Chronic hepatitis B: Overview of management

- The diagnosis of chronic HBV infection is based upon the persistence of hepatitis B surface antigen (HBsAg) for greater than six months.
- The management of chronic HBV infection is complex and depends upon multiple factors including clinical variables (eg, the presence or absence of liver inflammation and/or cirrhosis), the patient's immunologic response to infection (eg, hepatitis B e antigen status), virologic factors (eg, the HBV viral load and genotype), and risk factors for disease progression (eg, age >40 and family history of hepatocellular carcinoma).

Initial evaluation

1. History and physical examination*
2. Family history of HBV infection, liver disease, HCC
3. Laboratory tests to assess liver disease - complete blood counts with platelets, aminotransferase levels, total bilirubin, alkaline phosphatase, albumin, and INR
4. Tests for HBV replication - HBeAg, anti-HBe, HBV DNA
5. Tests to rule out viral coinfections - anti-HCV, anti-HDV (in persons from countries where HDV infection is common and in those with history of injection drug use), and anti-HIV[¶]
6. Tests to screen for HCC[Δ] - (eg, ultrasound)
7. Tests to screen for fibrosis[◊] - vibration-controlled transient elastography, serum fibrosis panel, or liver biopsy[§]

Indications for antiviral therapy

- **HBeAg-positive (immune active phase):**

  -For HBeAg-positive patients without cirrhosis, treatment should be initiated when the HBV DNA is >20,000 international units/mL (>105 copies/mL) and the ALT is >2 x ULN .

  -The ULN should be considered 30 U/L for males and 19 U/L for females; these levels should be used rather than individual laboratory cut-off levels.

  -Treatment should be delayed for three to six months in newly diagnosed HBeAg-positive patients with compensated liver disease to determine whether spontaneous HBeAg seroconversion will occur

- Patients with chronic hepatitis whose serum ALT is persistently below 2 X ULN can be observed, considering treatment if and when the serum ALTbecomes higher **. Exceptions to this rule include**:
  - those who have recurrent hepatitis flares that fail to clear HBeAg,
  -patients with icteric flares,
  - active or advanced histologic findings (such as moderate/ severe inflammation or bridging brosis/cirrhosis)
  -paitents with extrahepatic manifestations (eg, HBV-related polyarteritis nodosa),
  -patients above the age of 40 who remain HBeAg-positive with persistently high HBV DNA levels,
  -family history of hepatocellular carcinoma
  -health care providers performing exposure-prone procedures .

- **HBeAg-negative chronic hepatitis:**
  -Treatment may be initiated immediately once a diagnosis of HBeAg-negative chronic hepatitis (ALT >2 x ULN and HBV DNA >2000 international units/mL) is established because sustained remission is rare in the absence of treatment.
  -For those with an ALT <1 x ULN, serial follow-up is needed to differentiate an inactive carrier state from HBeAg-negative chronic hepatitis because of the fluctuating course of HBeAg-negative chronic hepatitis.
  -Patients with low HBsAg levels (<1000 international units/mL) are more likely to be in the inactive phase than those with higher HBsAg levels.
  - Liver biopsy should be considered in HBeAg-negative patients who have serum HBV DNA levels >2000 international units/mL and mildly elevated ALT (<2 x ULN) to determine if treatment is warranted.

- **Cirrhosis :**

  -Patients with compensated cirrhosis and an HBV DNA >2000 international units/mL (>104 copies/mL) should be treated with antiviral therapy regardless of the HBeAg status or the serum ALT level . Treatment should be considered even if HBV DNA levels are lower than 2000 international units/mL,particularly if ALT elevated.

  -Patients with decompensated cirrhosis and a detectable HBV DNA by polymerase chain reaction (PCR) assay (regardless of the ALT level. Such patients should also be evaluated for liver transplant

- **Pregnant women:**

  -For pregnant women, the indications for antiviral therapy are generally the same as those for patients who are not pregnant. However, women with high viral loads (>2 x 105 international units/mL) should initiate therapy in the third trimester, even if the aminotransferase levels are normal, to prevent transmission to their child.

