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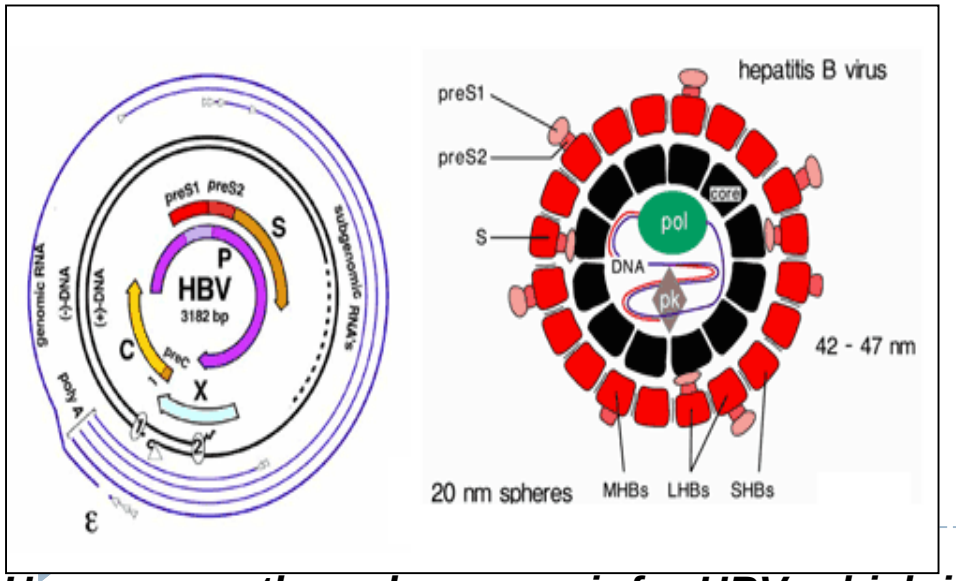
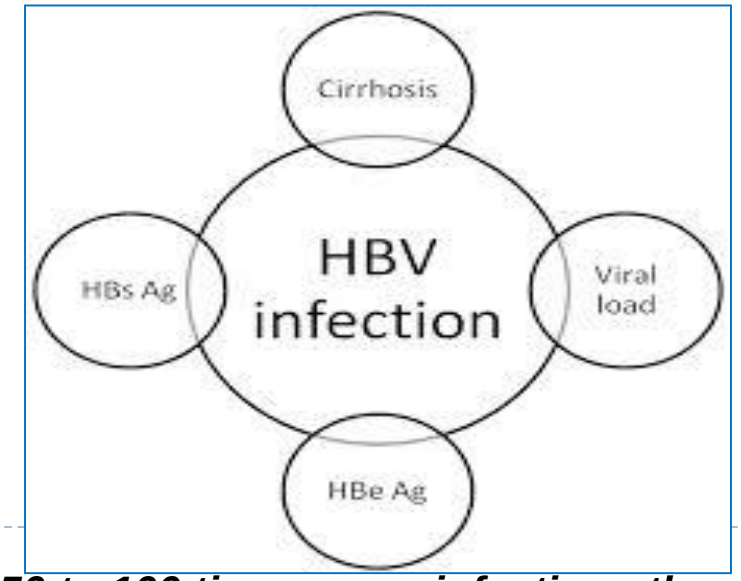
Chronic viral hepatitis B

by Adela Turcanu

Chronic Viral Hepatitis B

- chronic necroinflammatory disease of the liver caused by persistent infection (>6 month) with hepatitis B virus.





Humans are the only reservoir for HBV, which is 50 to 100 times more infectious than HIV

Burden of HBV Disease

- 15% to 25% risk of early death caused by liver cancer or end-stage liver disease among patients with chronic HBV infection.
- WHO global HBV estimates:
  - ~ 2 billion people infected with HBV
  - ~ 350 million people living with chronic HBV infection
- HBV is 50 - 100 times more infectious than HIV.
- Approximately 2 health care workers are infected each day with HBV.
- HBV infection accounts for 500 000 to 1.2 million deaths each year and is the 10th leading cause of death worldwide.
- Approximately 15-40% of infected patients will develop cirrhosis, liver failure, or hepatocellular carcinoma (HCC).

- *45% of the world population lives in areas where chronic HBV infection is highly endemic (> 8% of the population are HBsAg-positive);*
- *43% live in areas where endemicity is intermediate (2–7% HBsAg-positive);*
- *12% live in areas where endemicity is low (< 2% HBsAg-positive).*

Te HS, Jensen DM. Epidemiology of hepatitis B and C viruses: a global overview. *Clin Liver Dis*. Feb 2010;14(1):1-21
Lok AS. Chronic hepatitis B. *N Engl J Med* 2002; 346(22): 1682-1683

