

Chronic Hepatitis B

Care & Treatment Issues for Newly Diagnosed People

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Hepatitis B (HBV)

- Hepatitis B virus itself does not harm the liver, instead, liver damage is caused by the body's immune system attacking infected liver cells.
- HBV disease is a battle between the virus and the immune system, with the liver as the battle ground.
- This adverse relationship between HBV and the immune response fluctuates, goes through different stages, and can progress or reverse.
- Chronic HBV is complex and our knowledge about disease progression and treatment strategies are still evolving.

Hepatitis B (HBV) Roadmap

- Acute Infection & Spontaneous Clearance
- Chronic HBV Disease
- Diagnostics
- Stages of Chronic HBV
- Current Treatment Recommendations
- HBV Treatment & Responses

Acute HBV Infection

- Most acute infection in infants and young children have no symptoms.
- 30-50% of acutely infected adults may have symptoms:
 - nausea, vomiting, appetite loss, fever, fatigue, abdominal and joint pain, liver swelling, & jaundice.
- Symptoms range from mild to severe, fatal cases are extremely rare. Resolved after 3-6 months.
- Normally no treatment is needed during acute infection.

Spontaneous HBV Clearance

- The immune system can sometimes fight off HBV by itself without treatment.
- Infants and children have immature immune systems – 90% will develop chronic HBV.
- Most healthy adults can clear HBV without treatment – only 6% will develop chronic HBV.
- 30-90% of HIV positive people will develop chronic HBV.

Chronic HBV Infection

HBV Surface Antigen (HBsAg)

- **HBsAg** are viral proteins on the surface of hepatitis B virus, indicating the presence of HBV in the blood. It is a part of initial screening panel for HBV.
- **HBsAg negative** result in six months means spontaneous clearance has occurred, with protection against future infections by antibodies (HBsAb).
- A second **HBsAg positive** result in six months defines chronic (lifelong) HBV infection.

Chronic HBV Disease

- Chronic HBV is a slow progressing and fluctuating disease, can go through many years or decades of ups and downs, silently causing liver damage, usually with no symptoms.
- Can also remain inactive lifelong—not everyone will need treatment.
- Between **15-40%** of people with chronic HBV will develop serious liver disease:
 - Cirrhosis
 - Liver Cancer (HCC)
 - Liver failure

Progression Cofactors

More likely to progress:

- Family history of liver disease
- Male gender
- Older age (longer infection)
- Alcohol consumption
- HBV genotype C
- Coinfection with HIV, HCV, and/or HDV

Can Chronic HBV be Cured?

- Current treatment cannot eradicate HBV
- HBV deposits its genetic material, covalently closed circular DNA (cccDNA), into the nucleus of infected liver cells, a relatively stable reservoir.
- HBV can reactivate once therapy is stopped.
- Majority of chronically infected people likely need lifelong therapy to maintain viral suppression.

HBV Diagnostics

Diagnostics can assess:

- Viral activity
- Level of immune response
- Health of the liver
- Phases of chronic HBV

Knowing what these results mean can help people better understand chronic HBV disease.

HBV Diagnostics 1

HBV DNA (viral load)

- This test measures the amount of virus in the blood, indicating the level of viral activity.
- Having a high viral load in early phase of chronic HBV doesn't always mean the liver is being damaged.
- Persistently low or fluctuating viral loads in late stage of chronic HBV can signal trouble.
- People with higher viral loads are at greater risk for serious liver disease in the long run.
- Controlling viral load is one major goal of treatment.

HBV Diagnostics 2

Liver Enzyme Test (ALT)

- ALT (alanine aminotransferase) is an enzyme secreted by the liver cell when it is inflamed, indicating immune response.
- ALT level fluctuates and it's not a very accurate indicator of liver health. A single normal result doesn't mean there are no liver damage, needs to be regularly monitored.
- 24% of people with normal ALT has stage 2-4 fibrosis on liver biopsy.
- ALT >1 to 2 times upper limits of normal at high risk for disease progression.
- Normalization of ALT is another main goal of treatment.

HBV Diagnostics 3

Liver Biopsy

- More accurate than ALT in assessing liver damage.
- Most useful for people who don't meet clear cut guidelines for treatment.
- Help establish disease baseline.
- More important for people over 40 with persistent ALT slightly above normal.

