpenicillin or procaine penicillin.

It is important to know that although erythromycin and azithromycin treat pregnant women, they do not completely cross the placental barrier and therefore the fetus is not treated and the fetus is considered having a congenital syphilis.

Diagnosis of congenital syphilis can be difficult, as maternal nontreponemal and treponemal IgG antibodies can be transferred to the fetus via the placenta, complicating interpretation of reactive serological tests for syphilis in newborns. As a result, treatment decisions often need to be made on the basis of:

- Identification of syphilis in the mother;
- Adequacy of maternal treatment;
- Presence of clinical, laboratory, or radiographic evidence of syphilis in the neonate (bone abnormalities);
- Presence of neonatal nontreponemal serologic titers (not specific can be maternal).

Table 27: Syphilis treatment for an infected pregnant woman and exposed infants

Age	Treatment	Comment
Syphilis in pregnant women	IM Benzathine penicillin G 2.4M IU, once weekly for 3 consecutive weeks **OR** When it is not possible to use Benzathine penicillin due to different reasons, use with caution, erythromycin 500mg orally QID, 30 days	**Note:** 1. The interval between consecutive doses of Benzathine penicillin should not exceed 14 days. 2. Avoid stock out of Benzathine penicillin
In infants with confirmed congenital syphilis or infants who are clinically normal, but whose mothers had untreated syphilis, inadequately treated syphilis (including treatment within 30 days of delivery) or syphilis that was treated with non-penicillin regimens	IM Procaine penicillin 50,000 U/kg/day, 10–15 days	**Note**: If an experienced venipuncturist is available, aqueous Benzyl penicillin may be preferred instead of intramuscular injections of Procaine penicillin.
In infants who are clinically normal and whose mothers had syphilis that was adequately treated with no signs of reinfection	Close monitoring of the infants.	**Note:** The risk of transmission of syphilis to the fetus depends on a number of factors, including maternal titres from nontreponemal tests (e.g. RPR), timing of maternal treatment and stage of maternal infection, and therefore this recommendation is conditional. If treatment is provided, Benzathine penicillin G 50 000 U/kg/day single dose intramuscularly is an option

4.3. STIs in neonates

Table 28: Treatment of STIs in Neonates

Sign/Symptom	Disease	Etiology	Lab Test	Treatment
• Inflammation of the conjunctiva • Mucopurulent discharge from the eye	Gonococcal-ophthalmia	*Neisseria gonorrhea*	• Gram Staining • Culture • NAT	• Ceftriaxone of 25-50mg/kg IM or IV in one single dose not exceeding 125mg
• Mostly asymptomatic • Inflammation of the conjunctiva and mucopurulent discharge from the eye	Neonatal gonococcal conjunctivitis	*Neisseria gonorrhea*	• Gram Staining • Culture • NAT	• Ceftriaxone 50 mg/Kg in an IM single dose (do not exceed the maximum dose of 125mg) **AND** • Local care with physiological serum
Inflammation of the conjunctiva and mucopurulent discharge from the eye.	Neonatal chlamydial conjunctivitis		• Culture • ELISA • Direct Immunofluorescence • NAT	• Erythromycin syrup, 50mg/kg per day orally, QID, 14 days
Cutaneous, bony, and vascular accidents	Congenital syphilis (early congenital syphilis (up to 2 years of age)	*Treponema pallidum*	• Screening: VDRL, RPR • Confirmation tests: Treponemal tests: TPHA, PTA. Dark field microscopy, Direct fluorescent antibody test and NAT	• Aqueous benzylpenicillin 100,000-150,000 IU/kg/day administered as 50,000IU /kg/dose IV BID, during the first 7 days of life and TID, thereafter for a total of 10 days
• Ocular, dental, vascular, additive, bone and neurological accidents • These manifestations may lead to death or functional loss (blindness).	Congenital syphilis of 2 or more years	*Treponema pallidum*	• Screening: VDRL, RPR • Confirmation tests: Treponemal tests: TPHA, FTA. Dark field microscopy, Direct fluorescent antibody test and NAT	• Aqueous benzylpenicillin, 200,000-300,000 IU/kg/day IV **OR** IM, administered as 50,000 IU/kg/dose every 4-6 hours for 10-14 days **Alternative:** • Erythromycin, 7.5-12.5 mg/kg orally, QID, 30 days (TBD By Paediatricians)
Maternal virologic testing or presumed by observation of maternal lesions	Neonatal Herpes	*Herpes virus of the simplex type 2 (HSV- 2)*	• Diagnosed clinically • Antibody detection of HSV-2 • Culture • NAAT	• Acyclovir 20 mg/kg IV, TID, 21 days for disseminated and CNS disease **OR** for 14 days for disease limited to the skin and mucous membranes.

