World Health Organization
Pakistan

Ministry of National Health
Services Regulations & Coordination
GOVERNMENT OF PAKISTAN

National Guidelines for the Treatment of Hepatitis B Virus Infection in Pakistan

(2022)

ACKNOWLEDGEMENTS

Many professionals from a range of backgrounds and specialties have contributed to the development of these guidelines. We are sincerely grateful for their time and support.

Guidelines Development Group

The Chair of the Guideline Development Groups was Dr. Huma Qureshi, National Focal Person on hepatitis for government of Pakistan.

A Technical Working Groups (TWGs) was formulated to update the guidelines. The following experts served to update on the Guidelines; Dr. Huma Qureshi, Dr. Saeed Hamid, Maj Gen SI (M) Prof. Dr. Aamer Ikram, Dr. Safdar Kamal Pasha, Dr. Hassan Mahmood, Dr. Waqaruddin Ahmed, Dr. Hassan Zahid, Ms. Sandra, Dr. Masood Siddique, Dr. Saad Niaz, Dr. Hassan Abbas Zaheer, Dr. Ghias un Nabi Tayyab, Dr. Amir Ghafoor Khan, Professor Dr. Muhammad Umar, Dr. Syeda Zahida, Dr. Ismail Mirwani, Dr. Kalimullah Khan, Dr. Zulfiqar Dharejo, Dr. Laila Rizvi, Mr. Anwar Hussain Alvi, Dr. Amir Khan and Dr. Irfan Ahmed.

Steering Committee and Overall coordination

The following members formed the Guidelines Steering Committee and performed the overall coordination:

Dr. Huma Qureshi, Dr. Safdar Kamal Pasha (National Professional Officer, WHO) and Dr. Hassan Mahmood (National Consultant, WHO)

Message by Honorable Director General (DG), Ministry of National Health Services, Regulations and Coordination (M/o NHSR&C)

Dear colleagues, I am very thankful to the Technical Advisory Group (TAG on hepatitis) for realizing the need to develop hepatitis B treatment guidelines for Pakistan with the technical support of WHO. There has been so much happening in the testing and the treatment cascade of hepatitis that globally hepatitis guidelines are now universally a live document which are being updated regularly. Following the same trend, we have revised the hepatitis B treatment guidelines to keep our hepatitis program managers, the General Physicians abreast of the new developments and assist them in diagnosing the patients and treating them using simple steps. For the treatment, these guidelines tell us that unlike hepatitis C where everybody with a detected virus needs treatment, in HBV majority need to be monitored yearly and not started on antiviral treatment while a small percentage who are put on oral antiviral treatment will need this treatment lifelong. The guidelines also cover children and adolescents and pregnant women.

I would like to thank the WHO country office especially Dr. Palitha Mahipalla and Dr. Safdar Kamal Pasha for providing the technical assistance, Dr Huma Qureshi and Dr Hassan Mahmood for compiling them.

Dr. Shabana Saleem
Director General (DG),
Ministry of National Health Services, Regulations and Coordination

Message by WHO Representative in Pakistan

WHO estimates that in 2019, 296 million persons were living with chronic hepatitis B virus (HBV) infection worldwide, with 1.5 million new infections each year. Hepatitis B resulted in an estimated 820 000 deaths, mostly from cirrhosis and hepatocellular carcinoma (primary liver cancer), in 2019. While, in the Eastern Mediterranean Region (EMR) six million people are estimated chronically infected with hepatitis B infection.

The Global Health Sector Strategy (GHSS) on Viral Hepatitis 2022 - 2030, is poised to eliminate viral hepatitis as a public health threat by 2030 (90% reduction in incidence and 65% reduction in mortality).

Hepatitis B virus commonly spreads from mother to child at birth or through exposure to infected blood and body fluids, such as saliva and menstrual, vaginal and seminal fluids. Transmission of the virus may also occur through the reuse of contaminated needles and syringes or sharp objects either in health care settings, in the community or among persons who inject drugs.

WHO recommends that all infants receive the hepatitis B vaccine as soon as possible after birth, preferably within 24 hours, followed by 2 or 3 doses of hepatitis B vaccine at least 4 weeks apart to complete the vaccination series. Protection lasts at least 20 years and is probably lifelong.

WHO introduced 'Guidelines for prevention, care and treatment of persons diagnosed with chronic Hepatitis B virus infection' with the aim to provide evidence-based strategies and interventions structured along the continuum of prevention, care and treatment. The guidelines are intended to use as the basis for developing national hepatitis policies, plans and treatment guidelines. These include country programme managers and health-care providers responsible for planning and implementing hepatitis care and treatment programmes, particularly in low- and middle-income countries.

WHO recommends use of safe and highly effective antiviral drugs to suppress HBV replication, prevent progression to cirrhosis, and reduce the risk of HCC and liver-related deaths. Most people who start hepatitis B treatment must continue it for life.

I appreciate efforts of national Technical Working group (TWG) for adaptation and introducing national guidelines for management of all persons having hepatitis B, irrespective of the disease status.

I wish you all, including the federal, provincial departments of health and private sector for an effective implementation of the guideline for expansion and differentiation of Hepatitis B treatment services in the country.

Dr Palitha Mahipala
WHO Representative and Health of Mission
Pakistan

Contents

TESTS FOR ASSESSMENT AND MONITORING OF HEPATITIS B INFECTION

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)	Intracellular enzymes which, as they are released after cell injury or death, reflect liver cell injury
HBV DNA	HBV DNA correlates with levels of circulating viral particles. HBV DNA is measured as IU/mL or copies/mL. 1 IU/mL ~ 5.3 copies/mL, and so values given as copies/mL can be converted to IU/mL by dividing by a factor of 5. (i.e. 10 000 copies/mL = 2000 IU/mL
AFP (alpha-fetoprotein)	A host cellular protein. High levels can occur in persons with hepatocellular carcinoma.
Persistently abnormal or normal ALT level	ALT levels fluctuate in persons with chronic hepatitis B and require longitudinal monitoring to determine the trend. Upper limits for normal ALT have been defined as below 40 U/L irrespective of gender. It is preferred that local laboratory normal ranges should be applied where available. Persistently abnormal or normal may be defined as three ALT determinations above or below the upper limit of normal, made at unspecified intervals during a 6–12-month period or predefined intervals during a 12-month period.

ASSESSMENT OF LIVER FIBROSIS BY NON-INVASIVE TESTS

APRI	Aspartate aminotransferase (AST)-to-platelet ratio index (APRI) is a simple index for estimating hepatic fibrosis based on a formula derived from AST and platelet concentrations. A formula for calculating the APRI is given: APRI = * (AST/ULN) x 100) / platelet count (10^9/L). An online calculator can be found at: http://www.hepatitisc.uw.edu/page/clinical-calculators/apri
FIB-4	A simple index for estimating hepatic fibrosis based on a calculation derived from AST, ALT and platelet concentrations, and age. Formula for calculating FIB-4: FIB-4 = (age (yr) x AST (IU/L)) / (platelet count (10^9/L x [ALT (IU/L)$^{1/2}$]). An online calculator can be found at: http://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4
FibroTest (FibroSure)	Commercial biomarker test that uses the results of six blood markers to estimate hepatic fibrosis
Transient elastography (FibroScan)	A technique to measure liver stiffness (as a surrogate for fibrosis) and is based on the propagation of a shear wave through the liver

EXECUTIVE SUMMARY

Hepatitis B virus (HBV) causes HBV infection in the liver which can be either acute or chronic, and the illness can range from asymptomatic to symptomatic liver disease. If the hepatitis B surface antigen (HBsAg) persists for more than six months in someone's blood, it is s defined as chronic Hepatitis HB (CHB. There are an estimated 240 million CHB cases living globally with majority living in low- and middle-income countries (LMICs). About 650 000 people die annually due to CHB. Overall, 20-30% cases of CHB progresses to advanced disease like cirrhosis and hepatocellular carcinoma (HCC). A large majority of people are not aware of their infection, and therefore present late with advanced disease. Hepatitis B is a vaccine preventable disease, therefore hepatitis B immunization through the national childhood immunization program along with the first dose given at birth (HB-BD), has been very effective in reducing the incidence and prevalence of hepatitis B in many endemic countries.

Antiviral hepatitis B medicines have been found to suppress the viral replication, prevent disease progression and thus reduce the risk of HCC and liver-related deaths. These medicines have to be taken for life because none of them clear the virus.

Pakistan has 2.4% prevalence of HBsAg with majority getting infected within a year of their life. Realizing the need to develop the national HBV treatment guidelines, many GI liver societies, associations, hepatitis control program within Pakistan developed HBV treatment guidelines. There has been a lot of progress in the understanding of the liver disease with easier and accessible tests and newer cost-effective treatments been approved by WHO and FDA, therefore, the National Technical Advisory Group (TAG) on hepatitis recommended to revise the guidelines. The current guidelines have basically been adapted from the WHO's guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection 2015. The current guidelines for the treatment of hepatitis B have been developed through consultations with the national and provincial subject experts, researchers, and the hepatitis program mangers while the technical support was provided by WHO. The primary users of these guidelines are the provincial hepatitis programme managers, district focal persons, ministries of health and the general practitioners.

The recommendations are made following the continuum of care for persons with CHB, from initial assessment of stage of disease and eligibility for treatment, to initiation of first-line antiviral therapy and monitoring for disease progression, toxicity and HCC, and switch to second-line drugs in persons with treatment failure. They are intended for use across age groups and adult populations.

These guidelines promote the use of simple, non-invasive diagnostic tests to assess the stage of liver disease and eligibility for treatment; prioritize treatment for those with advanced liver disease and at greatest risk of mortality; and recommend the preferred use of nucleos(t)ide analogues with a high barrier to drug resistance (tenofovir or entecavir) for first- and second-line treatment. The recommended treatment is lifelong along with monitoring for disease progression, toxicity of drugs and early detection of HCC. The use of interferon (conventional or pegylated) has been excluded in these guidelines because it has a high cost, low viral clearance and many adverse effects that require drug dose modifications and even withdrawal of treatment in severe adverse reactions.

There are different chapters that deal with the Screening and management for specific populations like those coinfected with HDV, HCV, HIV, children and adolescents and pregnant women.

Summary of key recommendations for persons with chronic hepatitis B infection

Screening of HBsAg

- In populations where access to rapid testing would facilitate linkage to care and treatment, use of RDTs is recommended to improve access.
- For the screening of HBsAg, use WHO prequalified rapid diagnostic tests (RDTs).
- WHO prequalified RDTs available in Pakistan include the following ;
  - SD Bioline HCV by Abbott
  - SD Biosensor Inc from Korea
  - InTec HCV from China

Use noninvasive tests for the assessment of liver disease stage at baseline and during follow up

- APRI (aspartate aminotransferase [AST]-to-platelet ratio index) is recommended as the preferred non-invasive test (NIT) to assess for the presence of cirrhosis. In Pakistan we use APRI cut off of 1.5. APRI score of more than1.5 in adults suggests cirrhosis and less than 1.5 no cirrhosis. Transient elastography using fibroscan may be used in settings where they are available and cost is not a major constraint.

Who should be treated

- All persons who have cirrhosis
- All persons who have an APRI score more than 1.5 and have persistently abnormal ALT levels for more than 6 months. (Optional testing: HBVDNA levels more than 20,000 IU/ml).[1]
- In HBV/HIV-coinfected individuals, ART should be initiated in all those with evidence of severe chronic liver disease, regardless of CD4 count; and in all those with a CD4 count 500 cells/mm3, regardless of stage of liver disease.

Who should not be treated but constantly monitored

- All persons who do not have cirrhosis
- All persons with APRI score of less than 1.5 and persistently normal ALT levels.
- All persons without cirrhosis whose HBV DNA levels fluctuate between 2000 and 20,000 IU/ml, or they have intermittently abnormal ALT levels;

1st line of antiviral treatment

- Tenofovir or entecavir is recommended in all adults, adolescents and children aged 12 years or older. (Tenofovir alafenamide fumarate is an oral prodrug of tenofovir with reduced dose less toxicities
- In children aged 2–11 years, Entecavir is recommended (Strong recommendation, moderate quality of evidence)

2nd line of antiviral treatment for treatment failure

[1] ALT values vary with the kits. For Pakistan >1.5 IU/L upper limit of normal is taken as elevated

Persons suspected to have antiviral resistance (past history of using or non-response to lamivudine, adefovir or telbivudine), should be switched to tenofovir.

Treatment is lifelong in

- All persons with cirrhosis
- All patients having an APRI score >1.5.
- All patients with persistently abnormal ALT for over 6 months with APRI score of >1.5.

Discontinuation of antiviral therapy in all above cases can lead to disease reactivation and severe acute-on-chronic liver injury.

Discontinue antiviral therapy

- All persons without cirrhosis
- All persons with APRI score less than 1.5
- All persons with persistently normal ALT levels
- All persons who can be followed easily for reactivation
- All persons who show HBeAg loss and seroconversion to anti-HBe (in persons initially HBeAg positive) and have completed at least one additional year of treatment
- All persons with persistently undetectable HBV DNA levels or negative HBsAg.

