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# Chronic Hepatitis B

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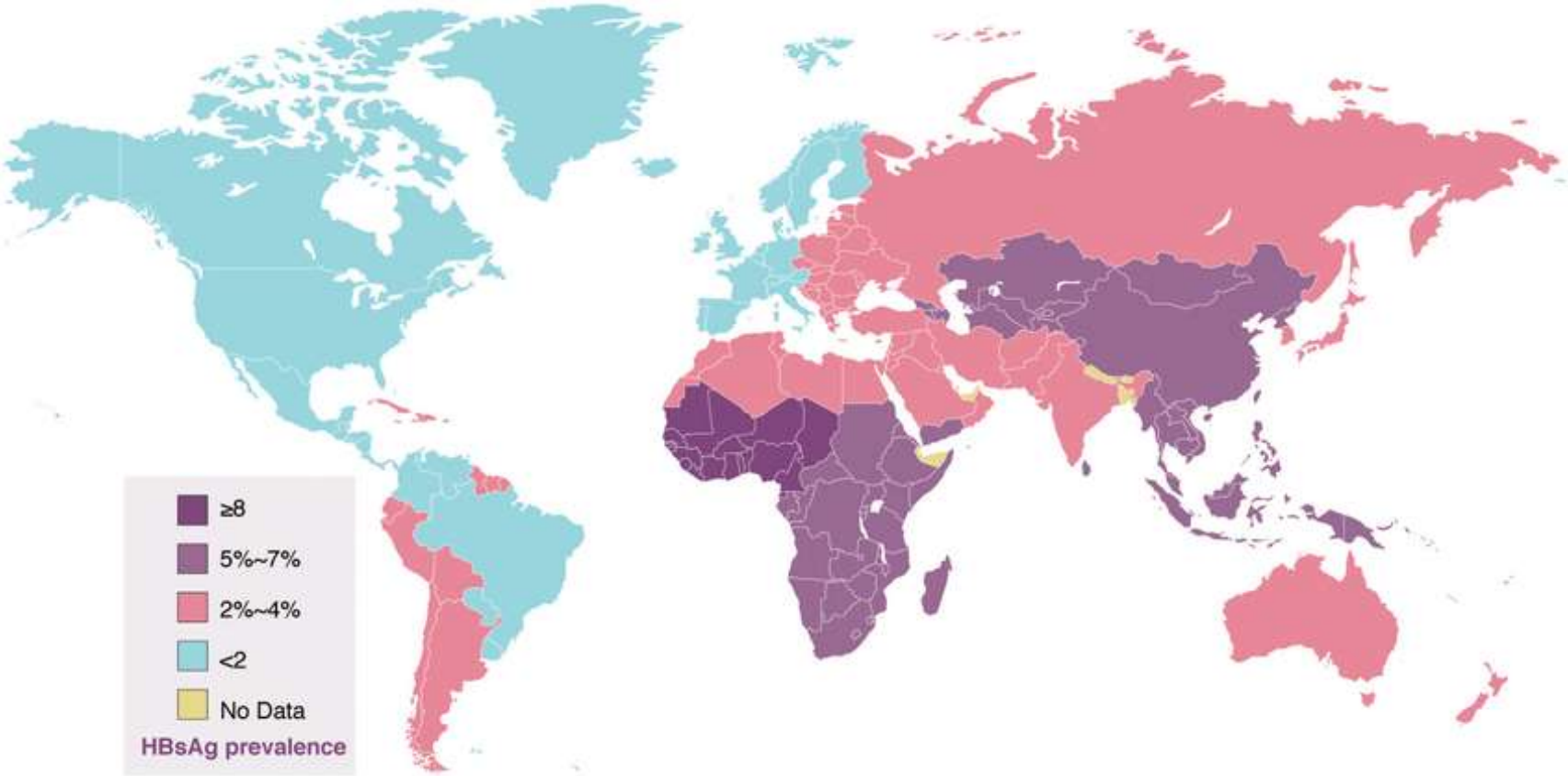
# Disclosures

- I have no disclosures to make.