Note:
- Ceftriaxone not to be used in case of Hyperbilirubinemia, use cefixime instead
- Consult a pediatrician for neonate chlamydia

4.3.1. Purulent conjunctivitis of the newborn

- Red eyes with purulent and sticky secretions;
- Contracted at birth through contact with infectious vaginal secretions of the mother;
- May lead to blindness, especially when due to Neisseria Gonorrhoea. In case of Chlamydia, the newborn may also develop pneumonia;
- Prophylaxis: meticulous cleaning of eyes immediately after birth and application of silver nitrate eye 1% lotion or tetracycline 1% ointment.

Table 29: Purulent conjunctivitis of the newborn

Pathogen	Clinical	Diagnosis	Treatment
Neisseria Gonorrhea	Conjunctivitis: red eyes with sticky, purulent discharge, pruritus	Gram-diplococci's "coffee bean" can be seen in secretions	IV/IM Ceftriaxone 50mg/kg single dose (max. 125mg)
Chlamydia Trachomatis	Conjunctivitis and pneumonia	Serology can be positive in a baby with severe chlamydial disease	IV/IM Erythromycin 50mg/kg/day, QID, 14 days

4.4. Cases of sexual abuse and aggression

Sexual abuse occurs when a person engages in sexual activities that she or he may not consent for. These sexual activities include any forms of sexual contact such as sexual relations (including oral, genital, ano-genital, genito-genital) and fondling.

4.4.1. Clinical signs of sexual abuse

Clinical signs of sexual abuse include: genital discharges, tear or the absence hymen, fissure or anal gaping, trauma of the perinea, recto-virginal fistula or vesico-vaginal fistula and pelvic pain. There can also be signs linked to physical trauma and behavioural disorders.