Retreatment

Restart tenofovir or entecavir if there is

- Signs of reactivation (HBsAg or HBeAg becomes positive)
- ALT levels increase and remain high for more than 6 months
- HBV DNA becomes detectable again.

Monitoring for disease progression and treatment response in persons prior to, during and post-treatment

- Undertake following tests at least annually:
  - CBC
  - ALT
  - AST
  - APRI score or Fibroscan to assess for cirrhosis
  - HBsAg
  - HBeAg (in HBeAg positive cases)
  - HBV DNA levels (where HBV DNA testing is available)

  For those who are on antiviral treatment, adherence should be monitored regularly and at each visit.

More frequent monitoring

- Frequent monitoring is indicated in persons who are not yet candidates for receiving antiviral therapy but they have
  - intermittently abnormal ALT levels
  - APRI is increasing
  - HBV DNA levels fluctuate between 2000 IU/mL and 20 000 IU/mL (where HBV DNA is available)
  - HIV-coinfected persons.

- Frequent monitoring is indicated in persons on treatment or following treatment discontinuation like:
  - Persons with cirrhosis (compensated or decompensated)
  - During the first year of treatment to assess treatment response and adherence
  - In HIV-coinfected persons
  - In persons after discontinuation of treatment.

Monitoring for tenofovir and entecavir toxicity

- Check baseline renal functions (Creatinine, creatine clearance and eGFR) in all persons prior to initiation of antiviral therapy.
- Monitor renal functions annually.

Monitoring for hepatocellular carcinoma

- Monitor for HCC using abdominal ultrasound, alpha-fetoprotein testing every six to 12 months in:
  - All cases with cirrhosis (compensated or decompensated)
  - Persons with a family history of HCC
  - Persons over 40 years without cirrhosis, APRI score >1.5, HBV DNA level >2000 IU/mL (where HBV DNA testing is available).

PREVENTION

Infant and neonatal hepatitis B vaccination

- All infants should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours, followed by two or three additional doses.[2]

Prevention of mother-to-child HBV transmission using antiviral therapy

- In HBV-mono-infected pregnant women[3], the indications for treatment are the same as for other adults, and tenofovir is recommended. Pregnant HBsAg positive women having HBVDNA of 20,000 IU or HBeAg positive should receive tenofovir in the last trimester of pregnancy and continued till delivery. No recommendation is made on the routine use of antiviral therapy to prevent mother-to-child HBV transmission.
- In HIV-infected pregnant and breastfeeding women[3] (including pregnant women in the first trimester of pregnancy and women of childbearing age), a once-daily fixed-dose combination of tenofovir + lamivudine (or emtricitabine)+ efavirenz is recommended as first-line ART. This recommendation applies both to lifelong treatment and to ART initiated for PMTCT and then stopped.

[2] WHO. Hepatitis B vaccines. Wkly Epidemiol Rec. 2009;84:405–20.

[3] Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013. These guidelines will be updated in 2015.

1. INTRODUCTION

1.1 Related materials and guidelines

The current guidelines though have been adapted from the 2015 WHO guidelines (1.) These guidelines provide a framework for the development or strengthening of hepatitis B treatment programmes in LMICs (2) but they also capture the materials from the WHO guidance on the prevention of perinatal and early childhood HBV infection through infant hepatitis B vaccination (3); treatment of HBV/HIV-coinfected persons in the consolidated antiretroviral (ARV) guidelines (4); prevention measures, including catch-up vaccinations in key affected populations (5), including PWID, men who have sex with men and sex workers (6–8), and prevention of HBV infection in health-care settings (9–11).

Prior to the development of these hepatitis B treatment guidelines, other guidelines developed by different societies, associations, hepatitis programs within Pakistan were also accessed. These included the Pakistan Society of gastroenterology's 2003 consensus statement on management of Hepatitis B(12), the Prime minister's program of hepatitis- 2005(13), Pakistan Society for the Study of Liver (PSSLD) management guidelines on hepatitis B- 2010(14), the Pakistan hepatitis B and C testing 2017 (15) and the hepatitis B testing and treatment guidelines developed by the Punjab hepatitis Program (16). Other international guidelines like the American Association for the Study of the Liver (17), Asian Pacific Association for the Study of the Liver (18) and the European Association for the Study of the Liver (19) have also been accessed and used in these guidelines.

The current guidelines have been developed through consultations with the national and provincial subject experts, researchers, and the hepatitis program mangers while the technical support was provided by WHO.

1.2 Target audience

These guidelines have been primarily made for use by the hepatitis program managers of the 4 provinces and the 2 regions, the district focal persons for hepatitis, the policy-makers in the ministry of health to assist in developing national hepatitis B prevention and treatment plans and policy, and country-specific treatment needs. The guidelines are also intended for use by the general physicians and other health professionals who manage persons with CHB.

1.3 Guiding principles

These guidelines address most bioethical issues that these HBsAg positive people face while undergoing testing or treatment.

2. METHODOLOGY

2.1 Guideline development process

The National Technical advisory group (TAG) on hepatitis realized the need to update the hepatitis B treatment guidelines. TAG requested the ministry of National Health Services regulations and Coordination (NHSRC) for supporting the process. Ministry agreed to the desire and suggested to use the TAG members as the guideline's development group. The country office of WHO agreed to provide technical assistance. Zero draft was developed in late 2021 and was shared with the TAG members. Comments were received from many members and these were incorporated and sent again as the 1st draft. Further comments were received from the members and again these were incorporated. 2nd draft was shared in a national consultation on 14 July 2022. The overall desire of the participants was to make them very simple and user friendly and use cirrhosis, APRI > 1.5 and persistently high ALT levels for over 6 -12 months as the prime indicators for starting antiviral therapy (1). Use of quantitative HBVDNA levels and fibroscan should be left for the specialists who shall cater for the patients having advanced disease. Defining the cut off of high ALT levels was also desired by the program managers to assist them in decision making. These have been catered in these guidelines.

3. BACKGROUND

3.1 Epidemiology and burden

Hepatitis B virus is an enveloped DNA virus that causes hepatitis B infection leading to acute or chronic liver disease. Acute hepatitis B is usually a self-limiting disease with death occurring in 0.5–1% cases (1). Chronic hepatitis B (CHB) infection is the persistence of hepatitis B surface antigen [HBsAg] in the blood for over six months. Age at infection is important in determining the risk of developing chronic liver disease. Chronicity is common after exposure to the HBsAg virus at birth or within 5 years of age (90% of neonates born to HBeAg positive mothers) and in young children under the age of 5 years (20–60%). Chronicity is rare (<5%) when infection occurs in adulthood (2,3). Worldwide, the majority of persons suffering from CHB were infected at birth or in early childhood.

Longitudinal studies of untreated persons with CHB show an 8–20% cumulative risk of developing cirrhosis over five years (2–6). In those with cirrhosis, there is an approximately 20% annual risk of hepatic decompensation (7) and 1-5% for developing HCC (7). Untreated patients with decompensated cirrhosis have a poor prognosis, with 15–40% survival at five years (5,7,8). Several host and viral factors, especially coinfections with HIV, HCV and hepatitis D virus (HDV), together with other cofactors such as alcohol use, may increase the rate of disease progression and risk of developing HCC (2,3,5,6) .

Worldwide, 2 billion people have evidence of past or present infection with HBV, and 240 million are chronic carriers of HBsAg (9). Age-specific HBsAg seroprevalence varies markedly by geographical region, with the highest prevalence (>5%) in sub-Saharan Africa and East Asia. Infection with HBV may present as either HBeAg positive or -negative disease. The prevalence of HBeAg- negative disease is increasing over the past few decades due to the ageing of the HBV-infected population (10).

Worldwide, around 650 000 people die each year from the complications of CHB (11). Overall, HBV accounts for around 45% of cases of HCC and 30% of cirrhosis, with much higher proportions in LMICs (11,12). In Pakistan, there are 500,000 living with cirrhosis and 25,000 HCC. Yearly 32 HBV cases die due to cirrhosis or its complications or HCC.

Many countries administer hepatitis B vaccine starting at birth or in early childhood (13, 15). This strategy has been effective in reducing the incidence and prevalence of hepatitis B in most endemic regions over the past few decades (9,12). In Pakistan Hepatitis B vaccine is given as a pentavalent vaccine by the EPI to all children at 6,10 and 14 weeks of birth. In 2021, hepatitis B birth dose has been procured by the provincial hepatitis programs and handed over to the birthing units for timely vaccination of all children irrespective of the mother's HBV status. Procurement of the birth dose by the federal EPI, through GAVI will not only be cost effective for the country but will also make Pakistan visible in the eastern Mediterranean countries for the long-awaited introduction of the birth dose of hepatitis B vaccine.

3.2. Virology

HBV is a hepatotropic virus that injures the liver through immune-mediation leading to killing of infected liver cells. It is a recognized oncogenic virus that leads to high risk of developing HCC. The virus circulates in serum as a 42-nm, double-shelled particle, with an outer envelope component of HBsAg and an inner nucleocapsid component of hepatitis B core antigen (HBcAg). HBV DNA can be detected in serum and is used to monitor viral replication.

Worldwide, at least nine genotypes of HBV (A - I) have been identified (14-16). Higher rates of HCC have been found in persons infected with genotypes C and F. Antiviral therapy is effective, and the HBV vaccine is protective against all HBV genotypes. A number of naturally occurring mutations in the pre-core region (pre-core mutants), which prevent HBeAg synthesis, have been identified in HBeAg-negative persons with CHB (17). In Pakistan mutations were found in 14% HBsAg sera. (18)

3.3. Transmission

The transmission of HBV is mostly through a breech in the skin or the mucosa with exposure to infected blood and various body fluids, including saliva, menstrual, vaginal, and seminal fluids (19). Sexual transmission of hepatitis B may occur in unvaccinated men who have sex with men and heterosexual persons with multiple sex partners or through contact with sex workers. Infection in adulthood leads to chronic hepatitis in less than 5% of cases. Transmission of the virus may also result from accidental inoculation of minute amounts of blood or fluid during medical, surgical and dental procedures, or from razors and similar objects contaminated with infected blood; use of inadequately sterilized syringes and needles; intravenous and percutaneous drug abuse; tattooing; body piercing; and acupuncture. In Pakistan all these risk factors are common. (20) .

Perinatal transmission: Perinatal transmission is the major route of HBV transmission in many parts of the world, and an important factor in maintaining the reservoir of the infection particularly in China and South- East Asia. In the absence of prophylaxis, a large proportion of viremic mothers, especially those who are HBeAg positive, transmit the infection to their infants at the time of, or shortly after birth (21). The risk of developing chronic infection is 90% following perinatal infection (up to 6 months of age) but decreases to 20–60% between the ages of 6 months and 5 years (21,22).

Horizontal transmission, including household, intrafamilial and especially child- to-child, is also important. At least 50% of infections in children cannot be accounted for by mother-to-infant transmission (23).

3.4 Natural history of chronic hepatitis B

The CHB progresses through several recognizable phases as shown in (Table 3.1).

TABLE 3.1 Phases of chronic hepatitis B

Phase	HBeAg serological status	Pattern	Indications for treatment
1. "Immune tolerant"	HBeAg positive	• Stage seen in many HBeAg-positive children and young adults, particularly among those infected at birth • High levels of HBV replication (HBV DNA levels >200 000 IU/mL)) • Persistently normal ALT • Minimal histological disease	Treatment not generally indicated, but monitoring required
2. "Immune active" (HBeAg-positive[a] chronic hepatitis)	HBeAg positive; may develop anti-HBe	• Abnormal or intermittently abnormal ALT • High or fluctuating levels of HBV replication (HBV DNA levels >2000 IU/mL) • Histological necroinflammatory activity present • HBeAg to anti-HBe seroconversion possible, with normalization of ALT leading to "immune- control" phase	Treatment may be indicated
3. Inactive chronic hepatitis "Immune control" (previously called inactive carrier)	HBeAg negative, anti-HBe positive	• Persistently normal ALT • Low or undetectable HBV DNA (HBV DNA levels <2000 IU/mL) • Risk of cirrhosis and HCC reduced • May develop HBeAg-negative disease	Treatment not generally indicated, but monitoring required for reactivation and HCC

4. "Immune escape" (HBeAg-negative chronic hepatitis)	HBeAg negative, with or without being anti-HBe positive	• HBeAg negative and anti-HBe positive • Abnormal ALT (persistent or intermittently abnormal) • Moderate to high levels of HBV replication (HBV DNA levels >20 000 IU/mL) • Older persons especially at risk for progressive disease (fibrosis/cirrhosis)	Treatment may be indicated
5."Reactivation" or "acute-on- chronic hepatitis"	HBeAg positive or negative	• Can occur spontaneously or be precipitated by immunosuppression from chemo– or immunosuppressive therapy, HIV infection or transplantation, development of antiviral resistance, or withdrawal of antiviral therapy • Abnormal ALT • Moderate to high levels of HBV replication • Seroreversion to HBeAg positivity can occur if HBeAg negative • High risk of decompensation in presence of cirrhosis	Treatment indicated

ALT alanine aminotransferase, anti-HBe antibody to hepatitis e antigen, HBeAg hepatitis B e antigen, HCC hepatocellular carcinoma

[a] Not all persons after HBeAg seroconversion enter the inactive phase. Up to 20% may progress directly from HBeAg immune active to anti-HBe immune escape phase

Phases of chronic hepatitis B (3–7)

1. The Chronic HBV Infection previously called as immune-tolerant phase occurs most commonly in HBsAg-positive children and young adults infected in the perinatal or early childhood period. Infection persists into young adulthood and may last 10–30 years after perinatal infection. Typically, serum HBeAg is detectable, HBV DNA levels are high (usually more than 200,000 IU/mL), and alanine aminotransferase (ALT) levels are normal or only minimally raised. There is minimal liver inflammation, no or slow progression to fibrosis, and low spontaneous HBeAg loss.