# Agenda

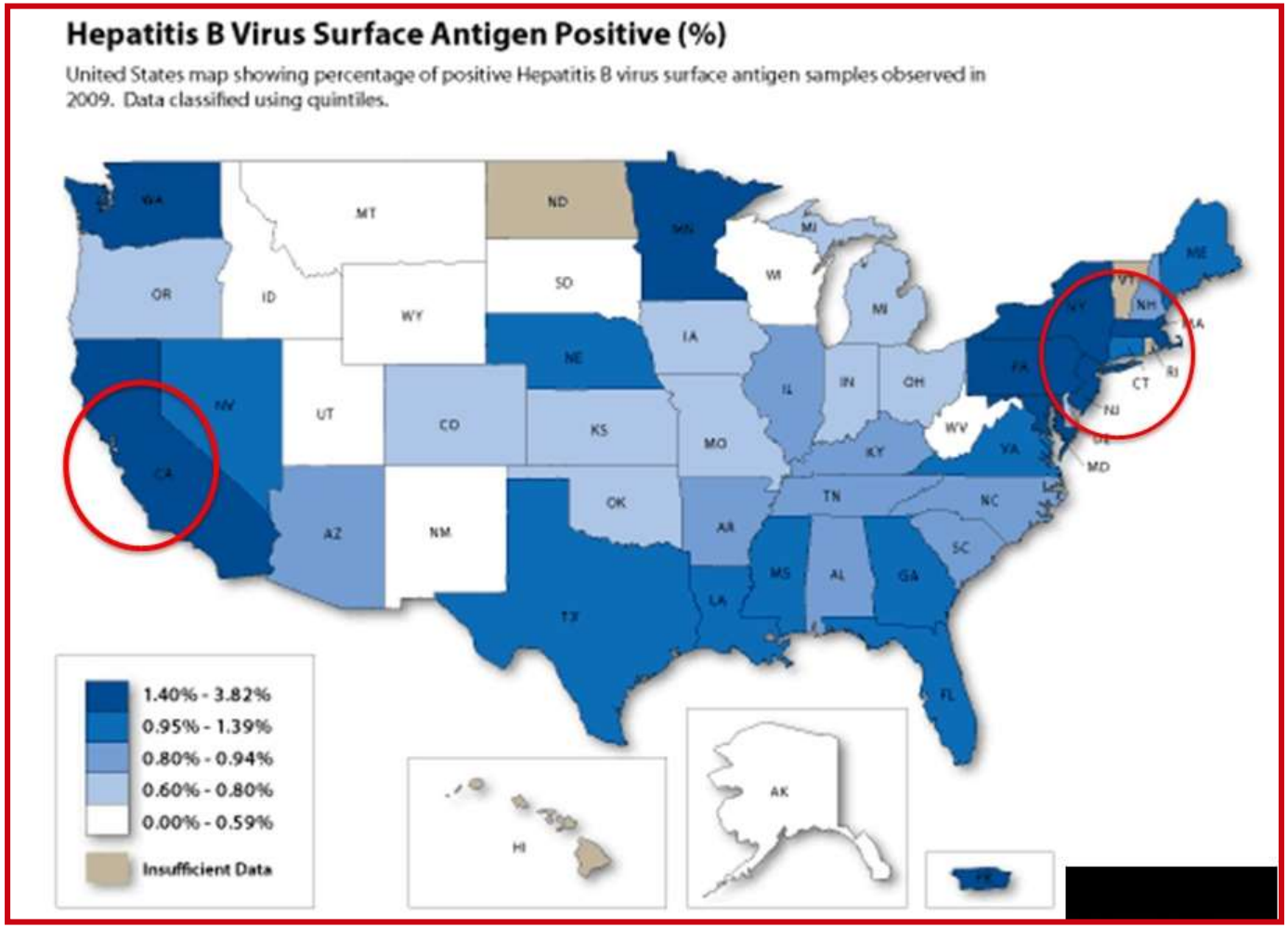
- Epidemiology
- Pathophysiology
- Risk factors
- Natural history of Chronic Hepatitis B
- Management of Chronic Hepatitis B
- New Emerging therapeutics

# Epidemiology




1- Ott JJ et al,. Vaccine 2012;30:2212-2219.

