Pacific Islands countries and territories Hepatitis B Treatment and Care guidelines

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Online location: https://path-png.org/clinical-guidelines/ (External reference version for Papua New Guinea Antibiotic Guidelines 2024

These guidelines are based on:

- Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection, WHO 29/3/24 https://www.who.int/publications/i/item/9789240090903
- Prevention of mother-to-child transmission of hepatitis B virus: Guidelines on antiviral prophylaxis in pregnancy, WHO 27/7/20 https://www.who.int/publications/i/item/978-92-4-000270-8
- Kiribati, Kingdom of Tonga, Vanuatu and Fiji Treatment and Care Guidelines (Hepatitis B Free Organisation)

Acknowledgments and authorship

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Summary of key recommendations:

1. Expand screening with the addition of decentralised testing strategies using HBsAg RDT.
2. Reflex HBV DNA testing if available to increase linkage to care.
3. Consider HDV testing.
4. Support linkage to care by expanding and decentralising hepatitis care services. Support strategies to ensure high rates of linkage to care and ongoing adherence to therapy/monitoring.
5. All of the following persons aged >12 years are eligible for antiviral therapy
    a. Cirrhosis based on APRI >1 or TE >12.5 kPa or clinical,
    b. Fibrosis based on APRI >0.5 or TE >7 kPa irrespective of the viral load or ALT,
    c. HBV DNA >2000 and ALT >ULN (on two occasions),
    d. ALT >ULN (two occasions) if HBV DNA not available,
    e. Coinfections (such as HIV, hepatitis D or hepatitis C),
    f. Family history of liver cancer or cirrhosis,
    g. Immune suppression (such as long-term steroid use, solid organ or stem cell transplants),
    h. Comorbidities (such as diabetes or metabolic dysfunction-associated steatotic liver disease),
    i. Extrahepatic manifestations (such as glomerulonephritis or vasculitis).
6. Treat with:
    a. Tenofovir disoproxil fumarate (TDF) or entecavir (ETV) remain preferred first-line regimens.
    b. Tenofovir alafenamide (TAF)is recommended for patients with established osteoporosis and/or impaired kidney function. TAF is also recommended in adolescents over the age of 12 years.
    c. Tenofovir + lamivudine or tenofovir + emtricitabine accessed through the existing antiretroviral procurement pathway where TDF/TAF is not available
7. Antiviral therapy is recommended for pregnant women for prevention of mother to child transmission starting at week 28 of gestation (HBV DNA > 200 000 IU/ml or HBeAg positive or HBsAg positive (if neither HBV DNA or HBeAg is available). Therapy can be continued after delivery until completion of family or long term if patient is a treatment candidate as above. Timely birth dose of newborn and testing after 9 months is recommended.
8. All cirrhotic patients should receive lifelong antiviral therapy.
   Stopping therapy can be considered in non-cirrhotic patients if they can be followed up for reactivation, become HBsAg negative, or HBeAg negative (if positive at baseline), followed by additional 12 months of treatment.

The first Pacific Islands and territories hepatitis B guidelines based on WHO hepatitis care guidelines (1) were prepared and shared in January 2022. Since then, a number of Pacific Island countries (PIC) have introduced hepatitis programs but face ongoing challenges. Kiribati, Tonga, Vanuatu, Fiji, Solomon Islands, Niue and PNG have established hepatitis programs and are working towards expansion. With the introduction of the WHO guidelines on the Prevention of Mother to Child transmission in 2020 (2), and subsequent triple elimination targets set by WHO, this has been highlighted as a priority. This document summarises the new WHO hepatitis B policy guidelines released in April 2024 (3). The purpose of this document is to provide health care providers, clinicians, program managers and health ministries with guidance on exploring pathways to support hepatitis B service delivery including technical elements. It is built on the previous guidelines including: Pacific Islands and Territories Hepatitis B Treatment and Care guidelines (2023), Pacific islands guideline for the Prevention of Mother to Child transmission of Hepatitis B (2020) (https://www.hepatitisbfree.org.au/document), and WHO guidelines.

Background

WHO estimates in 2022 that over 253 million people live with chronic hepatitis B infection leading to over 1.1 million deaths per year. Less than 13% of those infected have been diagnosed, with less than 3% on antiviral therapy.

Tenofovir and entecavir were recommended as first line antiviral therapy in 2015, both are safe and effective, reduce the risk of liver cancer and disease progression. In some, it can reverse fibrosis or even cirrhosis and is associated with increased long-term survival. Low cost licensed generic tenofovir is now available as tenofovir disoproxil fumarate (TDF) (as low as $2.50/bottle) and as tenofovir alafenamide ($5.80) for PIC.

