

# RECOMMENDATIONS FOR THE DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH CHRONIC HEPATITIS B INFECTION

## Definition

### Diagnosis of chronic hepatitis B infection

Chronic hepatitis B (CHB) infection is defined as positivity for hepatitis B surface antigen (HBsAg) for a period of at least six months.

### Evaluation

The following guidelines are suggested for the evaluation of persons identified as chronic hepatitis B carriers. Initial testing includes: LFT (liver function tests), including ALT, AST, alkaline phosphatase, bilirubin albumin and GGTP; AFP (alpha-fetoprotein), prothrombin time/INR, CBC, glucose, hepatitis B e antigen (HBeAg), antibody to hepatitis B e antigen (anti-HBe), HBV DNA quantitative level

### Routine follow-up of chronic hepatitis B carriers

1. Screen for hepatocellular carcinoma (**HCC**) with alpha-fetoprotein (**AFP**, a tumor marker) every 6 months. If **AFP**:
  - a. Is elevated  $\geq 10$ , do a liver ultrasound (**U/S**) with **AFP** every 3 months as long as AFP level continues to rise.
  - b. Remains  $\geq 10$  but stable (no longer rising) with normal **U/S**, continue **AFP** with **U/S** q 6 mo.
  - c. Was elevated (with normal **U/S**) but then drops  $< 10$ , return to 6 mo. monitoring of **AFP only**.
  - d. Is elevated and person is pregnant, high levels may be due to the pregnancy but **AFP** still needs repeating at the 6 week post partum check-up. (AFP should fall to normal by 6 weeks after birth.)
2. Do liver AFP and, if possible, U/S every 6 months also in high risk patients including:
  - a. Carriers with a family history of HCC
  - b. Carriers with cirrhosis
  - c. Male carriers  $> 40$  years old and females  $> 50$  years old.

- Consider a Hepatitis Clinic consult with any **AFP** elevation  $\geq 10$ , especially if a new finding. Even when the **U/S** is normal, the patient is at high risk for **HCC** or may have cirrhosis and may need further studies including a liver **CT and possible biopsy**.*
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3. Screen with **liver function tests** every 6 to 12 months, evaluating all new elevations.
  - Test for **HBsAg**, **HBeAg** (antigen) and **anti-HBe** (antibody) every 6 months to 12 months
  - In persons with elevated ALT or AST (>40 IU/ml), test for HBV DNA
  - In patients over age 40 years, test for HBV DNA in women with ALT >20 and men with ALT > 30

## Vaccine Guidelines

### Hepatitis A Vaccine:

Recommend 2 doses, 6 -18 months apart, to protect the liver in those with a negative HAV-Total (formerly anti-HAV IgG).

### Hepatitis B Vaccine recommendations for infants born to hepatitis B carrier mothers:

- Give a dose of hepatitis B vaccine within 12 hours of birth.

(This reduces the chance of hepatitis B carrier state in the child.)
- Complete the 3-dose vaccine series and
- Draw anti-HBs level when the child is 12-15 months old to verify protection against hepatitis B.
  
- **HBIG** (*Hepatitis B Immune Globulin*) may also be given with the hepatitis B vaccine at birth, especially if mom is **HBeAg positive**.

## Evaluation for treatment with antiviral therapy

Based on studies in Alaska Native people, >90% of carriers who are HBeAg + will clear HBeAg and HBV DNA by quantitative assays within 10 years without antiviral therapy. However, based on follow-up studies in Alaska Native people, 10%-20% of these carriers will have one or more reversions back to HBeAg+ with concomitant exacerbation of liver disease that could lead to scarring. In addition, 10%-25% of persons who have cleared HBeAg will have high levels of HBV DNA and elevated liver transaminase levels, which may represent active, ongoing liver disease. Some carriers with low levels of DNA will have exacerbation of hepatitis characterized by elevated ALT and HBV DNA level > 2,000 IU/ml ( $10^4$  copies/ml). This is why all carriers need at least yearly testing for HBeAg and anti-HBeAg as well as 6-12 month testing of ALT and AST. Sera drawn in the Bush if spun down in a couple of hours can be used for ALT/AST testing, as under these circumstances the enzymes are stable over time.

Candidates for Antiviral Therapy include all of the following:

1. HBV DNA > 2,000 IU/ml\*
2. HBeAg/ anti-HBe status
  - a. HBeAg positive: ALT > twice upper limit of normal
    - i. Wait 6-12 months if liver disease compensated to see if spontaneous seroconversion to anti-HBe occurs
    - ii. Treat immediately if liver disease decompensated
    - iii. In persons > 40 years with ALT < twice upper limit of normal do liver biopsy and treat if moderate or severe hepatitis and/or moderate or severe fibrosis.
  - b. HBeAg negative/anti-HBe positive:
    - i. If ALT elevated > 40, do liver biopsy and treat if moderate or severe hepatitis and/or moderate or severe fibrosis.
    - ii. In patients over 40 years of age with ALT between 30-40 U/L in men and 20-40 U/L in women, do liver biopsy and treat if moderate or severe hepatitis and/or moderate or severe fibrosis.
3. Elevated ALT (see above)
4. Liver Biopsy showing moderate or severe hepatitis and moderate or severe fibrosis