2. This is usually followed by an HBeAg-positive chronic active Hepatitis previously called as immune-active phase of active inflammatory disease. Serum ALT may be abnormal or fluctuate and is accompanied by variable decreases in HBV DNA levels. Symptoms of hepatitis may be present and there is more severe, histologically evident hepatitis and fibrosis. This phase may last from several weeks to years, and may result in successful seroconversion from an HBeAg-positive to an anti-HBe state. Seroconversion rates are higher in those with raised serum aminotransferases and those infected with genotypes D, A, F and (in Asia) B.

3. The non-replicative or inactive immune-control phase (previously called the inactive carrier phase) follows successful seroconversion from an HBeAg- positive to anti-HBe state, which occurs in 10–15% persons per year. Once HBeAg is cleared, the disease slows down, with minimal progression of fibrosis, and serum ALT levels revert to normal with low or undetectable levels of HBV DNA (less than 2000 IU/ mL). HBeAg seroconversion at a young age, prior to the onset of significant liver disease, confers a good prognosis, with a substantially reduced risk of cirrhosis and liver cancer. However, active viral replication can reappear in a proportion of persons.

4. In addition to HBeAg-positive chronic hepatitis, HBeAg-negative ("immune escape-mutant") active chronic hepatitis occurs in approximately 5–15% of HBeAg-negative, anti-HBe-positive persons in the inactive carrier state (8,25,26). This represents a later phase of disease, generally in older persons, and has a variable course, with abnormal or fluctuating levels of serum ALT and HBV DNA, necroinflammatory changes, and more rapid progression to cirrhosis (annual rate of 8–20%).

5. HBV reactivation may occur spontaneously or may be triggered by cancer chemotherapy and other immunosuppressive therapy, and may lead to fatal acute-on-chronic hepatitis, and pre-emptive nucleos(t)ide analogue (NA) therapy is therefore used. Occult HBV infection (defined as persistence of HBV DNA in the liver in persons in whom HBsAg is not detectable in the blood) may also be reactivated through prolonged chemo- or immunosuppressive therapy. Subjects with occult infection may also represent an important source of new infections in blood transfusion services in HBV-endemic LMICs where HBsAg is used as the sole marker of infection in donor populations. Persons who have cleared HBsAg and who are negative for HBV DNA but anti-HBc positive may reactivate if given potent immunosuppressive drugs.

3.5 Diagnosis and staging

Regular assessment of HBsAg-positive persons is needed to guide management and assess the need for treatment (24,25). This includes testing of HBeAg; measuring AST and ALT levels; quantification of HBV DNA levels; and stage of liver fibrosis by non-invasive tests (NITs) such as aspartate aminotransferase (AST)-to-platelet ratio index (APRI), transient elastography (FibroScan) or FibroTest.

HBV serological markers

Previous HBV infection is characterized by the presence of antibodies (anti-HBs and anti-HBc). Immunity to HBV infection after vaccination is characterized by the presence of only anti-HBs. CHB is defined as the persistence of HBsAg for more than 6 months. Recently, quantitative HBsAg level determination has been proposed to differentiate inactive HBsAg carriers from persons with active disease (26).

HBeAg: In persons with CHB, a positive HBeAg result usually indicates the presence of active HBV replication and high infectivity. Spontaneous improvement may occur following HBeAg-positive seroconversion (anti-HBe), with a decline in HBV replication, and normalization of ALT levels. This confers a good prognosis and does not require treatment. HBeAg can also be used to monitor treatment response, as HBeAg (anti-HBe) seroconversion in HBeAg-positive persons with a sustained undetectable HBV DNA viral load may be considered a potential stopping point of treatment. However, this is infrequent even with potent NA therapy.

Virological evaluation of HBV infection

Serum HBV DNA quantification using nucleic acid testing (NAT) can help to determine the disease progression (24,25,27) and is used to differentiate active HBeAg-negative disease from inactive chronic infection, and for decisions to treat. There is a lack of consensus regarding the level below which HBV DNA concentrations are indicative of "inactive" disease, or the threshold above which treatment should be initiated (25). HBV DNA concentrations are also used for optimal monitoring of response to antiviral therapy, and a rise may indicate the emergence of resistant variants. WHO standards are now available for expression of HBV DNA concentrations (28,29). Serum HBV DNA levels should be expressed in IU/mL to ensure comparability; values given as copies/mL can be converted to IU/mL by dividing by a factor of 5 to approximate the conversion used in the most commonly used assays (i.e. 10 000 copies/mL = 2000 IU/mL; 100 000 copies/mL = 20 000 IU/mL; 1 million copies/mL = 200 000 IU/mL). The same assay should be used in the same patient to evaluate the efficacy of antiviral therapy. Access to HBV DNA testing remains very poor in resource-limited settings.

Assessment of the severity of liver disease

This includes clinical evaluation for cirrhosis and decompensation. Blood tests include Liver function tests (LFTs), CBC including platelet count and prothrombin time. Other investigations include abdominal ultrasound and alpha-fetoprotein (AFP) for periodic surveillance for HCC.

Liver enzymes: Aminotransferase levels may fluctuate with time, and single measurements of ALT and AST do not indicate disease stage. Usually, the ALT concentrations are higher than those of AST, but with disease progression to cirrhosis, the AST/ALT ratio may be reversed. LFTs, CBC with platelet count, serum albumin, and prothrombin time are used to assess disease severity (24,25). A decline in serum albumin, rise in bilirubin and prolongation of the prothrombin time are signs of decompensated cirrhosis.

Liver biopsy: Liver Biopsy is not recommended due to its high costs, the risks of bleeding and other complications and discomfort to the patient.

Non-invasive tests (NITs): Non-invasive methods for assessing the stage of liver disease have been validated in adults with CHB. Blood and serum markers for fibrosis, including APRI and FIB-4, as well as commercial markers such as FibroTest or transient elastography (FibroScan) can be used to rule out advanced fibrosis (30-32).

3.6 Screening

All high-risk groups should be screened for HBsAg, and those who are not vaccinated should be offered hepatitis B vaccination. These include: household and sexual contacts of persons with CHB, HIV-infected persons, persons who inject drugs (PWID), men who have sex with men, sex workers, as well as other groups such as indigenous peoples, persons who are incarcerated, and persons of transgender. Blood and organ donors should also be screened for HBsAg and other bloodborne pathogens in accordance with WHO recommendations (33)

3.7 Prevention through vaccination

The primary hepatitis B immunization consists of three doses of vaccine. Vaccination of infants and, in particular, delivery of hepatitis B vaccine within 24 hours of birth is 90–95% effective in preventing infection with HBV as well as decreasing HBV transmission if followed by at least two other doses. WHO recommends universal hepatitis B vaccination for all infants, and that the first dose should be given as soon as possible after birth (13). This strategy has resulted in a dramatic decrease in the prevalence of CHB among young children in regions where universal infant vaccination programmes have been implemented. In Pakistan hepatitis B birth dose (HB-BD) is not included in the national expanded program of immunization (EPI). Hepatitis B vaccine is given as a pentavalent vaccine at 6,10,14 weeks. The coverage of 3rd dose of pentavalent vaccine is 77%(34).

Target groups for catch-up vaccination as well as other preventive strategies include young adolescents; household and sexual contacts of persons who are HBsAg-positive; and persons at risk of acquiring HBV infection, such as PWID, men who have sex with men, and persons with multiple sex partners.

3.8 Antiviral therapy

All persons having CHB should be offered antiviral therapy if they are at high risk of disease progression. Currently entecavir and tenofovir are approved for the treatment of CHB and have been shown to delay the progression of cirrhosis, reduce the incidence of HCC and improve long-term survival (Table 3.2). Both these antivirals are effective inhibitors of HBV replication, but they seldom result in cure, and clearance of HBsAg is rare. Therefore, at present, long-term (potentially lifelong) therapy is required in majority of the cases.

TABLE 3.2 Antiviral agents active against hepatitis B virus infection (in order of potency and barrier to developing resistance)

Antiviral agent	Potency against HBV	Resistance barrier	Activity against HIV	Cost
Interferons	Moderate	Not applicable	Moderate	High

Tenofovir/ TAF	High	High	High	Low (high in Hong Kong and other Asian countries)
Entecavir	High	High	Weak	High

The treatment is targeted at persons having CHB who have moderate or severe liver inflammation, and/or fibrosis and high viral replication and who are at high risk of disease progression to cirrhosis and HCC. The benefits of treatment for those with mild inflammation or fibrosis are less certain. If HBV replication can be suppressed, the accompanying reduction in chronic liver inflammation reduces the risk of cirrhosis and HCC, but generally lifelong treatment is required. Extrahepatic manifestations of hepatitis B such as glomerulonephritis or polyarteritis nodosa may also respond to treatment.

Tenofovir alafenamide fumarate (TAF) is an oral prodrug of tenofovir that enables enhanced delivery of the parent nucleotide and its active diphosphate metabolite into lymphoid cells and hepatocytes, so that the dose of tenofovir can be reduced and toxicities minimized (35,36).

3.9 Special populations

Coinfection with HIV, HDV, HCV and TB : Management considerations for specific populations: Coinfections)

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

HBV/HIV coinfection

HIV coinfection has a profound impact on almost every aspect of the natural history of HBV infection. This includes higher rates of chronicity after acute HBV infection, higher level of HBV replication and rates of reactivation, less spontaneous clearance, higher rates of occult HBV (i.e. detectable HBV DNA positivity in the absence of HBsAg seropositivity), more rapid progression to cirrhosis and HCC, higher liver-related mortality, and decreased treatment response compared with persons without HIV coinfection (37-41). In Western cohorts, liver disease has emerged as a leading cause of death in HIV-infected persons coinfected with either hepatitis B or C, as mortality due to other HIV-related conditions has declined following the introduction of antiretroviral therapy (ART) (42-45). While earlier studies found no consistent evidence for a significant effect of HBV on HIV disease progression (46,47), recent longitudinal cohort studies have found that coinfection with HBV also can lead to increased progression to AIDS-related outcomes and all-cause mortality (48,49).

HBV/HDV coinfection

Hepatitis D virus (HDV) is a small defective RNA virus that requires HBV for its transmission (50,51). The routes of HDV transmission are the same as for HBV but vertical transmission is rare. It is estimated that globally, 5% of HBsAg- positive carriers, or approximately 15 million people, are coinfected with HDV (50,51). High-prevalence areas include the Mediterranean, Middle East (the Gulf States, Saudi Arabia and Turkey), Pakistan (52-54), Central and northern Asia, Japan, Taiwan, Greenland and parts of Africa (mainly horn of Africa and West Africa), the Amazon Basin and certain areas of the Pacific. Vaccination against HBV prevents acute HDV coinfection, and expansion of childhood hepatitis B immunization programmes has resulted in a decline in hepatitis D incidence worldwide.

Severe or fulminant hepatitis is more frequently observed in HBV/HDV coinfection compared to HBV monoinfection (51, 55-57). Two major types of HDV infection are seen. In acute coinfection, persons are infected simultaneously with both HBV and HDV, leading to a mild-to-severe or even fulminant

hepatitis. Recovery is usually complete and chronic infection is rare (around 2%)(56). In superinfection, there may be HDV superinfection of a person who already has CHB, leading to a more severe disease course and accelerated progression to cirrhosis in all ages (57,58), including children (59,60), with occurrence of complications almost a decade earlier (61).

HBV/HCV coinfection

Coinfection with HCV is commonly found in HBV-endemic countries in Asia, sub-Saharan Africa and South America. In some populations, especially PWID, up to 25% of HCV-infected persons may be coinfected with HBV (62-64). Persons with coinfection are at higher risk of developing HCC (65), both a more aggressive form and at a younger age (66,67).

HBV/tuberculosis coinfection

Children and adolescents

CHB is generally benign and asymptomatic in children, as they are usually in the immune-tolerant phase. Children with minimal histological disease are usually not considered for treatment because of the relatively low immediate risk of progression, low response rates to treatment, and concerns over long-term safety and risks of drug resistance. However, children with severe ongoing necro inflammatory disease or cirrhosis may require antiviral therapy. The US Food and Drug Administration (FDA) has approved tenofovir as treatment for HBV in adolescents and children above the age of 12 years, and entecavir for children above 2 years of age.

4. RECOMMENDATIONS: Rapid diagnostic test for the Screening of HBsAg

Recommendation
In populations where access to rapid testing would facilitate linkage to care and treatment, use of RDTs is recommended to improve access.