More than 1.2 million new infections occur each year, most of these at birth or shortly after from mother to child transmission. These early infections lead to chronicity in over 90% of babies. Universal infant vaccination including timely birth dose (TBD) is recommended but coverage rates of TBD are variable with reports of <50% in some settings. Even with TBD, risk of transmission remains in babies born to mothers with high viral loads. The risk can be further reduced with the addition of TDF for high risk pregnant mothers for the purpose of prevention of mother to child transmission (PMTCT).

More than 129,000 people (9.4%) are infected with hepatitis B virus (HBV) in the PIC (https://cdafound.org/polaris-countries-dashboard/). After diabetes, chronic HBV infection, leading to liver cancer, cirrhosis, and death, is the second largest public health challenge in the region. Resource limitations mean that care of patients with advanced disease is often supportive only with palliation. In some cases, advanced liver disease can require a liver transplant which can only be provided in high-income neighbouring countries and paid for by the families or ministerial budgets. This results in a significant health and financial burden.

Low-cost interventions (diagnostics and treatment) have been further simplified with expanded treatment criteria as delineated in the WHO hepatitis B policy guidelines (April

2024). This new reality enables Pacific islands countries to introduce and expand current existing programs. A simplified, cascade approach taking local resource access into consideration removes geographic and economic barriers to treatment.

Key current recommendations:

1. Screening and assessing the hepatitis B positive patient
2. Service delivery models
3. Indications for antiviral therapy
4. Antiviral prophylaxis for the prevention of mother to child transmission (PMTCT)
5. Antiviral therapies of hepatitis B
6. When to stop and restart antiviral therapy

1. Screening and assessment of the hepatitis B positive patient:

Screening can be broadly considered as general population testing or focused testing for priority populations. General population screening is recommended for the PIC given the high prevalence of hepatitis B, with access to testing for all adults. Testing outside the hospital setting to expand access to testing should be considered in community-based settings/clinics including antenatal, TB, STI, HIV clinics and health posts.

General population screening should be supported by targeted priority screening of high-risk groups. This includes children and adults with clinical features of liver disease or raised liver function tests; persons at risk for infection; partners, family members and household contacts of positive patients; and health care workers. All blood donors should be screened at each donation. Antenatal screening as early as possible during pregnancy is recommended in conjunction with testing for HIV and syphilis.

Hepatitis B surface antigen (HBsAg) RDT remains the most widely utilised test in the Pacific, with a limited number of countries where lab-based immunoassays are readily available. WHO prequalified RDT are used but stock outs are frequent so that testing is often limited to high priority groups only. HBsAg RDT are cheap and easy to perform, require little training to perform with high sensitivity and specificity. Ensuring that positive results are delivered without stigma and discrimination needs to be supported through training (appendix-training module on counselling).

Following counselling, all hepatitis B positive patients should be linked to care. This step needs to be closely monitored to ensure high rates of linkage to care as many patients drop out after a positive diagnosis and do not attend for care until the disease is in the advanced stages. Supporting linkage to care can be explored through local channels (e.g., peer groups, community, nurse assistants, online forums).

Assessing the hepatitis B positive patient includes a careful history, physical examination, and laboratory tests. Medical officers, nurses, and medical assistants can be trained to undertake this task, supported remotely by hepatitis B focal points/experts including nurse trainers. Outreach to remote areas should be integrated into the routine service rotations as per

current ministerial programs (what is the terminology for this- explain further). Remoteness should not prohibit program roll out (see care cascade below).

Laboratory assessment includes FBC (platelets), Cr (for dose adjustment), ALT and AST (for treatment eligibility and staging), imaging with ultrasound or CT and transient elastography for staging. Reflex viral load testing (where available to promote linkage to care) is also recommended, either through a PCR platform or using the point of care GeneXpert system. Each nation should consider how best to implement this recommendation dependent on the financial constraints and available resources (e.g., consider viral load testing for patients where treatment indications are not clear – see suggested hepatitis B viral load testing algorithm).

Additional testing including screening for hepatitis C, D and HIV should also be considered in regions with high prevalence rates or resources permit (either universal or targeted for priority populations).

High risk HDV groups:

1. People at high risk of acquiring HDV (people who inject drugs, men who have sex with men, sex workers, people living with HCV or HIV and haemodialysis recipients);
2. Family members of people with HDV infection;
3. People with advanced liver disease: and those with persistently raised ALT already receiving HBV treatment.