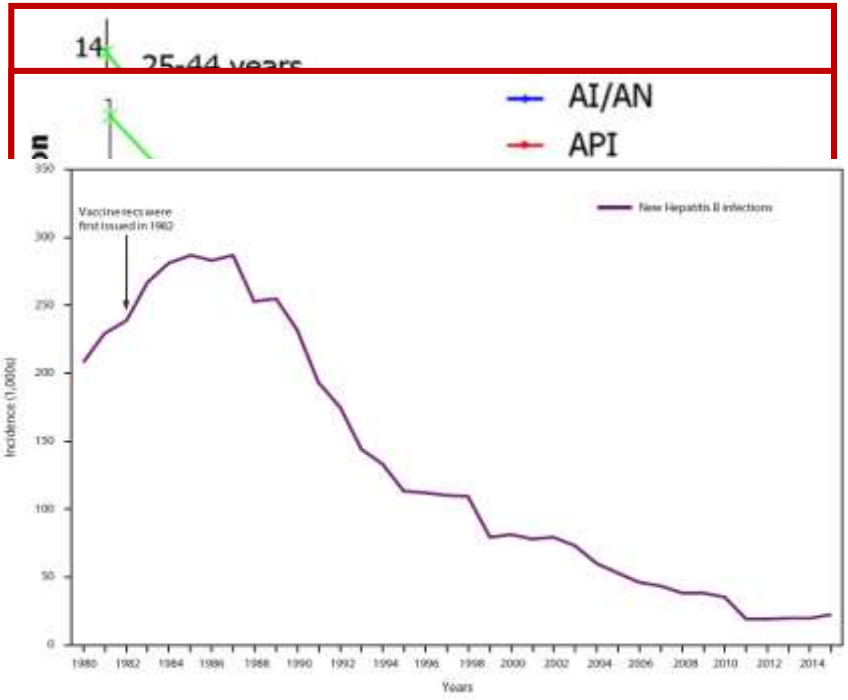
# US Data




CDC, 2009

# What about US?

- Prevalence ~2%[1]
- CDC: in 2016 862,000 of CHB[2]
  - 6th leading indication for OLT
- Decreasing incidence since 1980's[3]
  - Vaccination
  - Prevention perinatal infection
- Immigrant populations[3]
  - Underrepresented in surveys
  - 82% of CHB in North America are foreign born