- **Patients with hepatocellular carcinoma**
- **Patients with hepatitis C coinfection**

Overview of antiviral agents

- **Interferon:**

  -The main role of interferon is primarily treatment of young patients with well compensated liver disease who do not wish to be on long-term treatment.

  -The advantages of interferon compared to nucleos(t)ide analogues are its finite duration of treatment, the absence of selection of resistant variants, and a more durable response. On the other hand, side effects from interferon are troubling for many patients,. Furthermore, interferon should not be used in pregnant women and patients with decompensated disease or compensated cirrhosis and portal hypertension.

  -Interferon alfa is administered by subcutaneous injection. The preferred formulation is peginterferon alfa-2a, which should be administered as 180mcg once weekly for 48 weeks for HBeAg-positive or HBeAg-negative chronic HBV . Standard interferon should be used **only if PegIFN and**nucleos(t)ide analogues are not available.

Nucleos(t)ide analogues

- **Entecavir:**

  -The main advantages of entecavir are its potent antiviral activity and low rate of drug resistance in patients who are nucleos(t)ide-naïve (approximately 1 percent with up to five years of treatment). However, entecavir should **not be used for patients with** lamivudine-resistant HBV, since resistance has been observed in up to 50 percent of lamivudine-refractory patients after five years of treatment.

  - Entecavir is administered orally. The dose should be adjusted for patients with reduced kidney function . For nucleoside-naïve adults and adolescents older than 16, the recommended dose is 0.5 mg once daily. The dose should be increased to 1 mg daily for those with decompensated liver disease. The dose should also be increased to 1 mg daily if it is used for patients who have been treated with lamivudine in the past; however, for such patients, tenofovir is preferred.

Tenofovir:

-Tenofovir can be used as first-line therapy in treatment-naïve patients and also in those who have had prior exposure, or developed drug resistance, to other nucleos(t)ide analogues (eg, lamivudine). In clinical trials of patients receiving tenofovir disoproxil fumarate, no signature mutation for tenofovir resistance has been identified, even among those who have been treated for up to eight years.

-There are two formulations of tenofovir, tenofovir disoproxil fumarate and tenofovir alafenamide. For most patients, we recommend tenofovir alafenamide (25 mg daily) rather than tenofovir disoproxil fumarate (300 mg daily), if available. For those who were originally started on tenofovir disoproxil fumarate, generally suggest switching to tenofovir alafenamide, particularly in older patients and those with risk factors for renal impairment or osteoporosis.

- **Lamivudine :**

-The main advantages of lamivudine are its lower cost compared with the other oral agents and the many years of experience confirming its safety. However, the role of lamivudine in the care of patients with chronic HBV is diminishing given the high rate of drug resistance and the availability of new therapies, such as entecavir and tenofovir, which are associated with lower rates of resistance. The recommended dose of lamivudine for adults with normal renal function without concomitant HIV infection is 100 mg daily.

- **Adefovir :**

  The most important role of adefovir is in the treatment of patients with lamivudine-resistant HBV, preferably in combination with other agents. However, this role has been replaced by tenofovir, which is more potent and effective when used as monotherapy. If used, adefovir is administered orally, and the dose is 10 mg daily. Patients with impaired renal function should have the dosing interval adjusted

. **Telbivudine:** is administered orally. The recommended dose is 600 mg once daily. Dose should be adjusted in patients with impaired renal function.

Telbivudine appears to have slightly more potent antiviral effects compared with lamivudine and adefovir. generally do not recommend this agent given the increased risk of drug resistance and other adverse events (eg, myopathy and peripheral neuropathy).

Choice of initial agent

- **Pregnancy** : For pregnant women who require treatment, we prefer tenofovir disoproxil fumarate rather than other antiviral agents.
- **Patients without cirrhosis:** Pegylated interferon, tenofovir, and entecavir are the preferred agents for treatment-naïve patients without cirrhosis.
- **Patients with cirrhosis** : In patients with clinically compensated cirrhosis, we generally administer entecavir or tenofovir (tenofovir alafenamide or tenofovir disoproxil fumarate). Although interferon may be used with caution in patients with compensated cirrhosis,but in patients with decompensated cirrhosis, interferon is **contraindicated.** monotherapy with lamivudine, adefovir, or telbivudine should be avoid due to high risk of developing resistance with long-term use, and in the case of adefovir, its weak antiviral activity.