Access to the full hepatitis B serology panel is not readily available in many of the PIC and addition of HBeAg, HBcAb and HBsAb should be considered a priority (many labs already have the hardware). These markers will support vaccination programs as well as expansion of antiviral Rx for those who are receiving immunosuppressive therapies (HBsAg neg and HBcAb positive). Regional technical support for this is readily available.

Lack of access to lab testing (e.g., HBV DNA) should not pose barriers to commencement of antiviral therapy. In remote settings where HBsAg RDT is the only test available, each PIC should consider a test and treat approach. This strategy would treat all patients based on HBsAg status alone with consideration for full assessment when/if available.

Hepatitis B positive patients should be linked to care and undergo a clinical assessment by a trained health care worker. Based on the clinical assessment and laboratory and imaging findings, patients can be considered for therapy or be monitored.

2. Service delivery models

Where resources are limited, options for alternative models of hepatitis B care should be explored.

A decentralised program with a referral national hospital staffed by experts (nurses and doctors) can support a wide network of regional hospitals, outreach clinics and health posts where screening, counselling and treatment can be offered. Where logistics allow, review by a clinical team can be accomplished with particular focus on those with advanced liver

disease. This process should be supported by community health workers to optimise adherence to follow up and therapy.

3. Indications for antiviral therapy

Lifelong antiviral therapy is recommended for all patients 12 years or older with cirrhosis based on clinical assessment, and/or an APRI >1, transient elastography (FibroScan®) of >12.5 kPa, or imaging features.

For non cirrhotic patients, treatment is indicated for the following:

1. Patients with significant fibrosis (≥F2) (defined as APRI >0.5 orTE >7.0 kPa), are also eligible for antiviral therapy. (irrespective of ALT and HBV DNA); or
2. HBV DNA>2000 IU/mL and ALT above the upper limit of normal (ULN 30 for men and 19 for women) over 2 occasions in a 6-12m period; or
3. Where access to viral load testing is not available, treat if ALT persistently raised; or
4. Treat all (regardless of HBV DNA or ALT) with:
    a. Coinfections (such as HIV, hepatitis D or hepatitis C);
    b. Family history of liver cancer or cirrhosis;
    c. Immune suppression (such as long-term steroid use, solid organ or stem cell transplants);
    d. Comorbidities (such as diabetes or metabolic dysfunction–associated steatotic liver disease); or
    e. Extrahepatic manifestations (such as glomerulonephritis or vasculitis).

With these expanded treatment criteria, over 50% of those with chronic hepatitis B infection are now eligible for antiviral therapy.

Counselling patients prior to therapy by trained health care workforce is key in ensuring high rates of adherence to the retention to long term care. Adherence to long term therapy remains low in the PIC for many diseases. Hence exploring, implementing and monitoring strategies to optimise adherence and continued linkage to care should be integrated into the programmatic set up and roll out. In particular, the role of peer support worker, community volunteers, champions, health assistants, nurse assistants, community liaison should be explored, consistent with local acceptance and values.

4. Antiviral prophylaxis for prevention of mother-to-child transmission (PMTCT)

In 2020, WHO guidelines recommended TDF prophylaxis recommended for HBsAg-positive pregnant women with HBV DNA levels ≥200 000 IU/mL or a positive HBeAg. Where access to these assays is not available or limited, treating all HBsAg positive pregnant mothers is recommended.

Treatment should be continued after delivery in mothers who meet treatment criteria or are planning additional pregnancies.

TDF is recommended from week 28 of pregnancy but consider starting earlier if there are concerns about loss of follow up until delivery or start antivirals later if presenting for the first time in late stages of pregnancy.

Safety data on TAF during pregnancy for mothers, infants and pregnancy is increasing. WHO guidelines do not include use of TAF for PMTCT, but each PIC should consider the role of TAF where other antivirals are not readily available.

Service delivery models should be explored in line with the health care systems (e.g., consider commencement of antiviral therapy at the antenatal clinic), but all positive women should be linked to long term care.

Universal vaccination for babies (including timely birth dose hepatitis B vaccine) and completion of EPI is recommended. Testing babies born to positive mothers is recommended after 9 months. Strategies to ensure high rates of antenatal testing (including HIV/syphilis as part of triple elimination), antiviral therapy for positive mothers, linkage to care, testing and follow up of babies should be explored. This should be prioritised and monitored as a KPI.

5. Antiviral therapies of hepatitis B

Tenofovir disoproxil fumarate (TDF) or entecavir (ETV) remain preferred first-line regimens.

Tenofovir alafenamide (TAF) is recommended for patients with established osteoporosis and/or impaired kidney function. TAF is also recommended in adolescents over the age of 12 years.