Persons with persistently elevated ALT levels should be evaluated as follows:

1. Complete liver function tests, CBC, prothrombin time/INR.
2. anti-HCV.
3. HBV DNA quantitative level.
4. Percutaneous liver biopsy

### **Current Available Licensed Antiviral Agents Approved for Treatment of Chronic Hepatitis B**

Approved for Adults:

1. Alfa-2 Interferon : Both Regular (2a and 2b) and Pegylated (2a)
2. Lamivudine
3. Adefovir
4. Entecavir
5. Telbivudine
6. Tenofovir DP

Approved for Children < 18 years:

1. Alfa-2 Interferon: Regular
2. Lamivudine

### **Currently Licensed Antiviral Agents not yet approved for HBV but Effective**

1. Emtricitabine
2. Combination Emtricitabine and Tenofovir DF (Truvada®)

Duration of Treatment:

1. HBeAg-positive CHB:
  - a. 6-12 months pegylated Alfa-2a interferon or
  - b. Nucleoside/Nucleotide analogue until 6-12 months after HBeAg clearance and appearance of anti-HBe occurs.
2. HBeAg-negative (anti-HBe positive) CHB.
  - a. 1 year of pegylated alfa-2a interferon (success rate only 20%-30%)
  - b. Nucleoside/Nucleotide analogue indefinitely

## **Interferon Therapy**

**The best candidates for interferon therapy are those who meet the following criteria**

ALT greater than 2.0 times the upper limits of normal

HBeAg - positive

Level of HBV DNA that is >20,000 IU/ml (100,000 copies/ml)

Biopsies showing moderate chronic active hepatitis (Hepatic Activity Index > 8) and moderate to severe fibrosis (Knodell 3, 4 or Ishak 4-6)

Dose of Interferon:

1. HBeAg-positive Chronic Hepatitis B
  - a. Regular interferon 5 million units (mu) daily or 10 mu 3 times/week for 16 weeks or
  - b. Pegylated alpha-2a 180 ug weekly for 1 year (preferred)
2. HBeAg-negative Chronic Hepatitis B
  - a. Regular interferon 5 million units (mu) daily or 10 mu 3 times/week for 6 months to 1 year or
  - b. Pegylated alpha-2a 180 ug weekly for 1 year (preferred)

## **Nucleoside/Nucleotide Analogue Antiviral Drugs for Treatment of HBV**

### **FDA Approved for HBV**

#### **Lamivudine**

- 1) Lamivudine: Approved for the treatment of Hepatitis B at a dose of 100mg/day, lamivudine is a potent inhibitor of HBV and in almost all patients treated there is an immediate and dramatic fall in HBV DNA. This drug has few side effects. However, 10%-20% of treated patients per year develop resistance to lamivudine and resistance increases to 70% at 4 years.

## **Adefovir Dipivoxil**

Adefovir is active against HBV wild type and the lamivudine YMDD mutant strain. It is 5 times expensive as and less potent than lamivudine as 20%-30% of patients fail to respond to treatment. It can be used as first line therapy and in persons who develop Lamivudine resistance. A reversible rise in creatinine or phosphorous occurs in 1%-2% of treated persons and must be monitored.

## **Entecavir**

Entecavir is more potent than either lamivudine or adefovir and in persons who have never been treated before. Resistance has not been reported after 2 years of therapy (but resistance occurs in persons who became resistant to lamivudine). The drug is 6 times as expensive as lamivudine.

## **Telbivudine**

Telbivudine is structurally related and in the same class as lamivudine but more potent. Resistance, however, occurs at about half the rate as lamivudine, 10%-12%/year. The drug is considerably more expensive than lamivudine and its role for treatment of HBV is limited.

## **Tenofovir**

Tenofovir is a nucleotide analogue licensed for HIV therapy with a relatively safe side effect profile. Tenofovir is a potent inhibitor of HBV DNA. Resistance to tenofovir appears to be very low.

## **Other Medications Licensed but not Yet Approved for HBV**

### **Emtricitabine**

Emtricitabine is similar to lamivudine and telbivudine but more potent. It has the same problem with resistance as the other two drugs.

### **Truvada**

Truvada is the combination of Tenofovir and Emtricitabine

## **First Line Drugs for Treating HBV in Persons Naïve to Previous Nucleoside/Nucleotide Analogue Drugs**

**Alpha-Interferons:** The Interferons are more successful when used in HBeAg positive persons. Resistance to Interferons does not occur. The disadvantages are very high cost, significant side effects and 70% do not respond in one year.