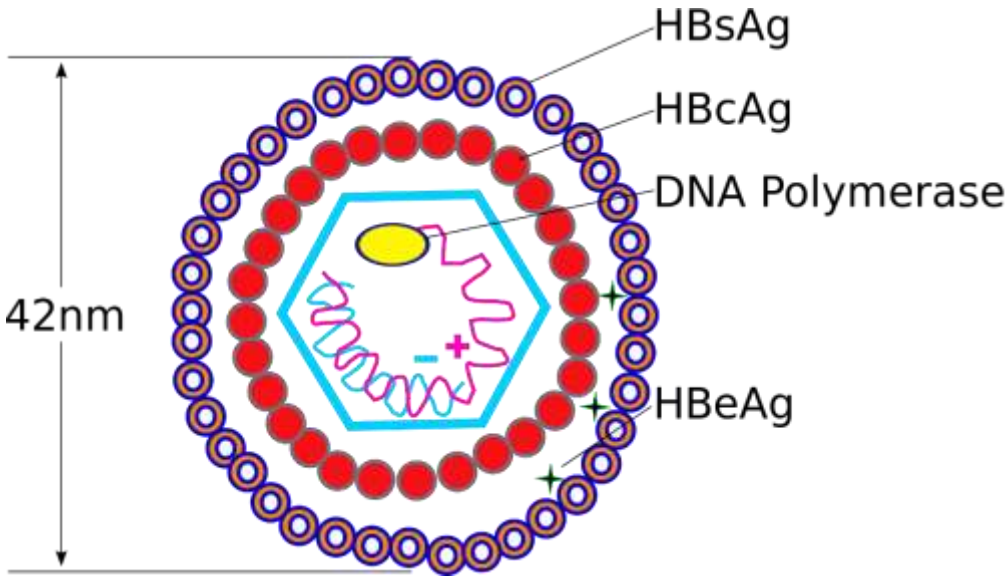



1. Ott. Vaccine, 2012
2. CDC MMRW 2008
3. Ray. Hepatology 2009
MMWR: Surveillance Summary Janury 12, 2018/ Vol. 67/ No. 1
Terrault et al, Hepatology Vol. 67, No. 4, 2018 (AASLD guidelines)

# Hepatitis B Virus

- It's an ancient disease first descriped in 5th Century BC
- HBV is a double stranded DNA- containing virus
- HBV has 8 genotypes
- 7 protiens:

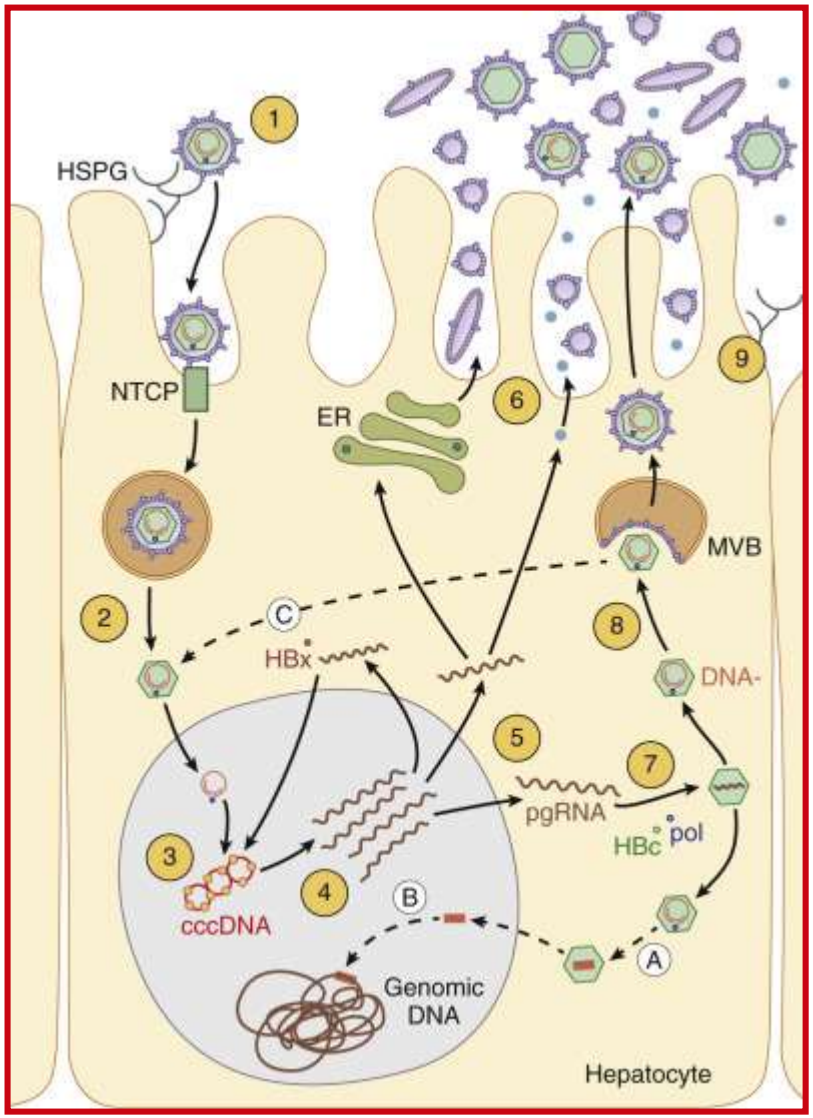
| Principal HBV proteins | |
|---|---|
| S | Small surface protein |
| M | Middle surface protein |
| L | Large surface protein |
| HBc | Core protein |
| HBeAg | Secreted e antigen |
| pol | Polymerase |
| HBx | X protein (nonsecreted) |