4.1 Background

For the diagnosis of chronic HBV infection, a serological assay (either RDT or laboratory-based immunoassay) that meets minimum quality, safety and performance standards (with regard to both analytical and clinical sensitivity and specificity) is recommended to detect hepatitis B surface antigen (HBsAg) (1).

In settings where existing laboratory testing is already available and accessible, laboratory-based immunoassays are recommended as the preferred assay format. - In settings where there is limited access to laboratory testing and/or in populations where access to rapid testing would facilitate linkage to care and treatment, use of RDTs is recommended to improve access.

WHO prequalified RDTs available in Pakistan include following;

- SD Bioline HCV by Abbott
- SD Biosensor Inc from Korea
- InTec HCV from China

5. RECOMMENDATIONS: Non- Invasive assessment of liver disease stage at baseline and during follow up

Recommendations

APRI (aspartate aminotransferase [AST]-to-platelet ratio index) is recommended as the preferred non-invasive test (NIT) to assess for the presence of cirrhosis (APRI score >1.5 in adults). Transient elastography (e.g. FibroScan) or FibroTest may be the preferred NITs in settings where they are available and cost is not a major constraint.*

*This recommendation was formulated assuming that liver biopsy is not a feasible option.

5.1 Background

Chronic hepatitis B may present as minimal fibrosis to cirrhosis and HCC. Compensated cirrhosis may progress over time to decompensated cirrhosis, which is associated with life- threatening complications of ascites and spontaneous bacterial peritonitis, upper GI bleeding due to esophageal varices, hepatic encephalopathy, sepsis and renal failure. Persons having cirrhosis with or without clinical decompensation, need antiviral therapy as a priority in order to prevent further disease progression.

Liver biopsy: Liver biopsy is no more used because of its high cost, invasiveness, patient discomfort, risk of complications, sampling error, as well as the need for expert histological interpretation. Several liver biopsy scoring systems have been developed, of which the METAVIR system (Table 5.1), Knodell and Ishak scores (2)are the most widely used.

TABLE 5.1 METAVIR liver-biopsy scoring system

METAVIR stage	F0	F1	F2	F3	F4
Definition	No fibrosis	Portal fibrosis without septa	Portal fibrosis with septa	Numerous septa without cirrhosis	Cirrhosis

Non-invasive tests (NITs): Several non-invasive fibrosis tests based on blood or serum indices (APRI, FIB-4 and a commercial assay – FibroTest,) transient elastography using FibroScan or abdominal ultrasound are now used for evaluating and staging liver fibrosis. (Table 5.2)

TABLE 5.2 Selected non-invasive tests to assess for stage of liver fibrosis

Test	Components	Fibrosis stages assessed	Requirements	Cost
APRI	AST, platelets	≥F2, F4 (cirrhosis)	Basic haematology and clinical chemistry	+
FIB-4	Age, AST, ALT, Platelets	≥F3	Basic haematology and clinical chemistry	+

FibroTest	Gamma glutamyl transpeptidase (gGT), haptoglobin, bilirubin, A1 apolipopotein, alpha2-macroglobulin	≥F2, ≥F3, F4 (cirrhosis)	Specialized tests. Requires testing at designated laboratories. Commercial assay	+ +
FibroScan	Transient elastography	≥F2, ≥F3, F4 (cirrhosis)	Dedicated equipment	+ + +

ALT alanine aminotransferase, APRI AST-to-platelet ratio index, AST aspartate aminotransferase

Blood tests such as the **APRI and FIB-4** scores consist of indirect markers of fibrosis such as ALT, AST and platelet count (Figure 5.1), which are more readily available and are associated with lower costs, do not require particular expertise in their interpretation, and can be performed in an outpatient setting. Other tests such as FibroTest must be performed in laboratories that meet certain quality standards, and are therefore more expensive and less readily available. Not all of these tests can assess all stages of fibrosis/cirrhosis. For example, APRI has been validated for the diagnosis of both significant fibrosis and cirrhosis, while FIB- 4 has not been validated for the diagnosis of cirrhosis. These markers of fibrosis have a high specificity but low sensitivity for significant fibrosis and cirrhosis at their specific cut-off ranges and, therefore, many persons with advanced fibrosis and cirrhosis are missed.

FIGURE 5.1 APRI and FIB-4 calculations

$$\text{APRI} = * \ (\text{AST/ULN}) \times 100) / \text{platelet count } (10^9/\text{L})$$

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

For APRI, ULN signifies the upper limit of normal for AST in the laboratory where these investigations were undertaken. For example, in a patient with an AST of 82 IU/L (where laboratory ULN for AST is 40 IU/L) and a platelet count of 90×10^9/L, the APRI would be: (82/40)x100/90=2.28. This value is >2 and is consistent with the presence of cirrhosis.

Online calculators can be accessed for APRI at:

http://www.hepatitisc.uw.edu/page/clinical-calculators/apri, and for FIB-4 at http://www.hepatitisc.uw.edu/page/ clinical-calculators/fib-4

Transient elastography performed with Fibro Scan measures the liver stiffness. It has been the most widely evaluated. It is non-invasive, takes less than 10 minutes to perform, can be undertaken in outpatient or community settings, and health-care staff can be easily trained in its use. Factors that limit the use of transient elastography include the high cost of the equipment, the need for preventive and corrective maintenance (regular service/ recalibration) and trained operators, and the lack of extensively validated cut-off values for specific stages of fibrosis.

6. RECOMMENDATIONS: Who should be treated and who should not be treated

Recommendations

Who should be treated

- All persons with cirrhosis (compensated or decompensated), regardless of ALT levels, HBeAg status or HBV DNA levels.
- All persons who do not have clinical evidence of cirrhosis but have an APRI score more than 1.5 and have persistently abnormal ALT levels for more than 6 months. If additionally, HBVDNA levels are affordable and available these should be more than 20,000 IU/ml.
  - Where HBV DNA testing is not available: Treatment may be considered if ALT levels are persistently abnormal for over 6 months and APRI is more than 1.5
- In HBV/HIV-coinfected individuals, ART should be initiated in all those with evidence of severe chronic liver disease, regardless of CD4 count; and in all those with a CD4 count ≤500 cells/mm3, regardless of stage of liver disease.

Who should not be treated but constantly monitored

- All persons who do not have cirrhosis
- All persons with APRI score of less than 1.5 and persistently normal ALT levels.

All persons without cirrhosis whose HBV DNA levels fluctuate between 2000 and 20,000 IU/ml, or they have intermittently abnormal ALT levels;

BOX 6.1 Key points in the initial assessment of persons with CHB prior to therapy

Assessment of the severity of liver disease should include

- A history
- Physical examination
- LFTs including AST
- Complete blood count including platelets
- APRI score
- Serum Albumin
- Prothrombin time
- Quantitative serum HBV DNA (where HBV DNA testing is available)
- HBeAg.

Look for comorbidities/coinfections:

- HCV
- HDV
- Diabetes mellitus
- HIV
- Non-alcoholic fatty liver disease

All persons having cirrhosis should be screened for HCC. Look for family history of HBV, HCC.

Disease Preventive measures:

- HBsAg screening with HBV vaccination of non-immune family members
- Other general measures to reduce HBV transmission

Counsel on lifestyle:

- Encourage healthy diet
- Encourage physical activity/exercise

Preparation/counselling before starting treatment:

- Counsel about indications for treatment, including the benefits and side-effects
- Ensure they are willing to take long-term treatment, shall come for follow-up during therapy and also when treatment is stopped

- Inform about the importance of adherence to treatment to reduce the risk of drug resistance
- Cost implications because treatment might be taken out of pocket

Measure baseline renal function in all persons prior to starting antiviral therapy.

[a] Clinical features of decompensated cirrhosis: Portal hypertension (ascites, variceal haemorrhage and hepatic encephalopathy), coagulopathy, or liver insufficiency (jaundice). Other clinical features of advanced liver disease/cirrhosis may include: hepatomegaly, splenomegaly, pruritus, fatigue, arthralgia, palmar erythema, and oedema.

[b] Measurement of baseline renal function includes: serum creatinine levels, and calculation of estimated glomerular filtration rate (eGFR) using the Cockcroft–Gault (CG) or modification of diet in renal disease (MDRD) formulas. An online calculator is available at http://nephron. com/cgi-bin/CGSI.cgi. For children, the Schwartz or similar formula can be used: http://nephron.com/bedsidepedsnic.cgi.

CG formula: eGFR = (140 – age) x (wt in kg) x 0.85 (if female)/(72 x Cr in mg%)
MDRD formula: eGFR = 175 x serum Cr–1.154 x age–0.203 x 1.212 (if patient is Black) x 0.742 (if female)
Estimation of GFR based on these formulas may underestimate the degree of renal dysfunction if muscle mass is lower than the age and sex standards, as is frequently the case in HIV-infected individuals (1).

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

Background

Chronic HBV infection has a complex history that passes through many phases expanding over variable duration. The CHB disease spectrum is quite diverse where in some people it does not lead to significant liver disease while in 10–30% it causes liver fibrosis, cirrhosis, decompensation and a high risk of hepatocellular carcinoma (HCC). It is therefore important that to understand the phases of chronic infection and decide that who requires antiviral therapy and who can wait and be monitored for any disease activity to start treatment.

The main reason to start treatment is to prevent the complications. The decision to start antiviral treatment is mostly supported by a history and clinical signs and symptoms along with the noninvasive tests like APRI score, ALT, fibroscan and ultrasound abdomen. HBV DNA will complement the decision making but should not be the deciding factor in imitating the antiviral treatment. The decision to start antiviral therapy is usually clear in persons who have life-threatening or advanced liver disease, such as acute liver failure or cirrhosis (compensated or decompensated cirrhosis) or acute-on-chronic liver failure. Persons who do not have cirrhosis as yet, the APRI score along with persistently high ALT levels for over 6 months will be the deciding factor to start antiviral therapy. If resources allow quantitative HBV DNA levels may be done. It must be remembered that not all persons will have high ALT levels and high HBV DNA levels. For example, during the immune-tolerant phase, there will be high levels of HBV DNA but low or normal levels of ALT. These persons have low chances of progression of fibrosis. Later on, during the immune-active phase, HBV DNA levels will be low, but ALT levels will be raised. These persons have a much higher risk of progression of fibrosis. It is therefore important that antiviral therapy should be started in the active phases of CHB when the risks of disease progression (fibrosis) are high. In contrast, persons in immune tolerant phase who have low chances of progression to chronicity should not be given antiviral therapy. Some known predictors of disease progression are age over 40 years, male gender, persistently high or fluctuating ALT, family history of HCC, Alcohol use, HIV infection and diabetes act as cofactors in disease progression.

7.RECOMMENDATIONS: FIRST-LINE ANTIVIRAL THERAPIES FOR CHRONIC HEPATITIS B

Recommendations

Tenofovir/TFA or entecavir is recommended in all persons aged 12 years or above in whom antiviral therapy is indicated.

Entecavir is recommended in children aged 2–11 years. *(Strong recommendation, moderate quality of evidence)*

In HBV/HIV-coinfected adults, adolescents and children aged 3 years or older, tenofovir+ lamivudine (or emtricitabine) + efavirenz as a fixed-dose combination is recommended to initiate ART[1]. *(Strong recommendation, moderate quality of evidence)*

[1]Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva, Switzerland: World Health Organization; 2013.

BOX 7.1 Key points in counselling and preparing the patient prior to initiation of therapy

Preparing to start treatment: Patients should be counselled about

- The indications for treatment
- Likely benefits and side-effects
- Willingness to take long- term treatment
- Agrees to come follow-up during therapy and also once the therapy has been stopped
- Understands that adherence to treatment shall reduce the risk of drug resistance
- Willing to undertake the cost related to the purchase of the treatment.

Note: HBV genotyping and resistance testing are not required to guide therapy when using nucleos(t)ide analogues (NAs) with a high barrier to resistance.

Measure baseline renal function [a] and assess risk for renal dysfunction[b] in all persons prior to initiation of antiviral therapy.

[a] Measurement of baseline renal function includes: serum creatinine levels, and calculation of estimated glomerular filtration rate (eGFR) using the Cockcroft–Gault (CG) or modification of diet in renal disease (MDRD) formulas. An online calculator is available at http://nephron.com/cgi-bin/CGSI.cgi. For children, the Schwartz or similar formula can be used: http://nephron.com/bedsidepedsnic.cgi.

CG formula: eGFR = (140 – age) x (wt in kg) x 0.85 (if female) / (72 x Cr in mg%)
MDRD formula = eGFR = 175 x serum Cr–1.154 x age–0.203 x 1.212 (if patient is Black) x 0.742 (if female).
Estimation of GFR based on these formulas may underestimate the degree of renal dysfunction if muscle mass is lower than the age and sex standards, as is frequently the case in HIV-infected individuals (1).
[b]Factors associated with a higher risk of renal dysfunction include: decompensated cirrhosis, CrCl <50 mL/min, older age, body mass index (BMI)
<18.5 kg/m2 (or body weight <50 kg), poorly controlled hypertension, proteinuria, uncontrolled diabetes, active glomerulonephritis, concomitant use of nephrotoxic drugs or a boosted protease inhibitor (PI) for HIV, and solid organ transplantation

7.1 Background

Six NAs (lamivudine, adefovir, entecavir, telbivudine, tenofovir, emtricitabine) are approved and widely used for the treatment of CHB. NAs with a low barrier to resistance, such as lamivudine, has led to high rates of resistance in those who have received treatment for CHB.