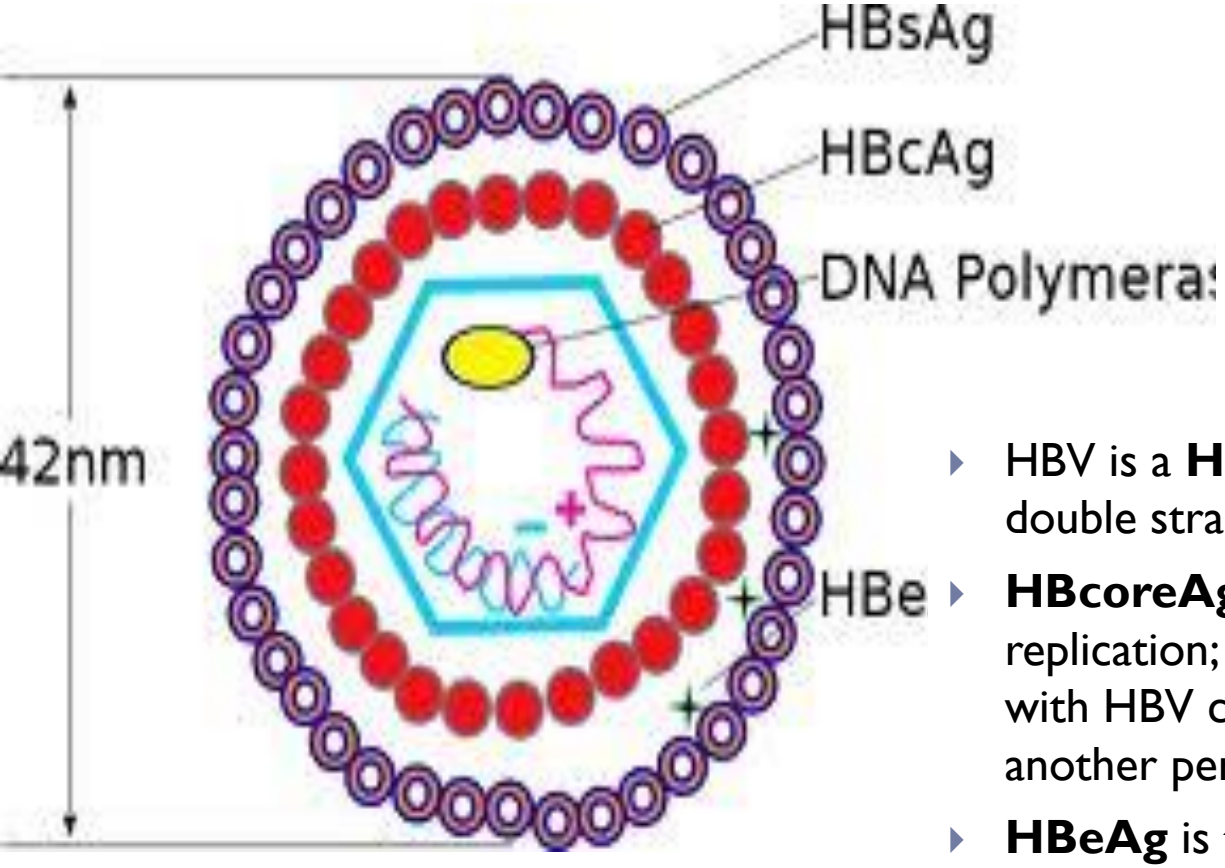
Modes of transmission of HBV:

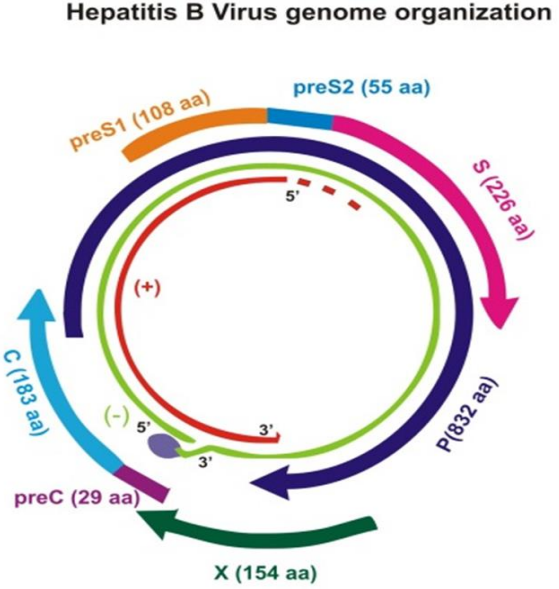
HBV can be detected in any biological fluid, and it presents in variable amount: it presents in high amount in blood, serum and wound exudate; in moderate amount in semen, vaginal fluid and saliva; in low amount in urine, feces, sweat, breast milk.

- **Sexual** transmission is the most mode of transmission.
- **Parenteral** transmission: 21 million HBV infections worldwide attributable to unsafe injection administration in healthcare settings
- **Perinatal** transmission: mothers who are HBeAg positive are much more likely to transmit to their offspring than those who are not.
- ✓ Most primary HBV infections in highly endemic countries occur during infancy or early childhood: vertical transmission or horizontal transmission involves highest chronic infection risk
- ✓ Most primary HBV infections in low prevalence countries occur during adolescence/young adulthood: transmission routes: unsafe sex practices or injection drug use

Gish RG, Locarnini S. Chronic hepatitis B viral infection. In: Yamada T, ed. *Textbook of Gastroenterology*. 5th ed. Oxford, UK: Blackwell Publishing; 2009:2112-38.

Structure of VHB





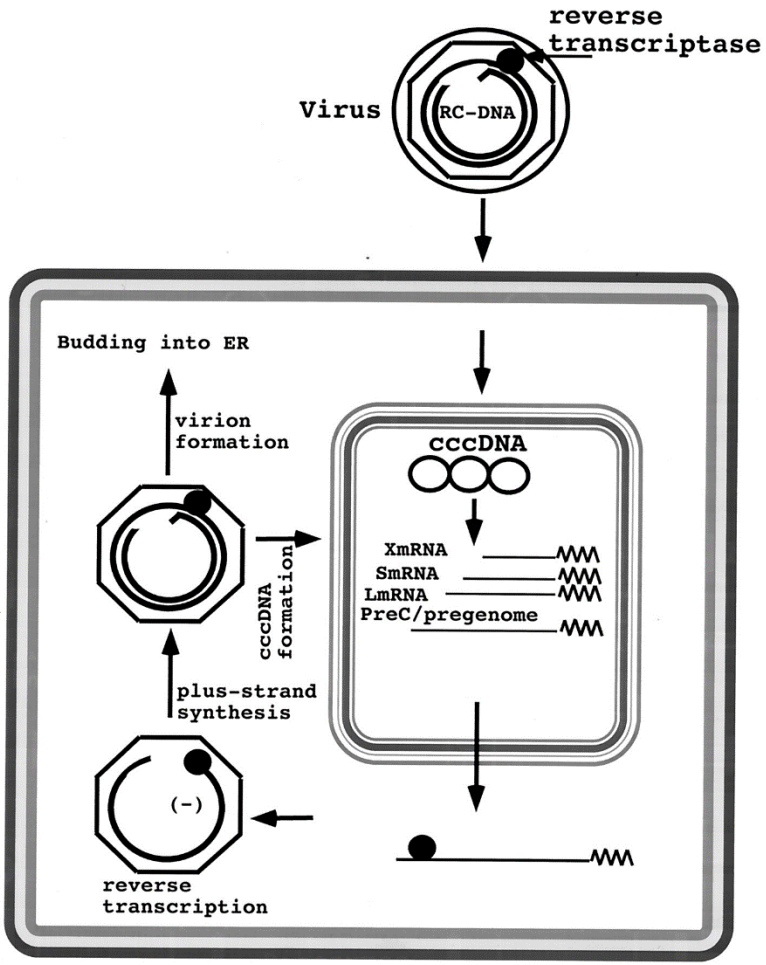
- HBV is a **Hepadnavirus**, is a 42 nm partially double stranded DNA.
- **HBcoreAg -** an indicator of active viral replication; this means the person infected with HBV can likely transmit the virus on to another person.
- **HBeAg** is the extracellular form of HBcoreAg. The presence of HBeAg suggests that the person is infectious and is able to spread the virus to other people.
- **HBsAg** – anvelope antigen is highly immunogenic and induces antiHBsAg.