High genetic variability > quasispecies > mutants HBV[3]

1. Seeger. Microbiol Mol Biol Rev, 2000
2. Bertoletti. Zakim and Boyer's Hepatology, 2017
3. Tong, J Hepatol, 2016

# Virology: life cycle




1. Bertoletti. Zakim and Boyer's Hepatology, 2017
2. Tong, J Hepatol, 2016

# Risk of transmission and Chronic Infection

- HBV means of transmissions:
  - Perinatal
  - Percutaneous
  - Sexual exposure
  - By close person-to-person contact

- The risk of developing chronic HBV infection after acute exposure (1,2)
  - **90%** in newborns of HBeAg-positive mothers
  - **25%-30%** in infants and children under 5
  - **<5%** in adults

1- McMahon BJ et al, J Infct Dis 1985;151:599-603.
2- Tassopoulos NC et al, Am J Epidemiol 1987;126:587-591.
Terrault et al, Hepatology Vol. 67, No. 4, 2018 (AASLD guidelines)

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# CDC recommends screening:

- People born in countries with an HBV prevalence of ≥2%
- People born in the United States not vaccinated as infants whose parents were born in regions with high rates of HBV infection (HBsAg prevalence of ≥8%)
- Men who have sex with men
- People who inject drugs
- People with HIV
- Household and sexual contacts of HBV-infected people
- People requiring immunosuppressive therapy
- People with end-stage renal disease (including hemodialysis patients)
- Blood and tissue donors
- People with elevated alanine aminotransferase levels (≥19 IU/L for women and ≥30 IU/L for men)
- Pregnant women (hepatitis B surface antigen [HBsAg] only is recommended)
- Infants born to HBV-infected mothers (HBsAg and antibody to hepatitis B surface antigen [anti-HBs] only are recommended)

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# Interpretation of HBV serology

| Screening Test Results | | | | | |
|---|---|---|---|---|---|
| HBsAg | Anti-HBc | Anti-HBs | Interpretation | Management | Vaccinate? |
| + | + | – | Chronic hepatitis B | Additional testing and management needed | No |
| – | + | + | Past HBV infection, resolved | No further management unless immunocompromised or undergoing chemotherapy or immunosuppressive therapy | No |
| – | + | – | Past HBV infection, resolved or false-positive | HBV DNA testing if immunocompromised patient | Yes, if not from area of intermediate or high endemicity |
| – | – | + | Immune | No further testing | No |
| – | – | – | Uninfected and not immune | No further testing | Yes |

Terrault et al, Hepatology Vol. 67, No. 4, 2018 (AASLD guidelines)