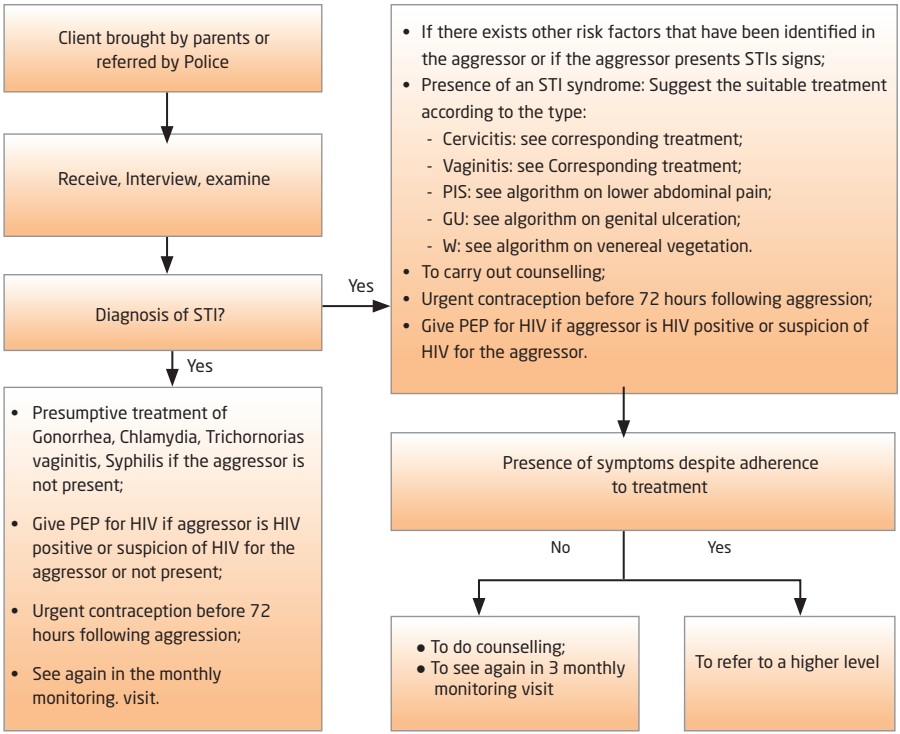


Figure 18: Algorithm of Care and treatment of STI in sex abuse in children.

Table 30: Clinical signs of sexual abuse

Signs	Females	Males
Genitals	• Absence or tear of the hymen; • Fissure or anal openness; • Trauma of the perineum; • Vesico-vaginal fistula; • Genital laceration • Recto-vaginal fistula; • Pelvic pain; • Presence of STI.	• Tear or laceration of penis; • Anal gaping; • Anal fissure; • Recto-anal fistula; • Presence of STI.
Other signs	• Cutaneous trauma; • Marked docility on examination; • Exaggerated fear by the patient of a parent or close relative.	• Cutaneous trauma; • Marked docility on examination; • Exaggerated fear by the patient of a parent or close relative.

4.4.2. Clinical examination

Initial clinical examination should include the following:

- Collect data and information on the circumstances in which the sexual abuse occurred;
- Determine, if possible, the time separating the aggression and the date of consultation;
- Carry out meticulous physical examination in search of the signs of STIs (genital discharges, ulcerations and genital vesicles, condyloma);
- Collect anal samples from both sexes; vaginal swab in females and urethral samples in males to search for Gonococcus, Chlamydia and Trichomonas vaginalis;

- To carry out serological tests for HIV, hepatitis B, C and syphilis;
- To carry out the pregnancy test for all girls and women in reproductive age;
- To search for clinical signs of STIs and carry out serological tests for HIV, hepatitis B, C and syphilis of the aggressor or the suspected perpetrator of the aggression if he/she has been identified;
- A follow-up examination should be done at 3 months to repeat the pregnancy test and serological tests for HIV, hepatitis B, C and syphilis (especially if the initial tests were negative).

4.4.3. Treatment

- If the pregnancy test is negative, prescribe within 72 hours (following the aggression or sexual abuse) urgent contraception;
- If HIV serology is positive in the aggressor or unknown status, offer HIV post exposure prophylaxis to the victim. HIV prophylaxis is effective if it is started within 6 hours that follow the aggression quite before 24 hours and do not exceed 72 hours;
- If HBV is positive in the aggressor or unknown status, offer HBV vaccine (if not vaccinated) and HBV Immunoglobulin;
- If a germ is isolated, it is necessary to treat the victim by taking into account its sensitivity to antibiotics (or treatment according to the STI syndrome identified);
- If no germ is isolated and if there exist other risk factors that have been identified in the aggressor or if the aggressor presents STI or has recent precedents of STIs, in this case there is a need to provide presumptive treatment. This treatment must take into account the syndrome of the suspected STI in the aggressor;
- In all cases, the victim should be monitored for psychological issues that may arise;
- In case the HIV serology is positive, monitoring and treatment of the victim must respect the recommendations for the medical care of HIV.

4.5. Management of STIs in sex workers

Sex workers are vulnerable groups and core groups for the transmission of HIV and other STIs. Given the high prevalence of HIV and other STIs in sex workers, active diagnosis of STIs is highly recommended.

In practice, during the first visit, every sex worker should be systematically treated for either PID and presumptive Gonococcus, Chlamydia and Trichomonas.

Prophylactic treatment should include:

- Ceftriaxone of 1g IV or IM or Cefixime 400mg in one single dose;
- Azithromycin 1g in one single dose;
- Metronidazole, 2g in a single dose in the evening during meals or Tinidazole, 2g in a single dose orally.