HBV retains infectivity when stored at 30°C to 32°C for at least 6 months and when frozen at –15°C for 15 years.
HBV present in blood can withstand drying on a surface for at least a week.

Kuo A, Gish R. Chronic hepatitis B infection. *Clin Liver Dis*. May 2012;16(2):347-69.

Replication of HBV

- Attachment of virus B to the liver cell and its subsequent entry is believed to be mediated through a specific hepatocyte receptor that recognizes the pre-Si protein of the virus.
- Following entry into the cell, uncoating takes place and the partially double stranded genome is transported to the nucleus where upon repair it is converted into a **covalently closed circular DNA** (**cccDNA**) molecule.
- Viral genome replication involves a reverse transcriptase phase.
- cccDNA is the form of persistence of the viral genome and each infected hepatocyte contains on estimated 1-50 copies of cccDNA.



- cccDNA persists in infected cells even after anti-HBs seroconversion, and the amount of cccDNA correlates with HBsAg levels.
- Reactivation of viral replication may occur from the cccDNA template in case of immune suppression.

Wang J, Zhao W, Cheng L, Guo M, Li D, Li X, et al. CD137-mediated pathogenesis from chronic hepatitis to hepatocellular carcinoma in hepatitis B virus-transgenic mice. *J Immunol*. Dec 15 2010;185(12):7654-6

Genotypes of HBV

- The virus is divided into **four major serotypes** (adr, adw, ayr, ayw) based on antigenic epitopes presented on its envelope proteins.

- Worldwide, at least **nine genotypes of HBV** (A through I) have been identified on the basis of more than 8% difference in their genome sequences.
- Higher rates of HCC have been found in persons infected with genotypes C and F (compared with genotypes B or D), and in those infected with certain subtypes of genotype A found in southern Africa, although aflatoxin exposure may play a role in sub-Saharan Africa.
- Antiviral therapy is equally effective, and the HBV vaccine protective against all HBV genotypes .

- The genotypes have a distinct geographical distribution and are used in tracing the evolution and transmission of the virus.

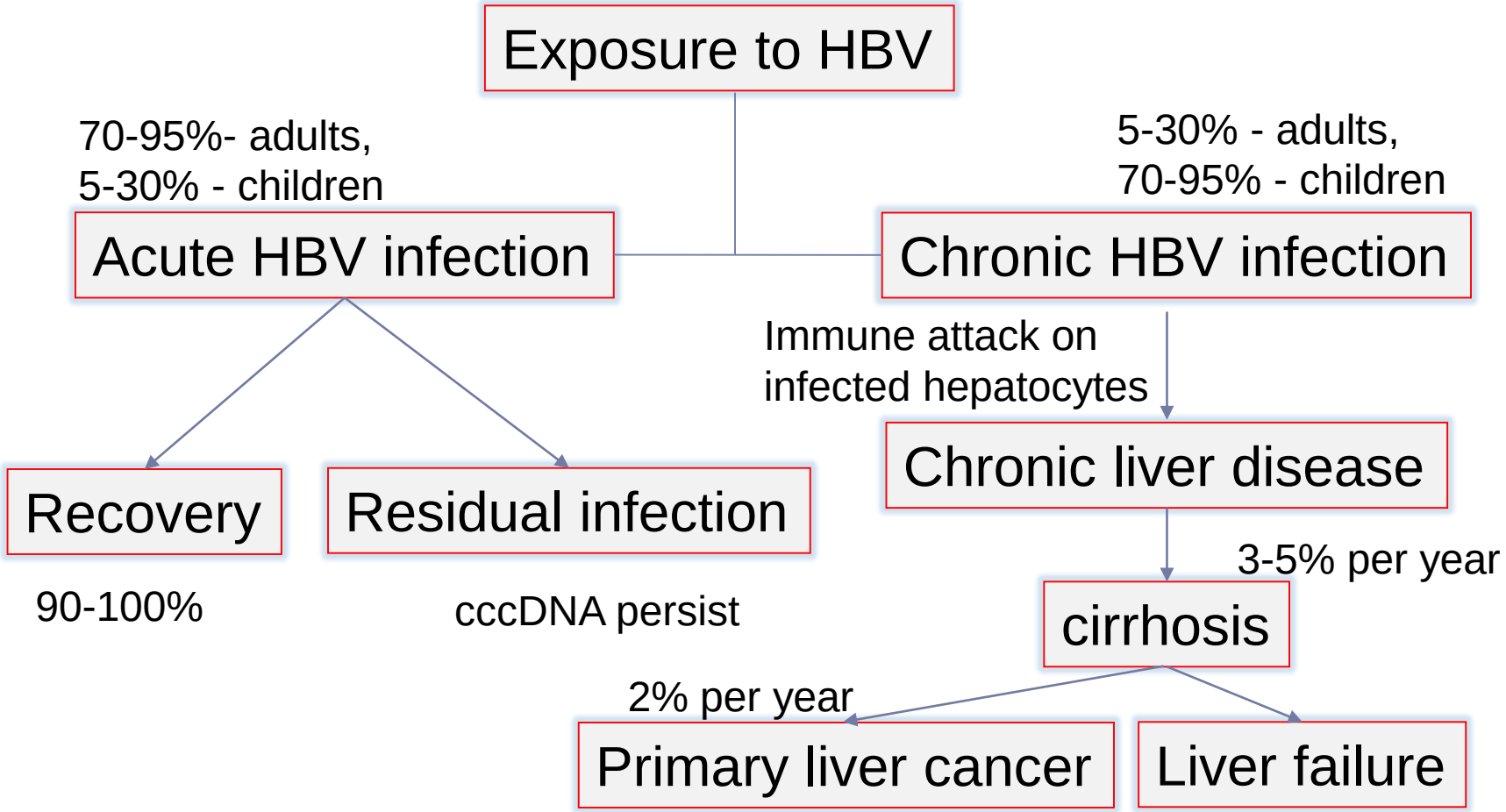
Genomic Heterogenety of Hepatitis Viruses (A-E): Role in Clinical Implications and Treatment
Zahid Hussain, 2013