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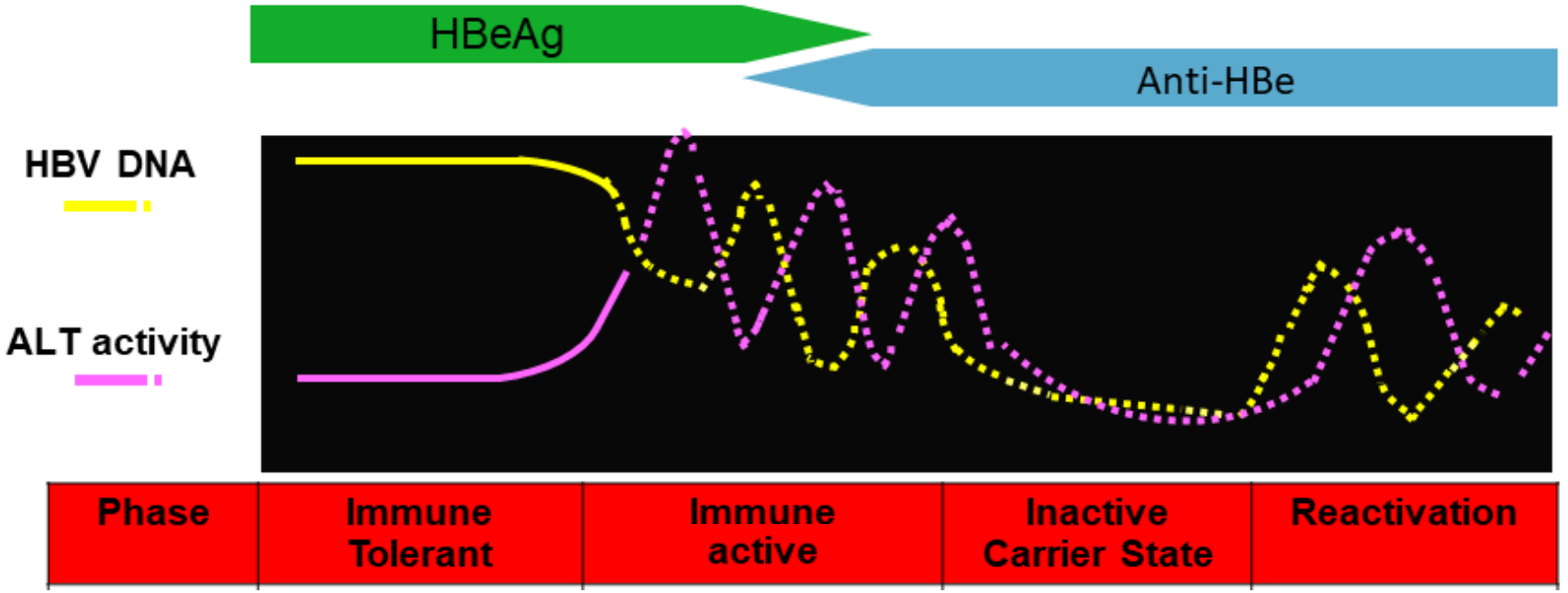
# Phases of CHB Infection

| | ALT | HBV DNA | HBeAg | Liver Histology | Treatment indicated |
|---|---|---|---|---|---|
| **"Immune-tolerant Phase"** | Normal | Elevated > 1 million IU/mL | Positive | Minimal inflammation and fibrosis | No |
| **HBeAg-positive "Immune-active phase"** | Elevated | Elevated ≥ 20,000 IU/mL | Positive | Moderate to severe inflammation or fibrosis | Yes |
| **"Inactive CHB phase"** | Normal | Low or undetectable <2,000 IU/mL | Negative | Minimal inflammation but variable fibrosis | No |
| **HBeAg-negative "immune reactivation phase"** | Elevated | Elevated ≥ 2,000 IU/mL | Negative | Moderate to severe inflammation or fibrosis | Yes |
| **Resolved CHB** | Normal | Undetected | Negative | **Varies** | **No** |

Terrault et al, HEPATOLOGY, Vol. 63, No. 1, 2016 (AASLD guidelines)

Terrault et al, Hepatology Vol. 67, No. 4, 2018 (AASLD guidelines)

# Natural History: chronic infection




Yim, Hepatology, 2006

# Evaluation of persons with CHB

- **History/Physical Examination**
  - Symptoms/signs of cirrhosis
  - Alcohol and metabolic risk factors
  - Family history of chronic hep B and HCC

- **Laboratory Tests**
  - CMP, CBC, INR
  - AFP, HBeAg/anti-HBe, HBV DNA quantitation
  - Test for co-infection (HCV, HDV and HIV)
  - Work-up to rule out other causes of chronic liver diseases
  - Anti-HAV to determine need for vaccination

Terrault et al, Hepatology Vol. 63, No. 1, 2016 (AASLD guidelines)

# Evaluation of persons with CHB

- **Imaging**
  - Abdominal ultrasound

- **Staging Studies**
  - Noninvasive assessment of fibrosis
    - Transient elastrography
    - AST-to-platelet ratio index (APRI)
    - FIB-4
    - FibroTest

  - Liver biopsy
    - Best method to assess the severity of inflammatory activity and fibrosis
    - Especially useful for persons who lack clear indications for treatment

Terrault et al, Hepatology Vol. 63, No. 1, 2016 (AASLD guidelines)

# Screening for HCC in CHB

- HCC surveillance is considered cost-effective if the annual risk of HCC is ≥ 0.2% per year