HBV Diagnostics 4

HBV "e" Antigen (HBeAg)

- HBeAg are viral particles secreted by HBV infected liver cells during viral replication in early phase of chronic HBV infection.
- But HBV mutates (Pre-core & Basal Core mutations) over time in some people, and will no longer produce HBeAg during viral replication in later phase of chronic infection.
 - **HBeAg Positive** = Earlier phase of chronic HBV
 - **HBeAg Negative** = Later phase of chronic HBV

Monitor or Treat?

Information provided by these diagnostic tests can distinguish stages of chronic disease and help guide treatment decisions.

- **When to monitor with no treatment**
- **When to start treatment**

Recommendations here are from the American Association of the Study of Liver Diseases: AASLD Practice guidelines: Chronic Hepatitis B, 2007

4 Stages of Chronic HBV

STAGE 1: Immune Tolerant

Early in chronic HBV. The virus is replicating but the immune system does not recognize infection, no immune activation and no inflammation. This stage is characterized by:

- **HBeAg Positive**
- **HBV DNA > 20,000 IU/ml** (100,000 copies/ml)
- **Normal ALT**
(ALT ULN: Upper Limits of Normal = 30U/l for men, 19U/l for women)

Recommendation:

1. **No treatment**
 - Monitor every 3-6 months for elevated ALT
 - If no change after one year, Monitor every 6-12 month
2. If persistent elevated ALT, move to stage 2.

4 Stages of Chronic HBV

STAGE 2: Immune Clearance

Immune system activates and starts attacking infected liver cells to get rid of HBV, causing inflammation. This stage is characterized by:

- **HBeAg Positive**
- **HBV DNA > 20,000 IU/ml** (100,000 copies/ml)
- **Elevated ALT but < 2X ULN**
(ALT ULN: Upper Limits of Normal = 30U/l for men, 19U/l for women)

Recommendation:

1. **No Treatment**, monitor 3-6 months and check for spontaneous clearance (HBeAg negative, normal ALT, undetectable HBV DNA).
2. **Consider biopsy** if persistent ALT 1-2X ULN if age > 40
3. **Start treatment** if persistent ALT > 2X ULN or biopsy shows moderate/severe inflammation or significant fibrosis.

4 Stages of Chronic HBV

STAGE 3: Inactive Carrier

HBV develops mutation, HBeAg no longer detectable. Low viral replication and minimal immune activation. This stage is characterized by:

- **HBeAg Negative**
- **HBV DNA \leq 2,000 IU/ml** (10,000 copies/ml)
- **Normal ALT**

Recommendation:

1. **No Treatment**, monitor every 3 months, if no change after one year, monitor every 6-12 months.
2. **Consider biopsy and treatment** if HBV DNA 2,000–20,000 IU/ml and ALT 1- 2X ULN
3. **Start treatment** if biopsy shows moderate/severe inflammation or significant fibrosis.

4 Stages of Chronic HBV

STAGE 4: Reactivation

HBV is reactivated, triggering immune response and causing liver inflammation. This stage is characterized by:

- **HBeAg Negative**
- **HBV DNA > 20,000 IU/ml** (100,000 copies/ml)
- **ALT > 2X ULN**
(ALT ULN: Upper Limits of Normal = 30U/l for men, 19U/l for women)

Recommendation:

- **Start treatment**

Treatment for Chronic HBV

Chronic HBV cannot be totally “**cure**” with currently available treatment. Viral DNA hides inside liver cells and can reactivate.

- Some people who are **HBeAg positive** can successfully stop treatment 6-12 months after undetectable viral load (with continue monitoring).
- Most people who are **HBeAg negative** will need to stay on treatment indefinitely, HBV will reactivate if stopped.

Main treatment goals are:

- Sustained HBV suppression (undetectable viral load).
- Remission of liver disease (normal ALT).
- Prevent progression to liver cirrhosis, cancer, or failure.