Pathogenesis of HBV

- HBV is **non-cytopathic** virus and symptoms and liver pathology associated with hepatitis B are thought to be due primarily to the immune responses directed against HBV.
- The immune response is more effective in immunocompetent adult patient than in infants, resulting in less than 5% of adults but 90% of infants becoming chronically infected.
- Host immune responses induced by hepatitis B virus infection not only control HBV replication, but also lead to hepatic inflammation, witch drives disease progression in HBV-infected individuals.
- Hepatitis B virus (HBV) may persist in the blood for decades after clinical recovery from acute hepatitis despite the presence of serum antibodies. Immunosuppressive conditions or drugs may allow dormant HBV to flare or reactivate.
- Additionally, genetic factors (eg, genetic mutations) may influence the risk for reactivation by affecting hepatitis B core antibody response.

Lau JY, Wright TL. Molecular virology and pathogenesis of hepatitis B. *Lancet*. Nov 27 1993;342(8883):1335-40

Natural history of HBV infection



People infected with HBV have both short-term and long-term outcomes.
On becoming infected, a person can have either a symptomatic disease, or an asymptomatic infection with no signs or symptoms of disease.
In people with acute HBV, the incubation period after becoming infected is usually 3–4 months, with a range of 6 weeks to 6 months.

Clinical manifestations in HBV

- Chronic viral hepatitis B is frequently hidden due to the **asymptomatic** nature of liver disease.
- The absence of symptoms and abnormal clinical signs, therefore, does not exclude significant liver disease.
- Symptoms and signs of chronic viral hepatitis B can be divided into those associated with:
  - *Early* or *slowly progressive liver disease* (acute or chronic hepatitis; nonspecific simptoms);
  - *Progressive liver disease* (progress to cirrhosis compensated);
  - *Advanced liver disease* complications (decompensated liver cirrhosis, liver cancer; portal hypertension);
  - *Extrahepatic manifestations*.

Kuo A, Gish R. Chronic hepatitis B infection. *Clin Liver Dis*. May 2012;16(2):347-69.

Clinical syndromes from chronic hepatitis B

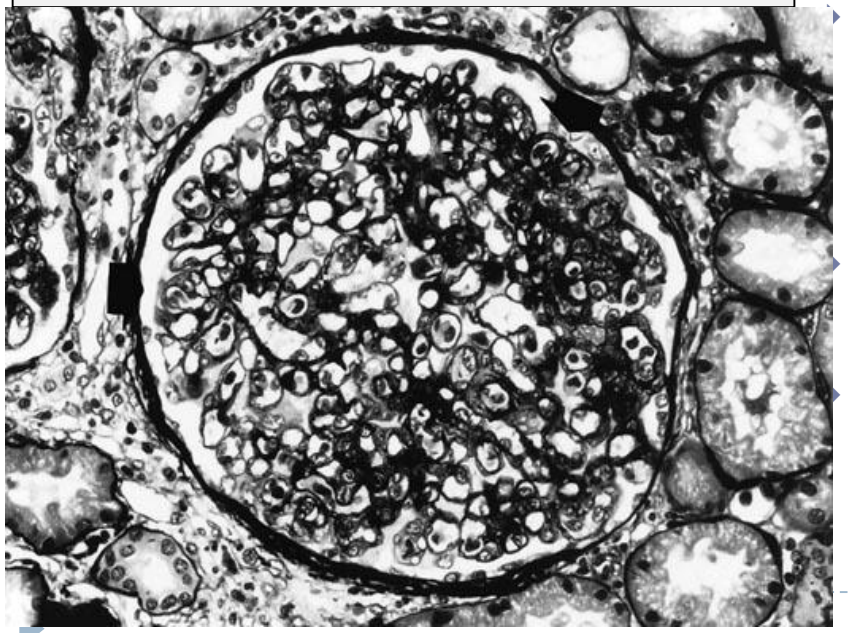
- Neurasthenic syndrome (fatigue, tiredness)
- Pain syndrome (abdominal pain in the right hypochondria)
- Icteric syndrome (jaundice, itching)
- Dyspeptic syndrome (nausea, diarrhea, constipation)
- Hemorraghic syndrome (epistaxis, gingivorhagia)



Extrahepatic manifestations

- Hepatitis B antigens and HBV DNA have been identified in extrahepatic sites, including:

1. lymph nodes,
2. bone marrow,
3. circulating lymphocytes,
4. spleen, and pancreas.