- Abd US +/- AFP every 6 months for HCC screening

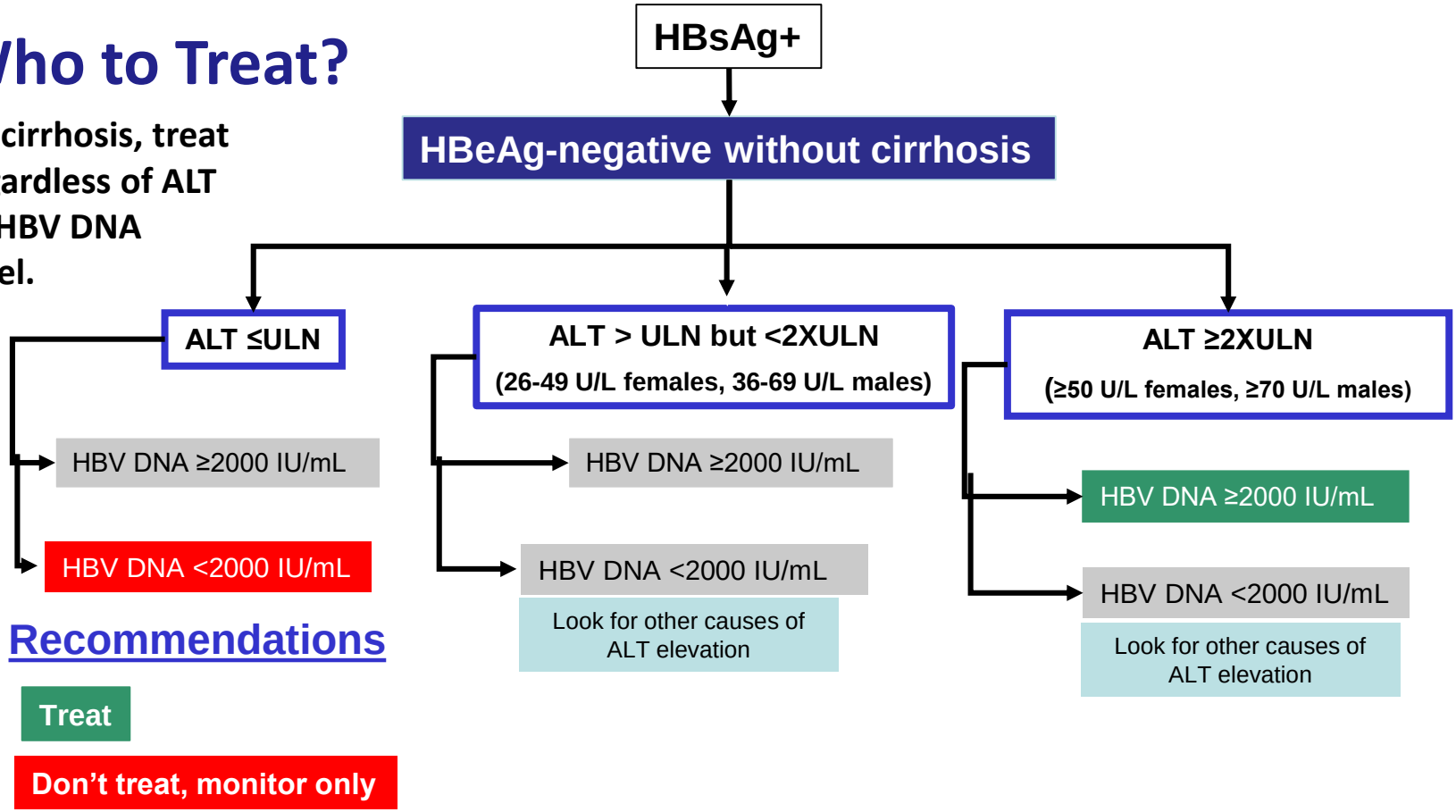
- Who to screen ?
  - All patients with cirrhosis
  - Asian or black man over 40 years
  - Asian women over 50 years of age
  - Persons with a first-degree family member with a history of HCC
  - Persons with HDV