The goal of antiviral therapy in CHB is to reduce (or reverse) hepatic necroinflammatory changes and fibrosis leading to cirrhosis, decompensation, liver failure, HCC and death. The surrogate that can be used to assess the response to the antiviral therapy are normalization of serum ALT, reduction in HBV DNA to undetectable levels by PCR and HBeAg loss or seroconversion to anti-HBe status or rarely, HBsAg loss and seroconversion to anti-HBs status (called "Functional Cure"- the best-case scenario with current treatment).

Although NAs are potent inhibitors of HBV DNA replication, they do not result in cure, because antiviral therapy cannot eliminate the cccDNA from the nucleus, which is the template for transcription of viral RNA. Therefore, at present, long-term (potentially lifelong) NA therapy is required in the majority of persons.

The recommended drugs and their dosage in adults and children are shown in tables 7.1a and 7.1b

TABLE 7.1.a Recommended drugs for the treatment of CHB and their doses in adults

Drug	Dose
Tenofovir	300 mg[a] once daily
Entecavir (adult with compensated liver disease and lamivudine naive)	0.5 mg once daily
Entecavir (adult with decompensated liver disease)	1 mg once daily

[a] Tenofovir disoproxil fumarate (TDF) 300 mg is equivalent to tenofovir disoproxil 245 mg or tenofovir 136 mg.

Tenofovir alafenamide fumarate (TAF) is an orally bioavailable prodrug of tenofovir with reduced renal and bone toxicities compared to tenofovir.

TABLE 7.1.b Recommended drugs for the treatment of CHB and their doses in children

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

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

8. RECOMMENDATIONS: 2nd line of antiviral treatment for the management of treatment failure

Recommendations
Switch to tenofovir all persons with suspected antiviral resistance (past history of taking lamivudine, entecavir, adefovir or telbivudine).

8.1 Background

Of the six approved NAs (lamivudine, adefovir, entecavir, telbivudine, tenofovir, emtricitabine) (1-6), lamivudine has the highest rate of drug resistance while entecavir has a very low rate of resistance (except in persons previously exposed to lamivudine and adefovir), and currently no resistance has been reported with tenofovir.

It is recommended to switch to tenofovir monotherapy as the most effective antiviral therapy for persons who have used lamivudine in the past

The most common reason for virological breakthrough is poor adherence to antiviral therapy, therefore regular counselling should be offered on the importance of treatment adherence.

9. RECOMMENDATIONS: When to stop antiviral treatment

Recommendations

Lifelong NA therapy

- All persons with cirrhosis
- All persons with APRI score >1.5.

Discontinuation of antiviral therapy can lead to disease reactivation with severe acute-on-chronic liver injury.

Discontinuation

Discontinuation of antiviral therapy may be considered exceptionally in:

- Persons without cirrhosis (no clinical evidence, APRI score <1.5 in adults)
- Who can be followed easily on long term for reactivation
- Persons who were initially HBeAg positive and now become HBeAg negative and develop Anti HBe and have completed at least one additional year of treatment
- Persons with persistently normal ALT levels
- Persons with undetectable HBV DNA levels (where testing is available).

Where HBV DNA testing is not available: Discontinue antiviral therapy if there is evidence HBsAg loss at 2 occasions 6 months apart and after completion of at least one additional year of treatment.

Retreatment

Relapse may occur after stopping antiviral therapy. Retreatment is recommended if there are consistent signs of reactivation like

- HBsAg or HBeAg becomes positive again
- ALT levels increase again and remain high for more than 6 months
- HBV DNA becomes detectable again (where HBV DNA testing is available)

9.1 Background

The main goal of antiviral therapy in CHB is to improve survival and quality of life by preventing its progress to severe liver disease (decompensated cirrhosis and liver failure), HCC and death. This can be achieved by suppressing HBV DNA to undetectable levels. HBsAg loss is the optimal goal of antiviral therapy, and a marker of sustained treatment response in both HBeAg-positive and HBeAg-negative persons. This is achieved in 10–15% HBeAg positive cases after 5 years) but is rare in HBeAg negative cases. HBeAg seroconversion to antiHBe may also be considered as a potential stopping point to guide treatment cessation, but again this is infrequent.

Although antivirals inhibit HBV DNA replication, yet they do not result in cure, because the antiviral therapy does not eliminate the replicative template cccDNA or the integrated viral genome. Therefore, antiviral therapy has to be continued for long term or lifelong

10. RECOMMENDATIONS: Monitoring

10.1 Monitoring for disease progression and treatment response in persons with CHB prior to during and post treatment

Recommendations

It is recommended to undertake following tests yearly:

- ALT levels
- AST levels for APRI
- HBsAg
- HBeAg (in HBeAg positive cases only)
- HBV DNA levels (where available)

More frequent monitoring is needed in:

Persons who do not yet meet the criteria for ANTIVIRAL therapy like:

- Those with intermittently abnormal ALT levels
- APRI is increasing but is still less than 1.5
- HBV DNA levels are fluctuating between 2,000 IU/mL and 20,000 IU/ml (where HBV DNA testing is available)
- HIV-coinfected persons. (Conditional recommendation, low quality of evidence)

In persons on treatment or following treatment discontinuation:

Monitor every 3 months for the first year in following:

- Persons with cirrhosis (compensated or decompensated)
- During the first year of treatment to assess treatment response and adherence
- HIV-coinfected persons
- Persons after discontinuation of treatment. (Conditional recommendation, very low quality of evidence)

[a] In persons on treatment, monitor for HBsAg loss (although this occurs rarely), and for seroreversion to HBsAg positivity after discontinuation of treatment.
[b] Monitoring of HBeAg/anti-HBe mainly applies to those who are initially HBeAg positive. However, those who have already achieved HBeAg seroconversion and are HBeAg negative and anti-HBe positive may serorevert.
[c] *See Chapter / Box on. Monitoring adherence to antiviral therapy.*
[d] ALT levels fluctuate in persons with CHB and require longitudinal monitoring to determine the trend. Upper limits for normal ALT have been defined as below 30 U/L for men and 19 U/L for women, though local laboratory normal ranges should be applied (1). Persistently abnormal or normal may be defined as three ALT determinations above or below the upper limit of normal, made at unspecified intervals during a 6–12-month period or predefined intervals during a 12-month period.
[e] *See Chapter: Who to treat and who not to treat.*
[f] Monitoring response to ART and the diagnosis of treatment failure (Chapter 7.3). In: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013. These guidelines will be updated in 2015.
[g] Decompensated cirrhosis is defined by the development of portal hypertension (ascites, variceal haemorrhage and hepatic encephalopathy), coagulopathy, or liver insufficiency (jaundice). Other clinical features of advanced liver disease/cirrhosis may include: hepatomegaly, splenomegaly, pruritus, fatigue, arthralgia, palmar erythema, and oedema.

BOX 9.1 Goals of monitoring

In persons who do not yet meet the criteria for antiviral therapy: Monitor to identify a change in clinical status (development of clinical features of cirrhosis) or APRI score >1.5 in adults, development of HCC, or a rise in ALT or HBV DNA levels, which may indicate progression to active disease requiring starting of antiviral treatment.

In persons on treatment or following treatment discontinuation: Monitor during and after treatment to assess treatment response, treatment adherence, adverse effects, disease progression and development of HCC, the potential for treatment discontinuation, and to identify reactivation early on after treatment discontinuation.

10.1.1 Background

Regular monitoring should be done for all persons with CHB before, during and after discontinuation of antiviral therapy. This is done to assess treatment response, disease progression, development of HCC and drug toxicity. Monitoring before starting antiviral treatment is done to identify the disease progression and when to start antiviral therapy. Monitor yearly or earlier with ALT APRI, HBeAg (HBV DNA where available). Persons who have fluctuating or persistently high serum ALT and AST levels, and increasing APRI (if available HBV DNA levels >20 000 IU/ml) indicate disease progression and antiviral treatment should be started in such cases. If there is improvement in symptoms with, normalization of ALT levels, lowering of APRI and loss of HBV DNA levels and HBeAg followed by appearance of anti HBe (seroconversion); his indicates good prognosis and there is no need to start antiviral treatment. All persons who are HBeAg-negative with normal ALT levels and low HBV DNA levels (previously called inactive HBsAg carriers), require regular monitoring of APRI, ALT levels and HBV DNA or fibroscan to check their inactive status or, to determine when to start treatment if ALT/AST levels increase, APRI goes up plus there is rise in HBV DNA levels, or there is clinical evidence of disease progression to cirrhosis.

Monitoring during and after treatment discontinuation is required to assess the treatment response, treatment adherence and any adverse effects. It is also done to identify when to stop treatment whether there is disease reactivation early on after treatment discontinuation (1). These persons also require monitoring for the development of HCC

How frequently of testing before starting the treatment and during treatment are not clear (1). Antiviral therapy is not recommended and can be deferred in persons without clinical or other evidence of cirrhosis, APRI score <1.5, persistently normal ALT levels. (HBV DNA <2000 IU/ml where available). Where HBV DNA testing is not available: Treatment can be deferred when person has persistently normal ALT levels).

10.2 Monitoring for tenofovir and entecavir toxicity

Recommendations

Measure baseline renal functions and assess for risk for renal dysfunction in all persons prior to starting antiviral therapy.

Renal function should be monitored annually in persons on long-term tenofovir or entecavir therapy, and growth monitored carefully in children. *(Conditional recommendation, very low quality of evidence)*

[a] Measurement of baseline renal function includes: serum creatinine levels, and calculation of creatinine clearance (CrCl)/estimated glomerular filtration rate (eGFR) using the Cockcroft–Gault (CG) or modification of diet in renal disease (MDRD) formulas. An online calculator is available at http://nephron.com/cgi-bin/CGSI.cgi. For children, the Schwartz or similar formula can be used: http://nephron.com/bedsidepedsnic.cgi.
CG formula: eGFR = (140 – age) x (wt in kg) x 0.85 (if female) / (72xCr in mg%)

MDRD formula: eGFR = 175 x serum $Cr^{-1.154}$ x $age^{-0.203}$ x 1.212 (if patient is Black) x 0.742 (if female).
Estimation of GFR based on these formulas may underestimate the degree of renal dysfunction if muscle mass is lower than the age and sex standards, as is frequently the case in HIV-infected individuals (1).

[b] Factors associated with a higher risk of renal dysfunction include: decompensated cirrhosis, CrCl <50 mL/min, older age, body mass index (BMI) <18.5 kg/m^2 (or body weight <50 kg), poorly controlled hypertension, proteinuria, uncontrolled diabetes, active glomerulonephritis, concomitant use of nephrotoxic drugs or a boosted protease inhibitor (PI) for HIV, and solid organ transplantation.

BOX 10.2 Assessment and monitoring of renal function

1. Entecavir should be given to all patients who are at risk of developing renal dysfunction including those with eGFR of <50 mL/min, long-term diabetes, uncontrolled hypertension or severe osteopenia/osteoporosis be given entecavir. Avoid using tenofovir in these cases. Tenofovir is not recommended in children aged 2–12 years, or in any child with renal impairment.
2. Tenofovir should be avoided with concurrent/recent use of adefovir or other nephrotoxic drugs (e.g. aminoglycosides, amphotericin B, foscarnet, ganciclovir, vancomycin, cidofovir) due to the increased risk of renal adverse reactions.
3. During treatment, adjust the dose of tenofovir or stop tenofovir and monitor renal function if the creatinine clearance (CrCl) falls below 50 mL/min, or there is progressive decline of renal function when no other cause has been identified.
4. If therapy is discontinued, monitor liver functions closely, as severe acute exacerbations of hepatitis may occur and resumption of antiviral therapy may be required.
5. Monitoring during antiviral therapy in individuals with normal renal function could include annual urine dipstick testing and creatinine measurement for eGFR.
6. Frequency of monitoring during antiviral therapy depends on the presence of risk factors for renal dysfunction and should be more frequent in persons at higher risk.

a. Persons at high risk of renal toxicity: every 6 months, unless there is evidence of worsening. Closer renal monitoring is required in persons with CrCl <50 mL/min.
b. Persons at low risk of renal toxicity: either no routine monitoring of renal function, or every 12 months unless there is evidence of worsening.

7. If low bone mineral density is detected or suspected because of a fracture, then appropriate consultation should be obtained.

Measure baseline renal function: Renal functions include serum creatinine, creatinine clearance (CrCl)/estimated glomerular filtration rate (eGFR) using the Cockcroft–Gault (CG) or modification of diet in renal disease (MDRD) formulas. An online calculator is available at http://nephron.com/cgi-bin/CGSI.cgi. For children, the Schwartz or similar formula can be used: http://nephron.com/bedsidepedsnic.cgi.

Estimation of GFR based on these formulas may underestimate the degree of renal dysfunction if muscle mass is lower than the age and sex standards, as is frequently the case in HIV-infected individuals (2).