- **Dermatological presentations** include porphyria cutanea tarda, lichen planus and vasculitic rashes associated with cryoglobulinaemia.
- **Rheumatological manifestations** include arthropathy, Sjogren's syndrome and polyarteritis nodosa, cryoglobulinemia, vasculitis.
- **Neurological complications** may be related to cryoglobulinemia and present with mononeuritis of cranial or peripheral nerves.
- A variety of **thyroid diseases:** autoimmune thyroiditis, hipothyroidia.
- **Renal** diseases: glomerulonephritis - membranous, mebranoproliferative.

Hepatitis B virus–related membranous nephropathy mixed with mesangiocapillary glomerulonephritis demonstrating duplication of capillary wall with a "tram-track" appearance (arrows). Fmak-Mouni Lai et al. Modern pathology. 2000, 13(2)

Willson RA. Extrahepatic manifestations of chronic viral hepatitis. Am J Gastroenterol 1997;92:4-17.

Diagnosis from chronic HBV infection

Diagnosis from HBV based on:
History and physical examination
Family history of liver disease, HCC
Laboratory tests to assess liver disease: CBC with platelets, hepatic panel (cytolitical, hepatodepresive, cholestatic and immunoinflamatory syndromes)
Tests for HBV replication:HBsAg, HBeAg/anti-HBe, anti-HBV core, HBV DNA
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 in those at risk
Tests to screen for HCC: AFP and ultrasound as appropriate
Consider liver biopsy to grade and stage liver disease: for patients who meet criteria for chronic hepatitis

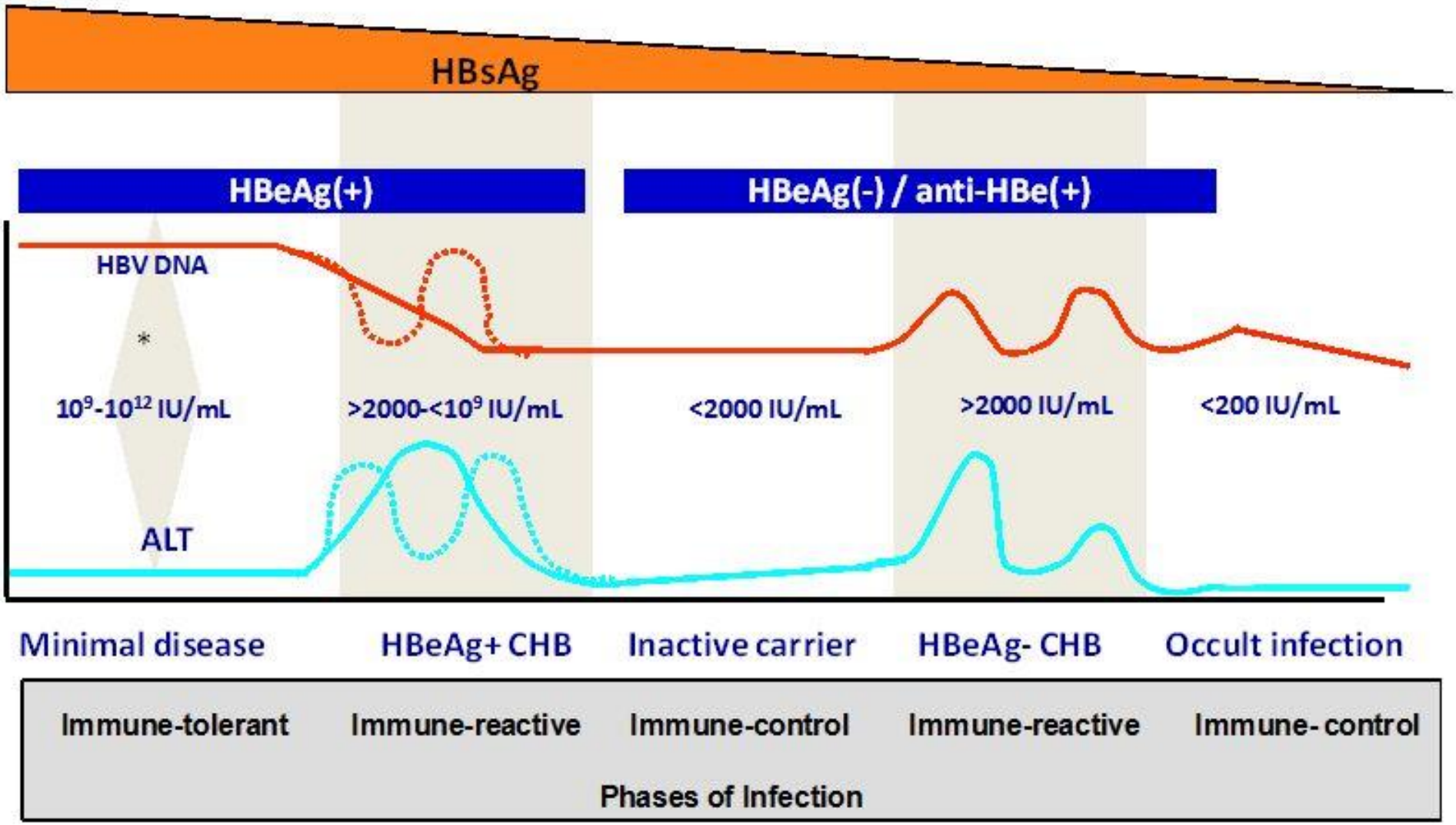
Centers for Disease Control and Prevention. Hepatitis B information for health professionals: hepatitis B FAQs for health professionals