Resistance to TDF/TAF is rarely reported, and there are no indications to switch to alternative regime where this is suspected. Case by case consideration should be evaluated.

Entecavir is recommended for patients with established osteoporosis and/or impaired kidney function. Entecavir is recommended for children over the age of 2 years. However, rates of antiviral resistance to entecavir needs to considered where adherence rates are suboptimal. Generally, the higher cost of entecavir and limited access to licensed generic supplies may make it prohibitive for PIC. In those with evidence of treatment failure to ETV due to confirmed or suspected antiviral resistance, switching to TDF or TAF (if available) is recommended.

Where neither TDF/TAF or ETV is available, tenofovir-based dual HIV therapy or pre-exposure prophylaxis regimes (tenofovir + lamivudine or tenofovir + emtricitabine) accessed through the existing antiretroviral procurement pathway is recommended.

Monitoring for people receiving treatment

In the first year, more frequent monitoring (3-6 monthly) is suggested to assess adherence and treatment response.

Thereafter, 3-6 monthly review is recommended for people with advanced liver disease, renal impairment and HIV coinfection or to support adherence.

Otherwise, after the first year, annual review with ALT, AST, HBsAg and HBeAg (if available) and HBV DNA (if available) is adequate. Use of viral load testing should be considered in the context of local resources. APRI and TE at each annual review is also suggested.

Monitoring for people not yet receiving treatment

Lifelong monitoring for those yet to start therapy is recommended with annual review including clinical assessment, ALT and viral load where available. Restaging (APRI and TE) and consideration for therapy is required at each visit.

Monitoring the safety of nucleoside analogues

Patients receiving TDF should have baseline renal function followed by annual testing. Dose adjustments are required for reduced renal function.

Measurement of baseline renal function includes serum creatinine level and calculation of eGFR using the Cockcroft– Gault (CG) or MDRD formulas.

An online calculator is available at http://nephron.com/cgi-bin/CGSI.cgi.

Factors associated with a higher risk of renal dysfunction include: decompensated cirrhosis, CrCl <50 mL/min, >60 years, body mass index (BMI) <18.5 kg/m2 (or body weight <50kg), poorly controlled hypertension, proteinuria, uncontrolled diabetes, active glomerulonephritis, concomitant use of nephrotoxic drugs or a boosted protease inhibitor for HIV and solid organ transplantation.

Dosage adjustments for tenofovir disoproxil in renal impairment are as follows:

CrCl >50 ml/min	one tablet a day
CrCl 30-49	one tablet every 2 days
CrCl 10-29	one table every 3 days
CrCl <10	one table every 7 days

Tenofovir alafenamide (25mg) is a prodrug of tenofovir disoproxil and has been documented to have similar antiviral efficacy as tenofovir disoproxil. It is associated with smaller decreases in glomerular filtration rate and in bone mineral densitometry and is preferred if available. Dose adjustments are not required down to an eGFR of 15 ml/min.

In children, growth as well as renal function should be monitored.

For children, the Schwartz or similar formula can be used:
http://nephron.com/bedsidepedsnic.cgi.

CG formula: eGFR = (140 – age) Í (weight in kg) Í 0.85 (if female)/(72 Í Cr in micromol/l)

MDRD formula: eGFR = 175 Í serum Cr–1.154 Í age–0.203 Í 1.212 (if the person is Black) Í 0.742 (if the person is female)

Surveillance for hepatocellular carcinoma (HCC) among people with CHB

Routine surveillance for HCC with abdominal ultrasound and alphafetoprotein (where available) testing every six months is recommended for:

people with cirrhosis, regardless of age or other risk factors;

people with a family history of HCC;

people older than 40 years (lower age depending on the regional incidence of HCC)

and with HBV DNA level >20,000 IU/mL (if HBV DNA testing is available).

6. When to stop and restart antiviral therapy

Lifelong antiviral therapy in all people with cirrhosis.

In patients without cirrhosis:

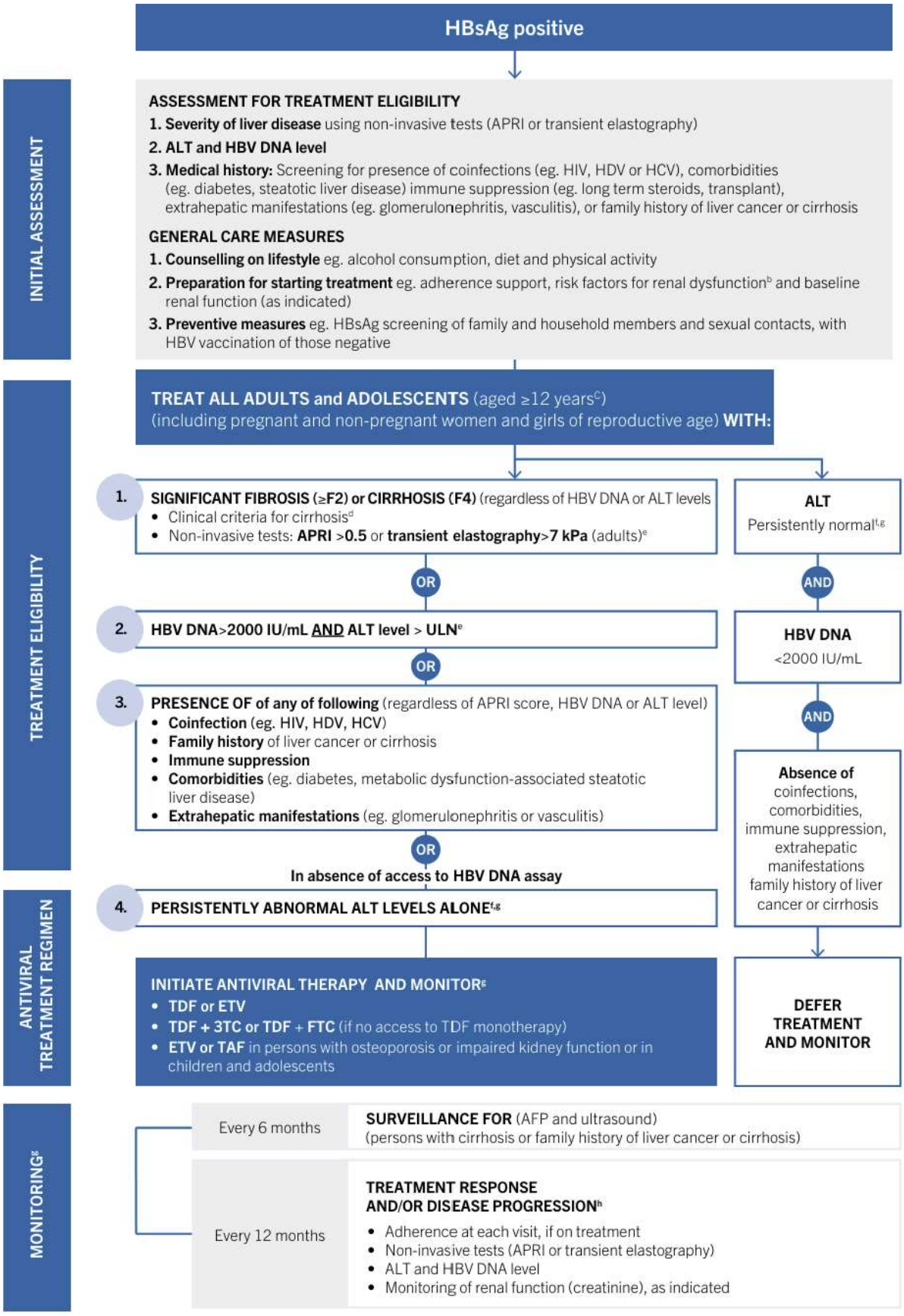
If **HBV DNA testing available,** discontinuation of antiviral therapy may be considered only if patients can be carefully followed for reactivation and potential need for recommencement of treatment. If HBeAg is available and positive, consider stopping antivirals after HBeAg loss followed by 12 months of additional antivirals. This should be associated with normal ALT and undetected HBV DNA.

If **HBV DNA testing is unavailable**, discontinuation of antiviral therapy may be considered only if patients can be carefully followed for reactivation and potential need for recommencement of treatment, consider stopping antivirals after HBsAg loss followed by 12 months of additional antiviral treatment.

After stopping therapy, monitor with 3 monthly ALT for the first 6 months, thereafter every 12 months. Consider role of liver cancer surveillance (even after stopping treatment).

Relapse is common after cessation of treatment, retreatment is recommended if there are signs of reactivation (HBsAg or HBeAg becomes positive), ALT increases or HBV DNA is detected again.

ALGORITHM FOR ASSESSMENT, TREATMENT AND MONITORING OF PEOPLE WITH CHRONIC HEPATITIS B INFECTION



ALGORITHM ON USE OF ANTIVIRAL PROPHYLAXIS FOR PREVENTION OF MOTHER-TO-CHILD TRANSMISSION IN PREGNANT WOMEN AND ADOLESCENT GIRLS WITH CHB AND ASSESSMENT OF TREATMENT ELIGIBILITY FOR THEIR OWN HEALTH