Factors associated with a higher risk of renal dysfunction include: persons with decompensated cirrhosis, CrCl <50 mL/min, older age, body weight <50 kg, poorly controlled hypertension and or diabetes, proteinuria, active glomerulonephritis, concomitant use of nephrotoxic drugs or a boosted protease inhibitor (PI) for HIV, and solid organ transplantation. The recommended dosage in renal impairment is shown in table 10.1

TABLE 10.1. Recommended dosage in adults with renal impairment

Drug	Recommended dose reduction or dosing interval			
	CrCl (mL/min)[c]			
	≥50	30–49	10–29	<10, Haemodialysis or CAPD
Tenofovir [a,b]	One 300 mg tablet every 24 hours (7.5 scoops of powder every 24 hours)	One 300 mg tablet every 48 hours (or 160 mg [3 scoops] of powder every 24 hours)	One 300 mg tablet every 72–96 hours (or 60 mg [1.5 scoops] of powder every 24 hours)	Every 7 days or one 300 mg tablet following completion of approximately every 12 hours of dialysis (or 20 mg [0.5 scoops] of powder following completion of approximately every 12 hours of dialysis)
Entecavir	0.5 mg once daily[d]	0.25 mg once daily OR 0.5 mg every 48 hours	0.15 mg once daily OR 0.5 mg every 72 hours	0.05 mg once daily OR 0.5 mg every 7 days
Entecavir (decompensated liver disease)	1 mg once daily	0.5 mg once daily OR 1 mg every 48 hours	0.3 mg once daily OR 1 mg every 72 hours	0.1 mg once daily OR 1 mg every 7 days

CAPD continuous ambulatory peritoneal dialysis CrCl creatinine clearance
[a] Tenofovir disoproxil fumarate (TDF) 300 mg is equivalent to tenofovir disoproxil 245 mg or tenofovir 136 mg.
[b] Tenofovir is also available in a granule formulation (33 mg/g in 60 g pack) for ease of swallowing. Dosing is the same for oral granules and tablets.
[c] Calculated using lean body weight
[d] For doses less than 0.5 mg, oral solution is recommended. Entecavir is not recommended for those with lamivudine resistance.

10.2.1 Background

Tenofovir is excreted via the kidneys and therefore may cause proximal tubular cell dysfunction leading to mild renal tubular dysfunction leading to Fanconi syndrome and impaired glomerular filtration (1–4). Small decreases in bone mineral density with osteopenia or osteoporosis during the early phases of treatment have also been reported (5–8). Known risk factors for the development of tenofovir-induced nephrotoxicity include underlying renal dysfunction, low CD4 count and low body weight (9– 11). Although tubular dysfunction is reversible in most cases after withdrawal of tenofovir but persistent renal dysfunction has been reported (13). Entecavir is also excreted through kidneys, but proximal tubular dysfunction is less common. In addition to the effects of antiviral therapy, HBV infection may also impact on renal function (14,15).

10.3 Monitoring for hepatocellular carcinoma (HCC)

Recommendations

Yearly screen for HCC using abdominal ultrasound and alpha-fetoprotein in:

- All persons with cirrhosis (Strong recommendation, low quality of evidence)
- All persons having a family history of HCC (Strong recommendation, low quality of evidence)
- All persons aged over 40 years (Conditional recommendation, low quality of evidence)

10.3.1. Background

Persons suffering from CHB are at a higher risk of dying from liver cirrhosis and liver cancer, with an estimated 650 000 annual deaths from HCC (1). In Pakistan many people are not aware about their disease status and antiviral treatment is unaffordable. They present with advanced liver disease and large hepatomas. HCC is often rapidly progressive and treatment options are limited with overall poor survival. The prognosis of HCC is affected by the size and number of tumors, and the underlying liver function. Prognosis is better if the treatment is started at an early stage of the disease, when the tumor is small. Surveillance is therefore important to detect HCC at an early stage (tumor size <3 cm in diameter). The treatments include alcohol injection or radiofrequency ablation of small tumors. Current surveillance tools include ultrasound and/or alpha-fetoprotein (AFP) measurement. Six monthly monitoring for HCC in persons with cirrhosis is likely to detect HCC at an earlier stage and improve the survival.

11.COINFECTIONS

Routes of transmission are same for HBV, HIV, HCV and HDV. Coinfections often result in more severe liver disease with higher chances of cirrhosis, HCC and mortality. Coinfected persons are therefore more likely to need antiviral treatment. In general, the dominant virus responsible for liver disease should be identified and initial treatment targeted toward this virus. For example, if HCV is dominant, treatment should first be given to achieve HCV clearance and cure, followed by determination of whether treatment for hepatitis B is warranted based on ALT and HBV DNA levels.

11.1 HBV/HDV coinfection

HDV coinfection means that a person gets infected simultaneously with both HBV and HDV. This leads to either a mild-to-severe or even fulminant hepatitis (1,2), but recovery is usually complete and development of chronic delta hepatitis is rare (3). Superinfection with HDV in a person already chronically infected with HBV, accelerates the course of chronic disease in all age groups in 70–90% cases(4-7). Prevention and control of HDV requires prevention of HBV infection through hepatitis B immunization (8), although there is no protection against HDV for those who are already HBV infected.

There are limited data to inform definitive guidance on the management of persons with HDV infection.

11.2 HBV/HCV coinfection

HCV coinfection accelerates progression of liver disease and increases the risk of HCC (9-11). HBV DNA levels are usually low or undetectable because HCV is responsible for the disease activity in most persons. All anti HCV positive cases should be tested for HCVRNA and if found positive they should be treated using national HCV testing and treatment guidelines. HBV DNA monitoring may be needed as there is a risk of HBV reactivation during treatment or after clearance of HCV, which can be treated with NAs (11).

11.3 HBV/Tuberculosis

Groups at increased risk of infection with HBV are also at risk of infection with TB, largely because they live in regions of the world that are endemic for both infections. PWID and prisoners have a high risk of acquiring HBV and HCV, and are also at increased risk of coinfection with TB (12,13. Screening of HIV-positive patients is recommended using a four-symptom screening algorithm to rule out active TB. In the absence of a cough, weight loss, fever and night sweats, active TB can be confidently ruled out. Otherwise, further investigations for TB and other disease would be recommended (14-16). Drug-induced liver injury with elevation of aminotransferases is three- to sixfold higher in persons coinfected with HBV, HCV or HIV who are receiving antituberculosis drugs, due to hepatotoxicity with isoniazid, rifampicin and pyrazinamide (17).

11.4 Decompensated cirrhosis and advanced liver disease

Older CHB persons may develop cirrhosis and its complications and HCC. These are rarely seen in younger age (< 20 years). Compensated cirrhosis may progress over time to decompensated cirrhosis with associated weight loss, weakness, wasting, oedema, dark urine, jaundice, ascites, hepatomegaly, spontaneous bacterial peritonitis, esophageal varices or encephalopathy, and eventually to liver failure, renal failure and sepsis, all of which are life-threatening. As the disease advances to cirrhosis, the laboratory tests also become more abnormal. AST:ALT ratio increases, platelet count go down (suggesting the development of portal hypertension), ALP and gGT increase, serum albumin falls, and prothrombin time prolongs. Rising bilirubin with low albumin and prolonged prothrombin time are poor prognostic markers that have an increased risk of liver-related death. The exacerbations associated with either a decline in viral replication or reactivation of viral replication and recurrence of disease can be severe and life threatening.

Regular clinical examination and monitoring (every 6–12 months) of LFTs, albumin, international normalized ratio (INR) and liver ultrasound before and during treatment is essential to detect disease progression, including decompensation and evidence of HCC. All persons with decompensated cirrhosis should be considered for urgent antiviral therapy with tenofovir or entecavir, even if the HBV DNA level is low or undetectable. In unstable persons with deteriorating renal function, entecavir can be used as 1 mg daily and persons should be monitored for lactic acidosis. Antiviral therapy should usually be continued indefinitely in persons with cirrhosis. The risk of developing HCC is high in these persons, even with effective antiviral therapy and therefore long-term HCC surveillance is mandatory.

11.5 HBV/HIV coinfection

HIV coinfection has a profound impact on almost every aspect of the natural history of HBV infection and results in more rapid progression to cirrhosis and HCC, higher liver-related mortality, and decreased treatment response compared with persons without HIV coinfection (18-24). Other challenges with coinfection include cross-resistance between HIV and HBV drugs (25,26) increased liver injury, either due to direct hepatotoxicity (27,28) or ART-related immune-reconstitution hepatitis, with elevation of ALT and even fulminant hepatitis if ART does not cover both HIV and HBV infections adequately (29-31).

HBV screening and vaccination: The risk of HBV infection is higher in HIV- infected adults, and therefore all persons newly diagnosed with HIV should be screened for HBsAg and anti-HBs, and vaccinated if indicated (HBsAg negative and anti- HBs negative). Response to HBV vaccine is lower in persons with HIV or with a low CD4 count. The need of four double (40 µg) doses of the vaccine is reported to provide a higher protective anti-HBs titre than the regular three 20 µg dose schedule (32).

All HBV/HIV-coinfected persons should be referred to HIVAIDS program sites in each district or province where the experts will decide who to start ART and when.

11.6 Extrahepatic manifestations

HBsAg-positive persons with HBV-related extrahepatic manifestations (skin manifestations, polyarteritis nodosa and glomerulonephritis) and active HBV replication may respond to antiviral therapy.

11.7 Acute hepatitis B

Antiviral therapy is not necessary for uncomplicated symptomatic acute hepatitis B, as >95% of immunocompetent adults will spontaneously clear HBV infection (33). Persons with fulminant or severe acute hepatitis may benefit from entecavir or tenofovir, to improve survival and reduce the risk of recurrent hepatitis B (34,36). The duration of treatment is not established, but continuation of antiviral therapy for at least 3 months after seroconversion to anti-HBs or at least 12 months after anti-HBe seroconversion without HBsAg loss is generally advised.

11.8 Children and adolescents

CHB is usually asymptomatic in children, as they are generally in the immune-tolerant phase. Although many children will not require antiviral therapy, early identification and monitoring of children at risk for progression of liver disease remains important. The use of NITs and identification of appropriate cut-offs have not yet been defined in children. The FDA has approved tenofovir for use in adolescents and children above the age of 12 years for HBV treatment (and 3 years or older for HIV treatment). In 2014, the FDA approved entecavir for children with CHB above 2 years of age.

11.9 Pregnant women

Indications for treatment in adults with CHB also apply to pregnant women. Based on safety data (16), tenofovir is the preferred antiviral, because it has a better resistance profile in pregnant HBV-positive women. The safety of entecavir in pregnancy is not known, and IFN-based therapy is contraindicated.

For prevention of mother-to-child HBV transmission, the most important strategy is to deliver the first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours followed by at least two timely subsequent doses.

11.10 Persons who inject drugs (PWID)

PWID are at increased risk of acute and chronic HBV infection (in addition to HIV and HCV infection) and liver- related disease, as well as all-cause morbidity and mortality, and therefore require additional care. When caring for PWID, the central tenets of respect and non- discrimination should be followed, and additional adherence and psychological support provided as required.

11.11 Dialysis and renal transplant patients

HBV is common in persons with end-stage renal disease, including renal transplant recipients, who should be screened for HBV infection, and HBV-seronegative persons vaccinated. Tenofovir and entecavir require dose adjustment and should be used with caution in persons with renal impairment or in renal transplant recipients. Renal function should be monitored during antiviral therapy. Unexpected deterioration of renal function during antiviral therapy may necessitate a change of treatment or further dose adjustment. All HBsAg-positive persons undergoing renal transplantation should receive prophylactic entecavir to prevent HBV reactivation.

11.12 Health-care workers

Health-care workers need special consideration for HBV screening and vaccination. Those who are HBsAg positive and undertake exposure-prone procedures, such as surgeons, gynaecologists, nurses, phlebotomists, personal care attendants and dentists, should be considered for antiviral therapy to reduce direct transmission to persons. In accordance with 2013 ARV recommendations (37), they should receive entecavir or tenofovir to reduce levels of HBV DNA ideally to undetectable or at least to <2000 IU/mL, before resuming exposure-prone procedures. Post-exposure prophylaxis should be considered following needlestick or other occupational exposures.