Serological markers in HBV infection

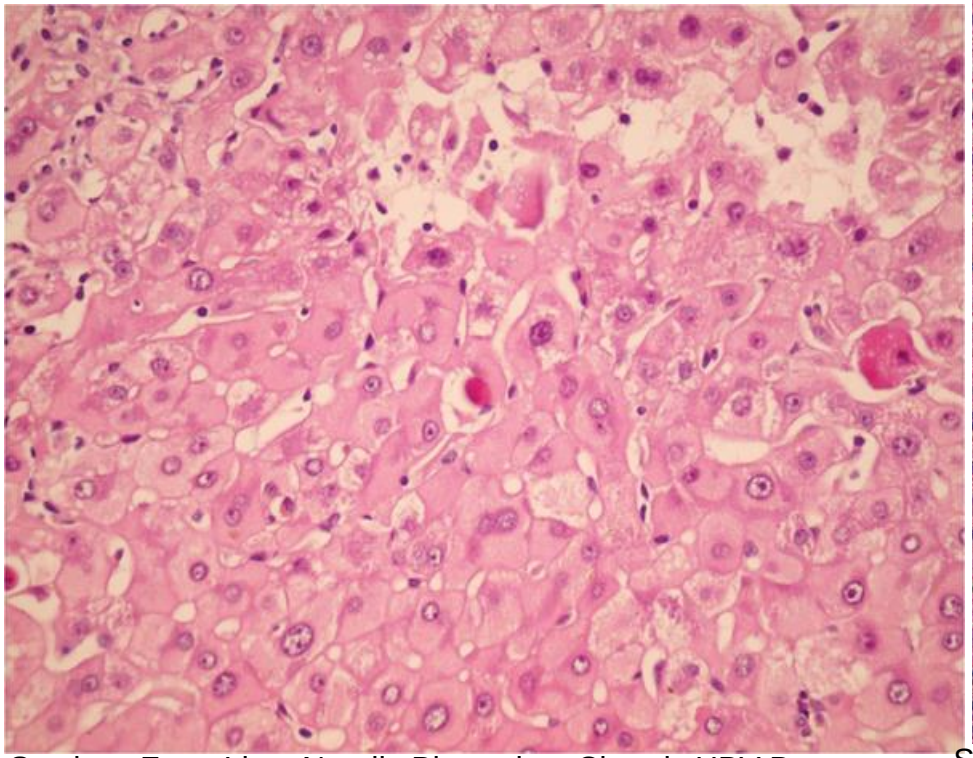
Antigens	Antibody
HBsAg - is the earliest indicator of acute infection and is also indicative of chronic infection if its presence persists for more than 6 months	**anti-HBs -** is the specific antibody to hepatitis B surface antigen. Its appearance 1 to 4 months after onset of symptoms indicates clinical recovery and subsequent immunity to HBV.
HBcAg - core antigen is the marker of the infectious viral material and it is the most accurate index of viral replication.	**anti-HBc -** is the specific antibody to hepatitis B core antigen. Antibodies to HBc are of class IgM and IgG. They do not neutralize the virus.
HBeAg - appearing during weeks 3 to 6 indicates an acute active infection at its most infectious period, and means that the patient is infectious. Persistence of this virological marker beyond 10 weeks shows progression to chronic infection and infectiousness.	**anti-Hbe -** is the specific antibody to hepatitis B e antigen. During the acute stage of infection the seroconversion from e antigen to e antibody is prognostic for resolution of infection.

HBV DNA is detectable by hybridization assays or PCR as soon as 1 week after initial infection. The tests are generally performed for monitoring of antiviral treatment or to detect mutants that escape detection by current methods

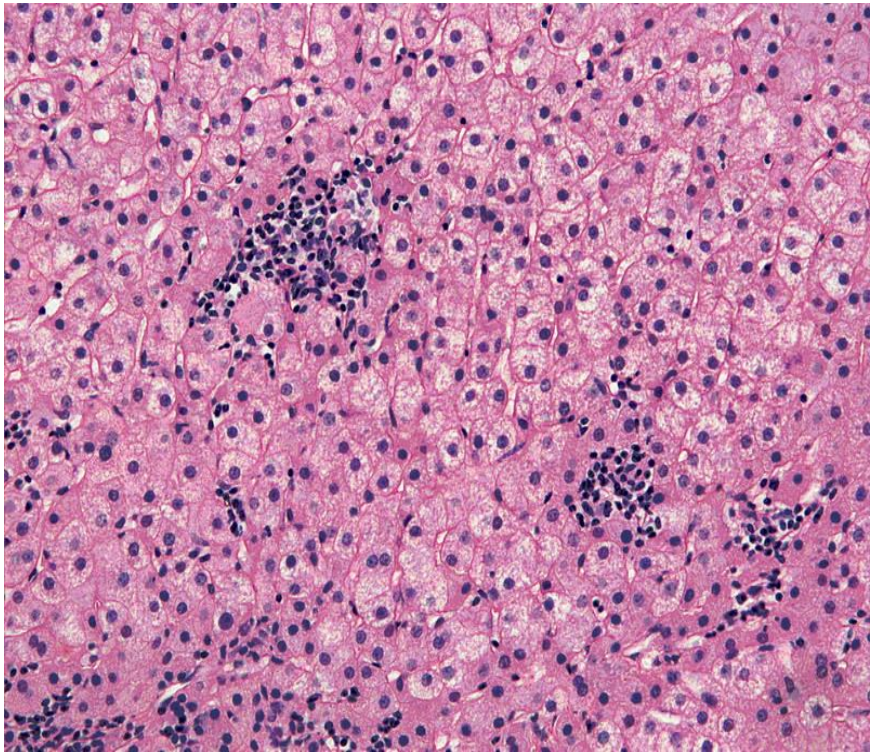
Phases of HBV infection



Liver biopsy in HBV



Sections From Liver Needle Biopsy in a Chronic HBV B shows Ground Glass Hepatocytes



Section of the liver biopsy specimen of a patient with chronic hepatitis B. Focal intralobular necroses in the middle zone of liver lobule

Liver biopsies from patients with chronic hepatitis B show pathognomonic **ground glass hepatocyte** inclusions distributed singly in a haphazard fashion with no zoning preference.