**Entecavir:** Entecavir has the advantage of high potency and very low resistance profile. However it is the most expensive oral drug for HBV

**Tenofovir:** Tenofovir has high potency and a high level against resistance. It is less expensive than Entecavir or interferons. Patients on tenofovir should be monitored for creatinine and phosphorous every 6 months

## **Second Line Drugs for Treatment of HBV**

**Lamivudine:** Could be used in

1. HBeAg-positive persons with ALT levels above 5 times upper limits of normal where chance of HBeAg seroconversion to anti-HBe is high.
2. Anti-HBe positive persons with lower levels of HBV DNA (2,000 to 20,000 IU/ml) where risk of resistance is much lower
3. As chemoprophylaxis for persons undergoing cancer chemotherapy, prolonged high dose corticosteroid therapy or anti-TNF agent therapy for rheumatoid arthritis, inflammatory bowel disease or other conditions.
4. In post liver transplant setting along with HBIG

**Emtricitabine:** Same as 1) and 2) above for lamivudine.

**Telbivudine:** Same as 1) and 2) above for lamivudine.

**Adefovir:** Adefovir is less potent but has a low level of resistance at 1 year. Disadvantage is that 30% fail adefovir in first 6 months (less than 1-2 log drop in HBV DNA levels) and resistance increases significantly after the first year but is still less than lamivudine, telbivudine and emtricitabine. Adefovir should be stopped and another drug used if response is not adequate in 6 months.

## Management of Patients on Oral Nucleosides/Nucleotides

Patients on oral nucleosides/nucleotides should be followed periodically with HBV DNA levels and ALT/AST determinations. Every 3 to 4 months for the first year seems reasonable. Thereafter, if HBV DNA levels are negative, test every 6 months.

### Lamivudine

1. ALT, AST and HBV DNA every 3 months. Suspect resistance to Lamivudine if:
  - a. HBV DNA fails to fall > 2 logs 3 months after initiating therapy
  - b. After initial fall of HBV DNA, subsequent level of HBV DNA rises > 1 log

\*If resistance is suspected, send sera to ANMC molecular biology lab to test for resistance to lamivudine.
2. If resistance occurs:
  - a. Add adefovir and continue lamivudine as combination. Both drugs should be continued indefinitely to prevent resistance from adefovir from occurring and because lamivudine is more potent against wild type HBV than adefovir. Wild type HBV will reemerge if lamivudine is stopped.
  - b. Or switch to entecavir
  - c. Tenofovir or Truvada may also be used as an alternative.

### Adefovir

1. ALT, AST, BUN, creatinine, phosphorous and HBV DNA every 3 months
  - a. If HBV DNA levels fail to fall by at least 2 logs, the drug is not effective. Switch to another drug (entecavir).
  - b. After initial fall of HBV DNA, if subsequent level of HBV DNA rises > 1 log, suspect adefovir resistance and send blood to ANMC for testing for adefovir resistance.
  - c. If resistance has occurred, add lamivudine or telbivudine (if patient has never previously been treated with lamivudine or telbivudine) or switch to either entecavir or Truvada.
  - d. If serum creatinine has risen above 0.5 X baseline or phosphorous has fallen below normal level, repeat these tests in one month and consider stopping adefovir and using another drug if abnormalities persist.

## **Entecavir**

1. Resistance is < 1% in patients naïve to all oral nucleoside analogues during the first 2 years of follow-up
2. If resistance occurs, switch to tenofovir or Truvada

**Tenofovir:** ALT, AST, BUN, creatinine, phosphorous and HBV DNA every 3 months for 1<sup>st</sup> year then every 3-6 months

1. If HBV DNA levels fail to fall by at least 2 logs, the drug is not effective. Switch to another drug (entecavir).
2. After initial fall of HBV DNA, if subsequent level of HBV DNA rises > 1 log, suspect adefovir resistance and send blood to ANMC for testing for resistance.
3. If resistance has occurred, add lamivudine or telbivudine (if patient has never previously been treated with lamivudine or telbivudine) or switch to either entecavir or Truvada.
4. If serum creatinine has risen above 0.5 X baseline or phosphorous has fallen below normal level, repeat these tests in one month and consider stopping adefovir and using another drug if abnormalities persist.

## **Treatment of HBV and HIV co-infection**

### **Treatment of HBV Only**

Pegylated Interferon or Adefovir

### **Treatment of HIV and HBV in Patients Naïve to Nucleoside/Nucleotide Analogues**

Agents effective against both viruses should be selected \*

Emtricitabine plus Tenofovir DF (Truvada®)

Lamivudine plus Tenofovir

### **Treatment of HIV and HBV in Patients with HBV resistance to Lamivudine or both Lamivudine and Adefovir**

Resistant to lamivudine only: Tenofovir DF included in HAART regime

Resistant to both drugs: Entecavir added to HAART regime

\* HIV infection should never be treated alone in co-infected patients without consideration for HBV therapy.

**The education and public health aspects of managing chronic HBsAg positive carriers:**

Household and sexual contacts of HBsAg-positive carriers should be screened for HBV markers and those persons who are seronegative should be offered hepatitis B vaccine.

HBsAg-positive carriers should be cautioned to practice barrier protection when having sexual intercourse with a person whose HBV status is unknown or who has not received hepatitis B vaccine.

HBsAg-positive carriers should be educated as to the lifetime risk of developing hepatocellular carcinoma and urged to have appropriate screening for HCC at least biannually.

HBsAg-positive carriers should be given educational materials on the carrier state such as that supplied by the **American Liver Foundation**.