Treatment for Chronic HBV

There are two types of FDA approved HBV treatment:

1. **Interferon (1992) & Pegylated Interferon/Pegasys (2005)** - \$2,256.68/month
2. **Oral Antivirals**
 - Lamivudine/Epivir-HBV (1998) - \$339.24/month
 - Adefovir/Hepsera (2002) - \$753.68/month
 - Entecavir/Baraclude (2005) - \$779.98/month
 - Telbivudine/Tyzeka (2006) - \$633.22/month
 - Tenofovir/Viread (2008) - \$621.49/month

*Prices from DrugStore.com accessed 9/26/08

Pegylated Interferon

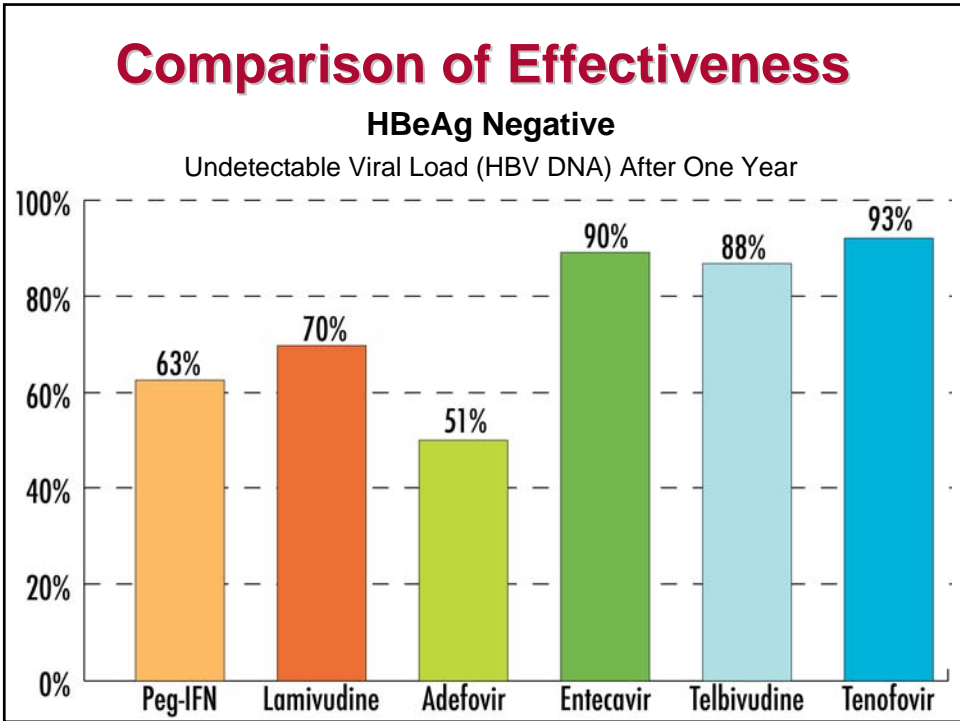
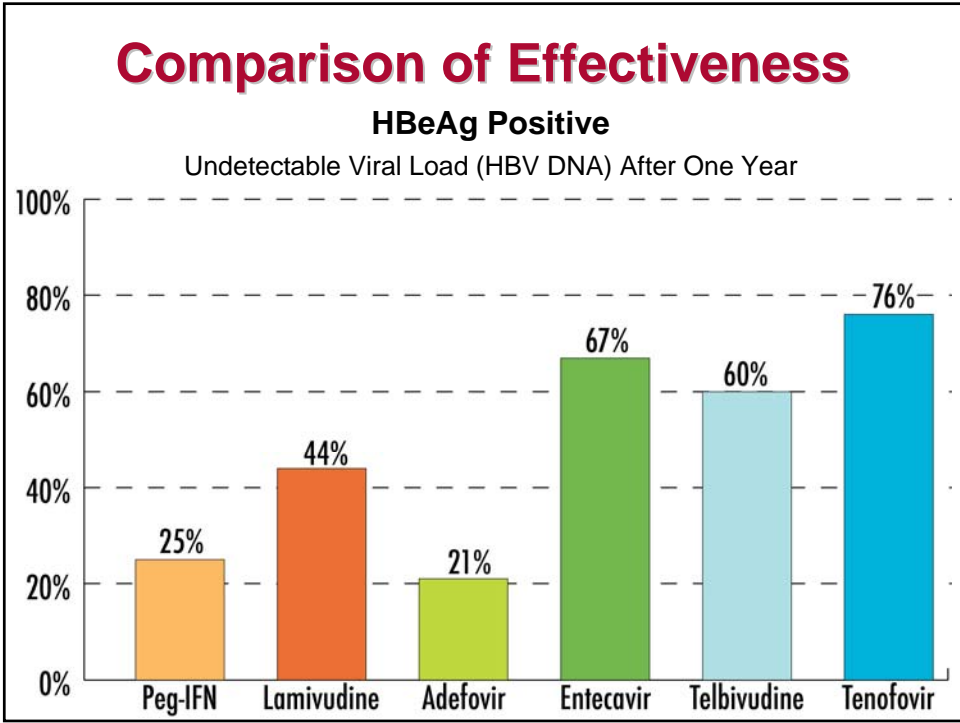
- **PROS:** Treatment only for one year. Better durability post treatment.
- **CONS:** Severe side-effects & lack of efficacy in viral suppression.
- Currently recommended as first-line treatment option for both HBeAg positive and negative patients.
- Recent studies from oral antivirals have erased the clinical advantages of Peg-Interferon from earlier data:

HBeAg positive on-treatment conversion to negative

Peg-IFN Year 1	ARV Year 1	ARV Year 3
30%	12-23%	>40%

HBsAg Loss

Peg-IFN	ARV Year 1	ARV Year 2
3-8%	2%	5%

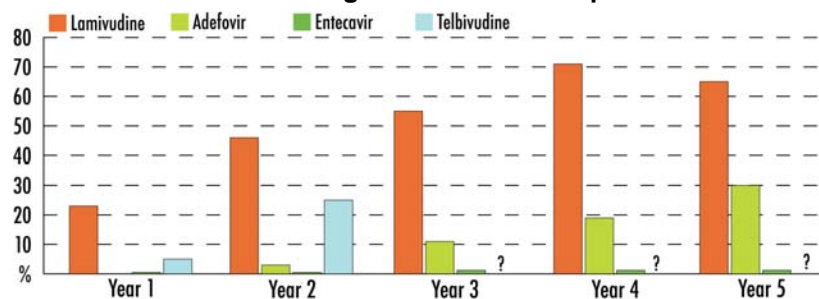


HBV Drug Resistance

One major drawback of oral antivirals is the development of drug resistance, and cross resistance.

- Lamivudine and telbivudine are no longer recommended as first-line therapy due to their weak resistance profiles.
- Adefovir and entecavir loses effectiveness in people with lamivudine and telbivudine resistance.
- Tenofovir resistance has not been well characterized.

Rates of drug resistance development



HBV Treatment Side Effects

Interferon: Flu-like symptoms, fatigue, anorexia, weight & hair loss, anxiety, irritability, depression, suicidal tendency.

Oral antivirals: Generally well tolerated.

- Adefovir and tenofovir have potential kidney toxicity.
- Decreases in bone density with long term tenofovir use have been observed.
- Telbivudine is currently one of 20 drugs on the FDA watch list over reports on peripheral neuropathy.

HBV/HIV Coinfection

HIV coinfection worsens chronic HBV

- 10% of HIV positive people are coinfecting with HBV
- Higher risk of developing serious liver disease
- Disease progression is faster and more severe
- Higher rate of developing HBV drug resistance
- Worse for people with CD4 < 200

Treatment guidelines are edging towards more aggressive approach to HBV/HIV coinfection

- Lower viral load starting point (HBV DNA > 2,000 IU/ml)
- Less specific ALT range (abnormal ALT)
- More emphasis on need for biopsy
- Less importance on HBeAg status
- Start ARV treatment at any CD4 count

HBV/HIV Coinfection

ARV combination should contain two drugs active against both HIV and HBV plus a PI or NnRTI

- Tenofovir + Lamivudine or Emtricitabine

Stopping or switching ARV regimens can cause severe liver enzyme flares that can be fatal

- HBV active drugs should not be switched or stopped.

If no ARV treatment (not indicated or refused)

- Do not use drugs active to HIV (HIV drug resistance can develop): Lamivudine, Entecavir, Tenofovir
- Use Peg-Interferon, Adefovir, or Telbivudine instead.

For more information

Treatment Action Group
www.treatmentactiongroup.org

Hepatitis B Foundation
www.hepb.org

CDC Viral Hepatitis Page
<http://www.cdc.gov/hepatitis/ChooseB.htm>

The logo for the Treatment Action Group (TAG) consists of the letters 'TAG' in a bold, red, sans-serif font. The letter 'A' is stylized with a dot above it, resembling a lowercase 'a'.

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