Quantitative Morphometric Analysis of Liver Biopsy: Problems and Perspectives
By Tokin Ivan B., Tokin Ivan I. and Filimonova Galina F. / chapter 9, book " Liver biopsy" 2011

Treatment in chronic HBV

- The indications for antiviral therapy of chronic hepatitis B infections are based on three main criteria:

1. Level of HBV DNA replication
2. Severity of liver disease based on liver biopsy
3. Elevation of ALT

- Prevention of fibrosis progression and hepatocellular carcinoma are two major goals of antiviral therapy and are clinically relevant in different patient populations.

	Interferons	**Nucleotide/ nucleozide analogues**
Approved drugs	Conventional IFN-a Peg-IFN a2a	*3 Nucleoside*: Lamivudine, Telbivudine and Entecavir *2 Nucleotide*: Adefovir and Tenofovir Clevudine (South Korea, Philippines)

Sorrell MF, Belongia EA, Costa J, Gareen IF, Grem JL, Inadomi JM, et al. National Institutes of Health Consensus Development Conference Statement: management of hepatitis B. Ann Intern Med. Jan 20 2009;150(2):104-10.

Who to treat?

- **As a priority**, all adults, adolescents and children with HBV and clinical evidence of compensated or decompensated cirrhosis (or cirrhosis based on APRI score >2 in adults) should be treated, regardless of ALT levels, HBeAg status or HBV DNA levels.
- Treatment is recommended for adults with HBV who do not have clinical evidence of cirrhosis (or based on APRI score ≤2 in adults), but are aged more than 30 years (in particular), **and** have persistently abnormal ALT levels **and** evidence of high-level HBV replication (HBV DNA >20 000 IU/mLf), regardless of HBeAg status.

Who not to treat but continue to monitor?

• Antiviral therapy is **not** recommended and can be deferred in persons without clinical evidence of cirrhosis, **and** with persistently normal ALT levels **and** low levels of HBV replication (HBV DNA <2000 IU/mLf), regardless of HBeAg status or age.

• Continued monitoring is necessary in all persons with HBV, but in particular those who do not currently meet the above-recommended criteria for who to treat or not treat, to determine if antiviral therapy may be indicated in the future to prevent progressive liver disease. These include:

- *persons without cirrhosis aged 30 years or less, with HBV DNA levels >20 000 IU/ mLe but persistently normal ALT;*
- *HBeAg-negative persons without cirrhosis aged 30 years or less, with HBV DNA levels that fluctuate between 2000 and 20 000 IU/mL, or who have intermittently abnormal ALT levels.*

Interferon-based Therapy for chronic HBV infection

Interferon alfa-2a	**5 million IU SQ/day or 10 million IU SQ 3 x/wk**	16-24 wks for HBeAg-positive patients; ≥ 12 mos for HBeAg-negative patients	Influenza-like symptoms, fatigue, anorexia, weight loss, hair loss, anxiety, depression
PegInterferon alfa-2a	**180 µg/wk SQ**	48 wks	

Contraindicated in patients with decompensated cirrhosis, pregnancy, acute infection, chemotherapy profilaxis

Virological responses on IFN/PEG-IFN therapy:

- **Primary non-response** has not been well established.
- **Virological response** is defined as an HBV DNA concentration of less than 2000 IU/ml. It is usually evaluated at 6 months and at the end of therapy as well as at 6 and 12 months after the end of therapy.
- **Sustained off-treatment virological response** is defined as HBV DNA levels below 2000 IU/ml for at least 12 months after the end of therapy.

EASL. Journal of Hepatology . 2009; 50: 227-242. Marcellin P, et al AASLD 2011. Abstract 1375

Therapy with nucleotide/nucleoside analogues for chronic HBV (first-line drugs)

Tenofovir	300 mg/day PO	Lactic acidosis, severe hepatomegaly, renal insufficiency, Fanconi's syndrome, osteomalacia, decrease in bone mineral density, severe acute exacerbations of hepatitis upon discontinuation	Also active against HIV; do not use as monotherapy in HIV-coinfected patients; dose adjustment for renal impairment; may be less effective in patients resistant to adefovir; monitor creatinine clearance and serum phosphorous on therapy for patients at risk for renal impairment
Entecavir	0.5 -1.0 mg/day PO for patients with lamivudine refractory/ resistance or decompensated disease	Lactic acidosis, severe hepatomegaly, severe acute exacerbations of hepatitis upon discontinuation	Not recommended for HIV-coinfected patients not receiving HAART; administer on an empty stomach; dose adjustment for renal impairment; not optimal for patients with lamivudine resistance

1. The oral nucleos(t)ide analogues are often continued indefinitely in the majority of patients who do not achieve a durable HBeAg response.
2. Extending therapy for a second year or longer can result in a higher rate of HBsAg loss in both HBeAg-positive and HBeAg-negative patients.
3. Prolonged and continuous suppression of serum HBV DNA to undetectable levels is necessary to reduce the risk of resistance to nucleos(t)ide analogues.

EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol. 2012;57:167-85.