REFERENCES

Background

1. Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. J Viral Hepat. 2004;11(2):97–107.
2. McMahon BJ. The natural history of chronic hepatitis B virus infection. Semin Liver Dis. 2004;24 (Suppl 1):17–21.
3. Hoofnagle JH, Doo E, Liang TJ, Fleischer R, Lok AS. Management of hepatitis B: summary of a clinical research workshop. Hepatology. 2007;45(4):1056–75.
4. Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology. 2007;45(2):507–39.
5. Ganem D, Prince AM. Hepatitis B virus infection—natural history and clinical consequences. N Engl J Med. 2004;350(11):1118–29.
6. Fattovich G. Natural history and prognosis of hepatitis B. Semin Liver Dis. 2003;23(1):47–58.
7. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. Gastroenterology. 2004;127:S35–S50.
8. Hadziyannis SJ, Papatheodoridis GV. Hepatitis B e antigen-negative chronic hepatitis B: natural history and treatment. Semin Liver Dis. 2006;26(2):130–41.
9. Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. Vaccine. 2012;30(12):2212–19.
10. Zarski JP, Marcellin P, Leroy V, Trepo C, Samuel D, Ganne-Carrie N, et al. Characteristics of patients with chronic hepatitis B in France: predominant frequency of HBe antigen negative cases. J Hepatol. 2006;45(3):355–60.
11. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095–128.
12. Goldstein ST, Zhou F, Hadler SC, Bell BP, Mast EE, Margolis HS. A mathematical model to estimate global hepatitis B disease burden and vaccination impact. Int J Epidemiol. 2005;34(6):1329–39.
13. WHO. Hepatitis B vaccines. Wkly Epidemiol Rec. 2009;84:405–20.
14. Do EC, Ghany MG. Hepatitis B virology for clinicians. Med Clin North Am. 2010;14:397–408.
15. McMahon BJ. The influence of hepatitis B virus genotype and subgenotype on the natural history of chronic hepatitis B. Hepatol Int. 2009;3(2):334–42.
16. Kim BK, Revill PA, Ahn SH. HBV genotypes: relevance to natural history, pathogenesis and treatment of chronic hepatitis B. Antivir Ther. 2011;16(8):1169–86.
17. Alexopoulou A, Karayiannis P. HBeAg negative variants and their role in the natural history of chronic hepatitis B virus infection. World J Gastroenterol. 2014;20(24):7644–52.
18. Harris BJ, Holzmayer V, Qureshi H, Khan MA, Khan SA, Salamat N, et al. Hepatitis B genotypes and surface antigen mutants present in Pakistani blood donors. (2017) PLoS ONE 12(6): e0178988.
19. Mast EE, Alter MJ, Margolis HS. Strategies to prevent and control hepatitis B and C virus infections: a global perspective. Vaccine. 1999;17(13-14):1730–3.
20. Qureshi H, Bile KM, Jooma R, Alam SE, Afridi HUR. Prevalence of hepatitis B and C viral infections in Pakistan: findings of a national survey appealing for effective prevention and control measures. Eastern Mediterranean Health Journal, Vol. 16 Supplement 2010, page 15-23

21. Beasley RP, Hwang LY, Lee GC, Lan CC, Roan CH, Huang FY, et al. Prevention of perinatally transmitted hepatitis B virus infections with hepatitis B immune globulin and hepatitis B vaccine. Lancet. 1983;2(8359):1099–102.
22. McMahon BJ, Alward WL, Hall DB, Heyward WL, Bender TR, Francis DP, et al. Acute hepatitis B virus infection: relation of age to the clinical expression of disease and subsequent development of the carrier state. J Infect Dis. 1985;151(4):599–603.
23. Szmuness W. Recent advances in the study of the epidemiology of hepatitis B. Am J Pathol. 1975;81(3):629–50.
24. McMahon BJ. The natural history of chronic hepatitis B virus infection. Hepatology. 2009;49(5 Suppl):S45–55.
25. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology. 2009;50(3):661–2.
26. Brunetto MR, Oliveri F, Colombatto P, Moriconi F, Ciccorossi P, Coco B, et al. Hepatitis B surface antigen serum levels help to distinguish active from inactive hepatitis B virus genotype D carriers. Gastroenterology. 2010;139(2):483–90.
27. Chen CJ, Iloeje UH, Yang HI. Long-term outcomes in hepatitis B: the REVEAL-HBV study. Clin Liver Dis. 2007;11(4):797–816, viii.
28. Saldanha J, Gerlich W, Lelie N, Dawson P, Heermann K, Heath A, et al. An international collaborative study to establish a World Health Organization international standard for hepatitis B virus DNA nucleic acid amplification techniques. Vox Sang. 2001;80(1):63–71.
29. Shyamala V, Cottrell J, Arcangel P, Madriaga D, Linnen J, Phelps B, et al. Detection and quantitation of HBV DNA in the WHO International Standard for HIV-1 RNA (NIBSC code: 97/656). J Virol Methods. 2004;118(1):69–72.
30. Castera L. Noninvasive methods to assess liver disease in patients with hepatitis B or C. Gastroenterology. 2012;142(6):1293–302.e4.
31. Park SH, Kim CH, Kim DJ, Suk KT, Cheong JY, Cho SW, et al. Usefulness of multiple biomarkers for the prediction of significant fibrosis in chronic hepatitis B. J Clin Gastroenterol. 2011;45(4):361–5.
32. Zhang YG, Wang BE, Wang TL, Ou XJ. Assessment of hepatic fibrosis by transient elastography in patients with chronic hepatitis B. Pathol Int. 2010;60(4):284–90.
33. Blood donor selection: guidelines on assessing donor suitability for blood donation Geneva: World Health Organization; 2012.
34. Imran H, Raja D, Grassly NC, Wadood MZ, Safdar RM, O'Reilly KM. Routine immunization in Pakistan: comparison of multiple data sources and identification of factors associated with vaccination. Int Health. 2018 Mar 1;10(2):84-91. doi: 10.1093/inthealth/ihx067. PMID: 29432552; PMCID: PMC5856161.
35. Bam RA, Birkus G, Babusis D, Cihlar T, Yant SR. Metabolism and antiretroviral activity of tenofovir alafenamide in CD4(+) T-cells and macrophages from demographically diverse donors. Antivir Ther. 2014;19(7):669–77.
36. Bam RA, Yant SR, Cihlar T. Tenofovir alafenamide is not a substrate for renal organic anion transporters (OATs) and does not exhibit OAT-dependent cytotoxicity. Antivir Ther. 2014;19(7):687–92.
37. Colin JF, Cazals-Hatem D, Loriot MA, Martinot-Peignoux M, Pham BN, Auperin A, et al. Influence of human immunodeficiency virus infection on chronic hepatitis B in homosexual men. Hepatology. 1999;29(4):1306–10.
38. Konopnicki D, Mocroft A, de Wit S, Antunes F, Ledergerber B, Katlama C, et al. Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. AIDS. 2005;19(6):593–601.
39. Puoti M, Spinetti A, Ghezzi A, Donato F, Zaltron S, Putzolu V, et al. Mortality for liver disease in patients with HIV infection: a cohort study. J Acquir Immune Defic Syndr. 2000;24(3):211–17.
40. Hawkins C, Christian B, Ye J, Nagu T, Aris E, Chalamilla G, et al. Prevalence of

hepatitis B co-infection and response to antiretroviral therapy among HIV-infected patients in Tanzania. AIDS. 2013;27(6):919–27.
41. Wandeler G, Gsponer T, Bihl F, Bernasconi E, Cavassini M, Kovari H, et al. Hepatitis B virus infection is associated with impaired immunological recovery during antiretroviral therapy in the Swiss HIV cohort study. J Infect Dis. 2013;208(9):1454–8.
42. Weber R, Sabin CA, Friis-Moller N, Reiss P, El-Sadr WM, Kirk O, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. Arch Intern Med. 2006;166(15):1632–41.
43. Salmon-Ceron D, Lewden C, Morlat P, Bevilacqua S, Jougla E, Bonnet F, et al. Liver disease as a major cause of death among HIV infected patients: role of hepatitis C and B viruses and alcohol. J Hepatol. 2005;42(6):799–805.
44. Joshi D, O'Grady J, Dieterich D, Gazzard B, Agarwal K. Increasing burden of liver disease in patients with HIV infection. Lancet. 2011;377(9772):1198–209.
45. Thio CL, Seaberg EC, Skolasky R, Phair J, Visscher B, Munoz A, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). Lancet. 2002;360(9349):1921–6.
46. Scharschmidt BF, Held MJ, Hollander HH, Read AE, Lavine JE, Veereman G, et al. Hepatitis B in patients with HIV infection: relationship to AIDS and patient survival. Ann Intern Med. 1992;117(10):837–8.
47. Sinicco A, Raiteri R, Sciandra M, Bertone C, Lingua A, Salassa B, et al. Coinfection and superinfection of hepatitis B virus in patients infected with human immunodeficiency virus: no evidence of faster progression to AIDS. Scand J Infect Dis. 1997;29(2):111–15.
48. Chun HM, Roediger MP, Hullsiek KH, Thio CL, Agan BK, Bradley WP, et al. Hepatitis B virus coinfection negatively impacts HIV outcomes in HIV seroconverters. J Infect Dis. 2012;205(2):185–93.
49. Nikolopoulos GK, Paraskevis D, Hatzitheodorou E, Moschidis Z, Sypsa V, Zavitsanos X, et al. Impact of hepatitis B virus infection on the progression of AIDS and mortality in HIV-infected individuals: a cohort study and meta-analysis. Clin Infect Dis. 2009;48(12):1763–71.
50. Rizzetto M, Canese MG, Arico S, Crivelli O, Trepo C, Bonino F, et al. Immunofluorescence detection of new antigen-antibody system (delta/anti-delta) associated to hepatitis B virus in liver and in serum of HBsAg carriers. Gut. 1977;18(12):997–1003.
51. Hughes SA, Wedemeyer H, Harrison PM. Hepatitis delta virus. Lancet. 2011;378(9785):73–85.
52. Mumtaz K, Hamid SS, Adil S, Afaq A, Islam M, Abid S, et al. Epidemiology and clinical pattern of hepatitis delta virus infection in Pakistan. J Gastroenterol Hepatol. 2005;20(10):1503–7.
53. Zaidi G, Idrees M, Malik FA, Amin I, Shahid M, Younas S, et al. Prevalence of hepatitis delta virus infection among hepatitis B virus surface antigen positive patients circulating in the largest province of Pakistan. Virol J. 2010;7:283.
54. Khan AU, Waqar M, Akram M, Zaib M, Wasim M, Ahmad S, et al. True prevalence of twin HDV-HBV infection in Pakistan: a molecular approach. Virol J. 2011;8:420.
55. Yurdaydin C, Idilman R, Bozkaya H, Bozdayi AM. Natural history and treatment of chronic delta hepatitis. J Viral Hepat. 2010;17(11):749–56.
56. Caredda F, Antinori S, Pastecchia C, Coppin P, Palla M, Ponzetto A, et al. Incidence of hepatitis delta virus infection in acute HBsAg-negative hepatitis. J Infect Dis. 1989;159(5):977–9.
57. Smedile A, Farci P, Verme G, Caredda F, Cargnel A, Caporaso N, et al. Influence of delta infection on severity of hepatitis B. Lancet. 1982;2(8305):945–7.
58. Farci P, Smedile A, Lavarini C, Piantino P, Crivelli O, Caporaso N, et al. Delta hepatitis in inapparent carriers of hepatitis B surface antigen. A disease simulating acute hepatitis B progressive to chronicity. Gastroenterology. 1983;85(3):669–73.

59. Bortolotti F, Di Marco V, Vajro P, Crivellaro C, Zancan L, Nebbia G, et al. Long-term evolution of chronic delta hepatitis in children. J Pediatr. 1993;122(5 Pt 1):736–8.
60. Farci P, Barbera C, Navone C, Bortolotti F, Vajro P, Caporaso N, et al. Infection with the delta agent in children. Gut. 1985;26(1):4–7.
61. Fattovich G, Giustina G, Christensen E, Pantalena M, Zagni I, Realdi G, et al. Influence of hepatitis delta virus infection on morbidity and mortality in compensated cirrhosis type B. The European Concerted Action on Viral Hepatitis (Eurohep). Gut. 2000;46(3):420–6.
62. Pontisso P, Ruvoletto MG, Fattovich G, Chemello L, Gallorini A, Ruol A, et al. Clinical and virological profiles in patients with multiple hepatitis virus infections. Gastroenterology. 1993;105(5):1529–33.
63. Liu CJ, Liou JM, Chen DS, Chen PJ. Natural course and treatment of dual hepatitis B virus and hepatitis C virus infections. J Formos Med Assoc. 2005;104(11):783–91.
64. Potthoff A, Manns MP, Wedemeyer H. Treatment of HBV/HCV coinfection. Expert Opin Pharmacother. 2010;11(6):919–28.
65. Donato F, Boffetta P, Puoti M. A meta-analysis of epidemiological studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma. Int J Cancer. 1998;75(3):347–54.
66. Benvegnu L, Noventa F, Bernardinello E, Pontisso P, Gatta A, Alberti A. Evidence for an association between the aetiology of cirrhosis and pattern of hepatocellular carcinoma development. Gut. 2001;48(1):110–15.
67. Kew MC, Yu MC, Kedda MA, Coppin A, Sarkin A, Hodkinson J. The relative roles of hepatitis B and C viruses in the etiology of hepatocellular carcinoma in southern African blacks. Gastroenterology. 1997;112(1):184–7.

Recommendations for Rapid diagnostic test and non invasive tests

1. WHO Guidelines on hepatitis B and C testing 2016.
2. Goodman ZD. Grading and staging systems for inflammation and fibrosis in chronic liver diseases. J Hepatol. 2007;47(4):598–607.