For subsequent visits, treatment will be given according to the present syndromes.

4.6. STI prevention, sexual reproductive health (SRH) and mental health among adolescent girls and young women (AGYW)

4.6.1. Enrollment criteria for the AGYW program

Who should be taken into account for the AGYW service package and enrollment requirements at the community and health facility levels (at least one requirement), including youth corners and safe spaces? All enrolled AGYW nationwide, living in both rural and urban areas, in and out of school, should benefit from integrated services and interventions, as these groups of AGYW are hard to reach and may require special attention or consideration when providing a comprehensive HIV/AIDS, STI, Viral hepatitis prevention, SRH, and mental health services.

4.6.1.1. Enrollment criteria for AGYW by age-band

Table 31: Enrollment criteria for AGYW by age-band

Age - band	Enrollment criteria in the AGYW program (at least one criterion).
10 -14 years	➢ Ever had sex. ➢ History of pregnancy ➢ Experience of sexual violence (lifetime) ➢ Experience of physical or emotional violence (within the last year) ➢ STI (diagnosed or treated) ➢ Use of alcohol and drug substances ➢ Out of school ➢ Orphanhood ➢ AGYW with disability
15 - 19 years	➢ Multiple sexual partners (in the last year) ➢ History of pregnancy ➢ STI (diagnosed or treated) ➢ No or irregular condom use. ➢ Transactional sex (including staying in a relationship for material or financial support) ➢ Experience of sexual violence (lifetime) ➢ Use of alcohol and drugs (in the last 12 months) ➢ Out of school ➢ Orphanhood
20 - 24 years	➢ Multiple sexual partners (in the last year) ➢ Sexually transmitted infections (STI) (diagnosed or treated) ➢ No or irregular condom use. ➢ Transactional sex (including staying in a relationship for material or financial support) ➢ Experience of sexual violence (lifetime) ➢ Use of Alcohol and drugs (in the last 12 months)

4.6.1.2. Age-appropriate service delivery for adolescent girls and young women (AGYW)

This is a comprehensive core of services specific to AGYW including STI, Viral Hepatitis, HIV/AIDS prevention, SRH, and mental health services. The list of services should be offered to AGYW enrolled in the program at community and healthcare facilities and their sexual partners. To highlight different service delivery models for AGYW-friendly services based on the category and health needs of each AGYW, it is organized by the level of health services.

Table 32: Age-appropriate service delivery for adolescent girls and young women (AGYW)

Age group	10 - 14 years	15 - 19 years	20 - 24 years
The initial intervention	Primary prevention of Sexual and gender violence, Teenage pregnancy, and HIV infection.	Social asset building	Social asset building
	HIV screening risk.	School/community-based HIV, SGBV teenager pregnancy prevention	School/community-based HIV, SGBV teenager pregnancy prevention
	Positive parenting/ caregiver programming	Comprehensive STI, Viral hepatitis, and HIV Prevention Education	Condom education and demonstration
	life skill education	Contraception IEC	STI, Viral hepatitis, HIV risk screening, testing and index, and PIT testing including social network.
	Social asset building	Financial capacity training (Literacy)	PMTCT, ANC, comprehensive STI, Viral hepatitis, HIV prevention Education
	Financial literacy		Contraception (IEC)
			Financial capacity training
			Entrepreneurship training

Subsequent intervention	Post-violence care	Post-violence care	Comprehensive STI, Viral hepatitis, HIV prevention provision
			Combination of socio-economic approaches (Vocational training internship
	Education subsidies	Combination of social -economic approaches	PMTCT, ANC, Prep provision
	HTS (linkage/referral)	Education subsidies	Contraceptive method
	STI, Viral Hepatitis screening	Entrepreneurship training	Post-violence care
Contextual level Intervention	Parenting/ caregiver programming Community mobilization and norms change Reducing the risk of sexual partners (link to STI, Viral hepatitis, HTS, HIV Care and treatment, VMMC services for ABYW and sexual male partners)		

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