Therapy with nucleotide/nucleoside analogues for chronic HBV (second–line drugs)

Drug	Dose	Adverse Effects	Notes
Lamivudine	100 mg/day PO; 300 mg/day PO for HBV/HIV-coinfected patients	Lactic acidosis, severe hepatomegaly, mild increase in ALT levels, severe acute exacerbations of hepatitis upon discontinuation	High rate of resistance has made other nucleos(t)ide analogues more attractive for first-line therapy; dose adjustment for renal impairment; also active against HIV; do not use as monotherapy in HIV-coinfected patients
Adefovir	10 mg/day PO	Lactic acidosis, severe hepatomegaly, nephrotoxicity, severe acute exacerbations of hepatitis upon discontinuation	Dose adjustment for renal impairment; monitor renal function and serum creatinine on therapy
Telbivudine	600 mg/day PO	Lactic acidosis, severe hepatomegaly, myopathy, peripheral neuropathy, severe acute exacerbations of hepatitis upon discontinuation	High rate of resistance; cross-resistant with lamivudine dose adjustment for renal impairment; should not be used with peginterferon alfa

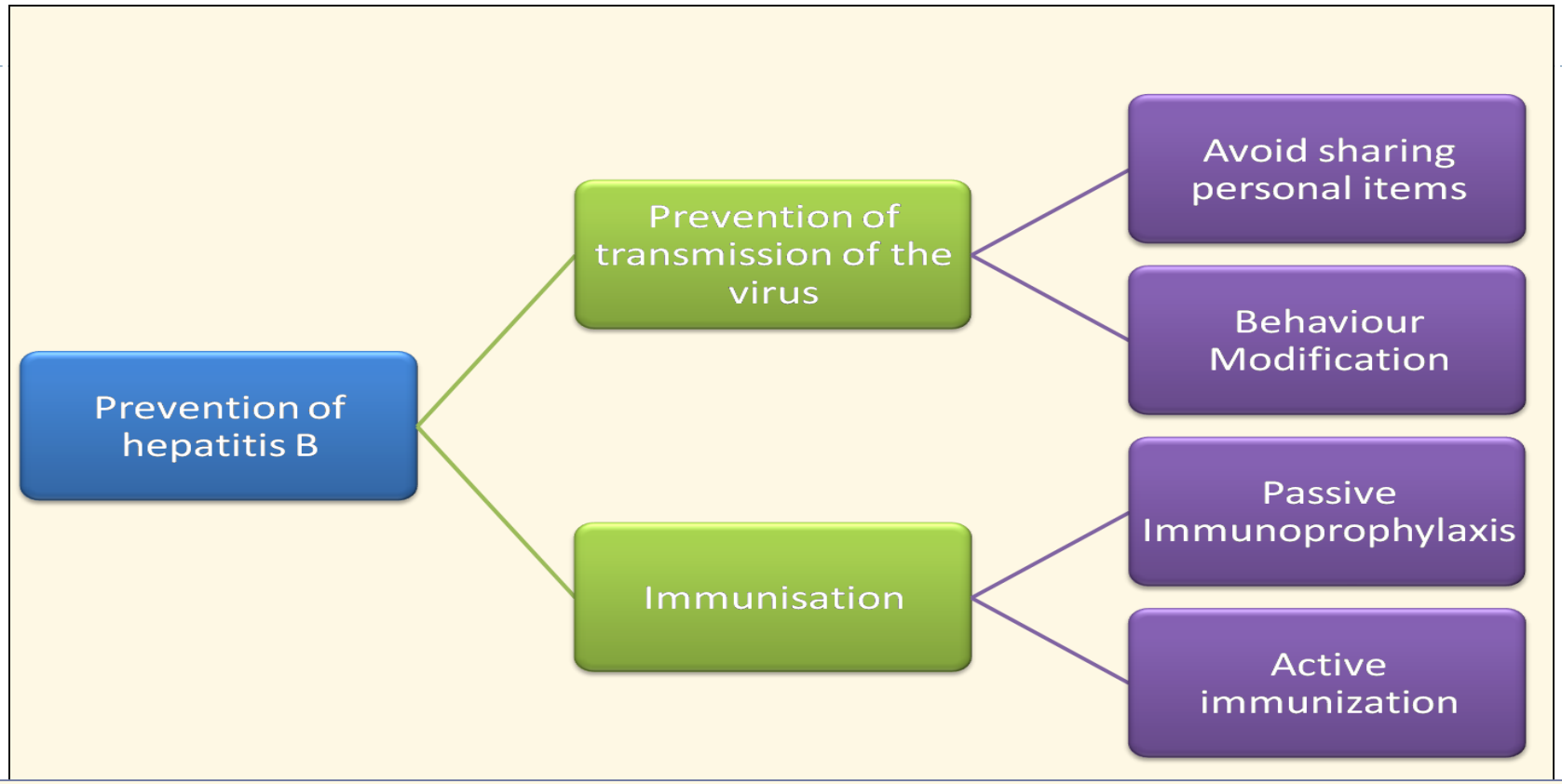
Yuen MF, Lai CL. Treatment of chronic hepatitis B: evolution over two decades.J Gastroenterol Hepatol 2011; 26, 138– 43

Advantages and Disadvantage for antiviral therapy on HBV

IFN/PEG-IFN	Nucleos(t)ide analogues
Advantages	
Finite duration No antiviral resistance Response more durable posttherapy Increase in HBsAg seroconversion rate	Daily oral dosing Potent HBV DNA suppression Minimal adverse events in the short term Safe and effective in advanced liver disease Less expansive during first year
Disadvantages	
Frequent adverse events Weekly sub/cutan injections Less effective on on treatment HBV DNA suppression Expensive	Risk of resistance Limited HBsAg seroconversion rate Response mostly not durable posttherapy Long-term or indefinite therapy may be required

- *Currently, pegylated interferon alfa (PEG-IFN-a), entecavir (ETV), and tenofovir disoproxil fumarate (TDF) are the first-line agents in the treatment of HBV.*
- *Lamivudine (3TC), telbivudine, and adefovir are of historical interest. These agents are currently considered second- or third-line therapy, or "nonpreferred" treatment.*

Prevention of HBV infection



- **The hepatitis B vaccine** consists of recombinant hepatitis B surface antigen produced in yeast. A series of 3 injections may achieve HBsAg antibody levels greater than **10 million IU/mL** in approximately 95% of vaccinated individuals. Vaccination with a single dose must be repeated every 5-10 years.
- **Postexposure prophylaxis (with HBIG) is indicated in the folowing setting:**

✓Sexual exposure with hepatitis B surface antigen;
✓Accidental percutaneous or permucosal exposure to HBs positive blood;
✓Perinatal exposure from HBsAg positive mothers