Monitoring on therapy

- HBV DNA every three months until undetectable for at least two consecutive visits. We then decrease the frequency to every six months.
- Aminotransferases every three months. The frequency can be decreased to every six months in patients with an undetectable HBV DNA or normalized ALT.
- HBeAg and antibody to HBeAg (anti-HBe) every six months in patients who are HBeAg-positive to determine if seroconversion has occurred. If HBeAg seroconversion has occurred, we repeat the HBeAg and anti-HBe to confirm the result.
- HBsAg should be tested yearly.
- In addition, we monitor for adverse reactions to the antiviral medications. If tenofovir disoproxil fumarate or adefovir are used, creatinine and phosphate should be monitored every three to six months.

Duration and treatment endpoints

- **HBeAg-negative chronic hepatitis** :
  Treatment may be discontinued in patients with HBeAg-negative hepatitis who have confirmed loss of HBsAg (by testing on two occasions at least six months apart) However, only a small minority of patients (approximately 5 percent) lose HBsAg after five years of continued therapy.
- **HBeAg-positive chronic hepatitis** :
  The endpoint of treatment for HBeAg-positive patients is HBeAg seroconversion (ie, HBeAgundetectable and the development of hepatitis B e antibodies confirmed by testing on two occasions at least two months apart). Treatment should be continued for at least 12 more months to reduce the rate of relapse after HBeAg seroconversion has been confirmed

- **Patients with cirrhosis:**

  -For patients with cirrhosis, lifelong therapy with oral agents is typically administered to reduce the risk of clinical decompensation if a relapse occurs. Therapy should be continued even with those who are HBeAg-positive and have seroconverted to anti-HBe on nucleos(t)ide therapy, as well as those with decompensated cirrhosis who have resolution of cirrhosis complications on treatment.

  -Although it is possible that treatment may be discontinued in those with compensated cirrhosis who have lost HBsAg, or those who have documentation of cirrhosis regression by histology or noninvasive assessment of liver fibrosis.

Persistent viremia/breakthrough infection

- **After interferon therapy:**

  Patients who failed to respond to interferon therapy (ie, failure to achieve HBeAg seroconversion six months post-treatment for HBeAg-positive patients or failure to achieve HBV DNA <2000 international units/mL six months post-treatment for HBeAg-negative patients) can be treated with any of the nucleos(t)ide analogs with the expectation of a similar response as treatment-naïve patients.

- **While receiving tenofovir or entecavir:**
  - For patients who remain viremic after 96 weeks, or have breakthrough infection (an increase in serum HBV DNA by >1 log10 [10-fold] from nadir or after HBV had been undetectable), we verify medication adherence since tenofovir- or entecavir-resistant virus rarely occurs in treatment naïve patients.
  - In patients who are adherent, we do not modify our therapy if there is persistent viremia as long as the HBV DNA levels are low (ie, <200 international units/mL) and continue to decrease
  - For those failing entecavir, we add tenofovir until the HBV DNA becomes undetectable; at that point, we discontinue entecavir and treat with tenofovir alone.

- **While receiving other nucleos(t)ide analogues:**
  - Although nucleos(t)ide analogues with a low barrier to resistance (eg, lamivudine, adefovir, or telbivudine) are not generally recommended for initial therapy, these agents are sometimes used in settings where cost is a consideration. Patients receiving these agents should be switched to tenofovir if the HBV DNA remains >4 log10 international units/mL after 12 months or the patients develop confirmed breakthrough infection (an increase in serum HBV DNA by >1 log10 [10-fold] from nadir or >2 log10 international units/mL after HBV had been undetectable).
  - Tenofovir monotherapy is effective in suppressing HBV replication in patients who have lamivudine-, telbivudine-, or adefovir-resistant virus. By contrast, there is a high risk of entecavir resistance developing in patients with pre-existing drug-resistant virus after lamivudine or telbivudine treatment