Antiviral treatment

1. Fung SK, Chae HB, Fontana RJ, Conjeevaram H, Marrero J, Oberhelman K, et al. Virologic response and resistance to adefovir in patients with chronic hepatitis B. J Hepatol. 2006;44(2):283–90.
2. Yim HJ, Hussain M, Liu Y, Wong SN, Fung SK, Lok AS. Evolution of multi-drug resistant hepatitis B virus during sequential therapy. Hepatology. 2006;44(3):703–12.
3. Lee JM, Park JY, Kim do Y, Nguyen T, Hong SP, Kim SO, et al. Long-term adefovir dipivoxil monotherapy for up to 5 years in lamivudine-resistant chronic hepatitis B. Antivir Ther. 2010;15(2):235–41.
4. Lok AS, Lai CL, Leung N, Yao GB, Cui ZY, Schiff ER, et al. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. Gastroenterology. 2003;125(6):1714–22.
5. Allen MI, Deslauriers M, Andrews CW, Tipples GA, Walters KA, Tyrrell DL, et al. Identification and characterization of mutations in hepatitis B virus resistant to lamivudine. Lamivudine Clinical Investigation Group. Hepatology. 1998;27(6):1670–7.
6. Pallier C, Castera L, Soulier A, Hezode C, Nordmann P, Dhumeaux D, et al. Dynamics of hepatitis B virus resistance to lamivudine. J Virol. 2006;80(2):643–53.

Monitoring for Disease progression

1. Dumolard L. Implementation of newborn hepatitis B vaccination - worldwide, 2006. MMWR Morbid Mortal Wkly Rep. 2008;57:1249–52.
2. WHO. Hepatitis B vaccines. Wkly Epidemiol Rec. 2009;84:405–20.

Monitoring for drug toxicity

1. Fernandez-Fernandez B, Montoya-Ferrer A, Sanz AB, Snachez-Nino M, Izquierdo M, Poveda J, et al. Tenofovir nephrotoxicity: 2011 update. AIDS Res Treat. 2011; Article ID 354908:http://dx.doi.org/10.1155/2011/354908.
2. Rule AD. Understanding estimated glomerular filtration rate: implications for identifying chronic kidney disease. Curr Opin Nephrol Hypertens. 2007;16(3):242–9.
3. Rodriguez-Novoa S, Alvarez E, Labarga P, Soriano V. Renal toxicity associated with tenofovir use. Expert Opin Drug Saf. 2010;9(4):545–59.
4. Sax PE, Gallant JE, Klotman PE. Renal safety of tenofovir disoproxil fumarate. AIDS Read. 2007;17(2):90–2, 9–104, C3.
5. Mateo L, Holgado S, Marinoso ML, Perez-Andres R, Bonjoch A, Romeu J, et al. Hypophosphatemic osteomalacia induced by tenofovir in HIV-infected patients. Clin Rheumatol. 2014;May 3. [Epub ahead of print]
6. Bedimo R, Maalouf NM, Zhang S, Drechsler H, Tebas P. Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents. AIDS. 2012;26(7):825–31.
7. Brown TT, McComsey GA, King MS, Qaqish RB, Bernstein BM, da Silva BA. Loss of bone mineral density after antiretroviral therapy initiation, independent of antiretroviral regimen. J Acquir Immune Defic Syndr. 2009;51(5):554–61.
8. Gallant JE, Staszewski S, Pozniak AL, DeJesus E, Suleiman JM, Miller MD, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. J Am Med Assoc. 2004;292(2):191–201.
9. Pradat P, Le Pogam MA, Okon JB, Trolliet P, Miailhes P, Brochier C, et al. Evolution of glomerular filtration rate in HIV-infected, HIV-HBV-coinfected and HBV-infected patients receiving tenofovir disoproxil fumarate. J Viral Hepat. 2013;20(9):650–7.
10. Scherzer R, Estrella M, Li Y, Choi AI, Deeks SG, Grunfeld C, et al. Association of tenofovir exposure with kidney disease risk in HIV infection. AIDS. 2012;26(7):867–75.
11. Tourret J, Deray G, Isnard-Bagnis C. Tenofovir effect on the kidneys of HIV-infected patients: a double-edged sword? J Am Soc Nephrol. 2013;24(10):1519–27.
12. Pushpakom SP, Liptrott NJ, Rodriguez-Novoa S, Labarga P, Soriano V, Albalater M, et al. Genetic variants of ABCC10, a novel tenofovir transporter, are associated with kidney tubular dysfunction. J Infect Dis. 2011;204(1):145–53.
13. Yoshino M, Yagura H, Kushida H, Yonemoto H, Bando H, Ogawa Y, et al. Assessing recovery of renal function after tenofovir disoproxil fumarate discontinuation. J Infect Chemother. 2012;18(2):169–74.
14. Mocroft A, Neuhaus J, Peters L, Ryom L, Bickel M, Grint D, et al. Hepatitis B and C co-infection are independent predictors of progressive kidney disease in HIV-positive, antiretroviral-treated adults. PLoS One. 2012;7(7):e40245.
15. Mweemba A, Zanolini A, Mulenga L, Emge D, Chi BH, Wandeler G, et al. Chronic hepatitis B virus coinfection is associated with renal impairment among Zambian HIV-Infected adults. Clin Infect Dis. 2014;59(12):1757–60.

Monitoring for HCC

1. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095–128.

Coinfections:

1. Hughes SA, Wedemeyer H, Harrison PM. Hepatitis delta virus. Lancet. 2011;378(9785):73–85.
2. Yurdaydin C, Idilman R, Bozkaya H, Bozdayi AM. Natural history and treatment of chronic delta hepatitis. J Viral Hepat. 2010;17(11):749–56.
3. Caredda F, Antinori S, Pastecchia C, Coppin P, Palla M, Ponzetto A, et al. Incidence of hepatitis delta virus infection in acute HBsAg-negative hepatitis. J Infect Dis. 1989;159(5):977–9.
4. Smedile A, Farci P, Verme G, Caredda F, Cargnel A, Caporaso N, et al. Influence of delta infection on severity of hepatitis B. Lancet. 1982;2(8305):945–7.
5. Farci P, Smedile A, Lavarini C, Piantino P, Crivelli O, Caporaso N, et al. Delta hepatitis in inapparent carriers of hepatitis B surface antigen. A disease simulating acute hepatitis B progressive to chronicity. Gastroenterology. 1983;85(3):669–73.
6. Bortolotti F, Di Marco V, Vajro P, Crivellaro C, Zancan L, Nebbia G, et al. Long-term evolution of chronic delta hepatitis in children. J Pediatr. 1993;122(5 Pt 1):736–8.
7. Farci P, Barbera C, Navone C, Bortolotti F, Vajro P, Caporaso N, et al. Infection with the delta agent in children. Gut. 1985;26(1):4–7.
8. Farci P. Treatment of chronic hepatitis D: new advances, old challenges. Hepatology. 2006;44(3):536–9.
9. Pontisso P, Ruvoletto MG, Fattovich G, Chemello L, Gallorini A, Ruol A, et al. Clinical and virological profiles in patients with multiple hepatitis virus infections. Gastroenterology. 1993;105(5):1529–33.
10. Liu CJ, Liou JM, Chen DS, Chen P J.Natural course and treatment of dual hepatitis B virus and hepatitis C virus infections. J Formos Med Assoc Taiwan. 2005;104(11):783–91.
11. Chu CJ, Lee SD. Hepatitis B virus/hepatitis C virus coinfection: epidemiology, clinical features, viral interactions and treatment. J Gastroenterol Hepatol. 2008;23(4):512–20.
12. Getahun H, Gunneberg C, Sculier D, Verster A, Raviglione M. Tuberculosis and HIV in people who inject drugs: evidence for action for tuberculosis, HIV, prison and harm reduction services. Curr Opin HIV AIDS. 2012;7(4):345–53.
13. Getahun H, Baddeley A, Raviglione M. Managing tuberculosis in people who use and inject illicit drugs. Bull World Health Organ. 2013;91(2):154–6.
14. Blal CA, Passos SRL, Horn C, Georg I, Bonecini-Almeida MG, Rolla VC, et al. High prevalence of hepatitis B virus infection among tuberculosis patients with and without HIV in Rio de Janeiro, Brazil. Eur J Clin Microbiol Infect Dis. 2005;24:41–3.
15. Patel PA, Voigt MD. Prevalence and interaction of hepatitis B and latent tuberculosis in Vietnamese immigrants to the United States. Am J Gastroenterol. 2002;97(5):1198–203.
16. Sirinak C, Kittikraisak W, Pinjeesekikul D, Charusuntonsri P, Luanloed P, Srisuwanvilai L, et al. Viral hepatitis and HIV- associated tuberculosis: risk factors and TB treatment outcomes in Thailand. BMC Public Health. 2008;8:245.
17. Padmapriyadarsini C, Chandrabose J, Victor L, Hanna LE, Arunkumar N, Swaminathan S. Hepatitis B or hepatitis C co- infection in individuals infected with human immunodeficiency virus and effect of anti-tuberculosis drugs on liver function. J Postgrad Med. 2006;52:92–6.
18. Hoffmann CJ, Thio CL. Clinical implications of HIV and hepatitis B co-infection in Asia and Africa. Lancet Infect Dis. 2007;7(6):402–9.
19. Easterbrook P, Sands A, Harmanci H. Challenges and priorities in the management of HIV/HBV and HIV/HCV coinfection in resource-limited settings. Semin Liver Dis. 2012;32(2):147–57.

20. Colin JF, Cazals-Hatem D, Loriot MA, Martinot-Peignoux M, Pham BN, Auperin A, et al. Influence of human immunodeficiency virus infection on chronic hepatitis B in homosexual men. Hepatology. 1999;29(4):1306–10.
21. Konopnicki D, Mocroft A, de Wit S, Antunes F, Ledergerber B, Katlama C, et al. Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. AIDS. 2005;19(6):593–601.
22. Puoti M, Spinetti A, Ghezzi A, Donato F, Zaltron S, Putzolu V, et al. Mortality for liver disease in patients with HIV infection: a cohort study. J Acquir Immune Defic Syndr. 2000;24(3):211–17.
23. Hawkins C, Christian B, Ye J, Nagu T, Aris E, Chalamilla G, et al. Prevalence of hepatitis B co-infection and response to antiretroviral therapy among HIV-infected patients in Tanzania. AIDS. 2013;27(6):919–27.
24. Wandeler G, Gsponer T, Bihl F, Bernasconi E, Cavassini M, Kovari H, et al. Hepatitis B virus infection is associated with impaired immunological recovery during antiretroviral therapy in the Swiss HIV cohort study. J Infect Dis. 2013;208(9):1454–8.
25. Zollner B, Petersen J, Puchhammer-Stockl E, Kletzmayr J, Sterneck M, Fischer L, et al. Viral features of lamivudine resistant hepatitis B genotypes A and D. Hepatology. 2004;39(1):42–50.
26. Benhamou Y, Bochet M, Thibault V, Di Martino V, Caumes E, Bricaire F, et al. Long-term incidence of hepatitis B virus resistance to lamivudine in human immunodeficiency virus-infected patients. Hepatology. 1999;30(5):1302–6.
27. Nunez M. Clinical syndromes and consequences of antiretroviral-related hepatotoxicity. Hepatology. 2010;52(3):1143–55.
28. Labarga P, Soriano V, Vispo ME, Pinilla J, Martin-Carbonero L, Castellares C, et al. Hepatotoxicity of antiretroviral drugs is reduced after successful treatment of chronic hepatitis C in HIV-infected patients. J Infect Dis. 2007;196(5):670–6.
29. DeSimone JA, Pomerantz RJ, Babinchak TJ. Inflammatory reactions in HIV-1-infected persons after initiation of highly active antiretroviral therapy. Ann Intern Med. 2000;133(6):447–54.
30. Shelburne SA, 3rd, Hamill RJ, Rodriguez-Barradas MC, Greenberg SB, Atmar RL, Musher DW, et al. Immune reconstitution inflammatory syndrome: emergence of a unique syndrome during highly active antiretroviral therapy. Medicine. 2002;81(3):213–27.
31. Lacombe K, Rockstroh J. HIV and viral hepatitis coinfections: advances and challenges. Gut. 2012;61:47–58.
32. Ni JD, Xiong YZ, Wang XJ, Xiu LC. Does increased hepatitis B vaccination dose lead to a better immune response in HIV- infected patients than standard dose vaccination: a meta-analysis? Int J STD AIDS. 2013;24(2):117–22.
33. Tassopoulos NC, Papaevangelou GJ, Sjogren MH, Roumeliotou-Karayannis A, Gerin JL, Purcell RH. Natural history of acute hepatitis B surface antigen-positive hepatitis in Greek adults. Gastroenterology. 1987;92(6):1844–50.
34. Tillmann HL, Hadem J, Leifeld L, Zachou K, Canbay A, Eisenbach C, et al. Safety and efficacy of lamivudine in patients with severe acute or fulminant hepatitis B, a multicenter experience. J Viral Hepat. 2006;13(4):256–63.
35. Neumann H, Malfertheiner P, Csepregi A. Tenofovir disoproxil fumarate in severe acute hepatitis B. Z Gastroenterol. 2008;46:A74.
36. Tillmann HL, Zachou K, Dalekos GN. Management of severe acute to fulminant hepatitis B: to treat or not to treat or when to treat? Liver Int. 2012;32(4):544–53.
37. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013.