Terrault et al, Hepatology Vol. 67, No. 4, 2018 (AASLD guidelines)

# Management of CHB/ HBeAg- negative

## Who to Treat?

***If cirrhosis, treat regardless of ALT or HBV DNA level.**




**Recommendations**

**Treat**

**Don't treat, monitor only**

If ALT ≤ULN, monitor ALT and HBV DNA every 3 months for one year then every 6 months

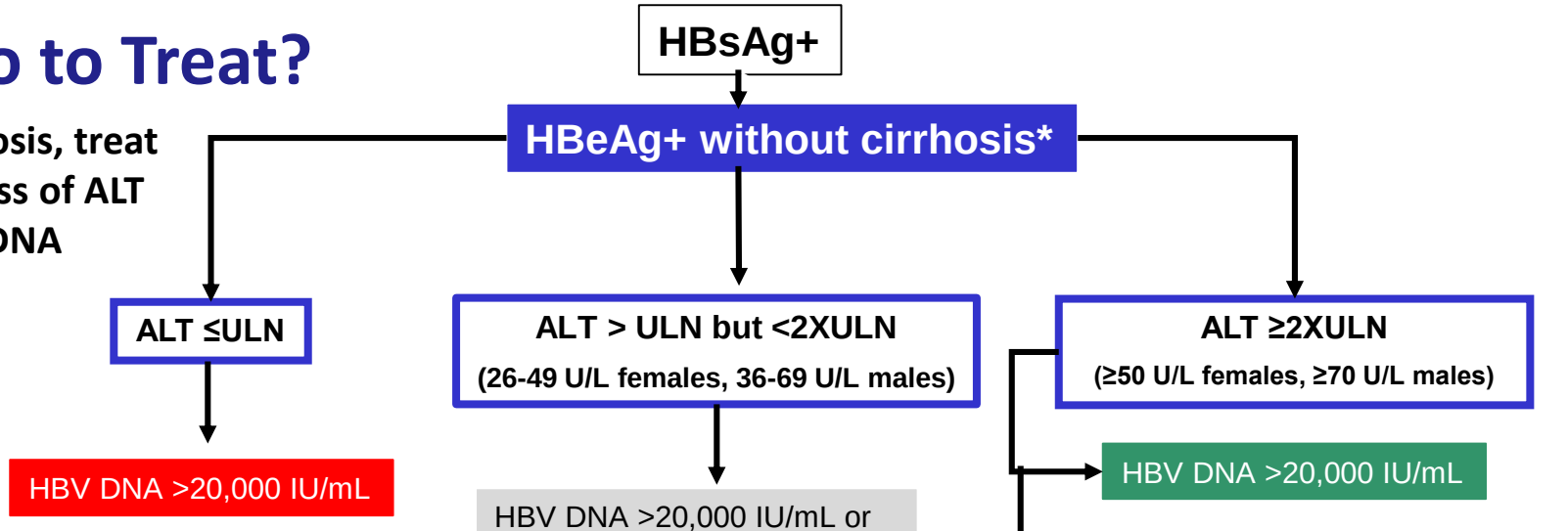
If staging indicates ≥F2 or ≥A3, or if other causes of ALT excluded and persistent, treat, **especially if ≥40 years of age**.

Terrault et al, Hepatology Vol. 67, No. 4, 2018 (AASLD guidelines)

# Management of CHB/ HBeAg-positive

## Who to Treat?

***If cirrhosis, treat regardless of ALT or HBV DNA level.**




**Recommendations**

**Treat**

**Don't treat, monitor only**

**Assess disease severity** using non-invasive tests and/or liver biopsy;

If staging indicates ≥F2 or ≥A3, or if other causes of ALT excluded and persistent, treat, **especially if ≥40 years of age**.

Terrault et al, Hepatology Vol. 67, No. 4, 2018 (AASLD guidelines)

# Management

- **Goals of Treatment:**
  - prevent progression of the disease, particularly to cirrhosis, liver failure, or hepatocellular carcinoma (HCC)
  - To decrease the morbidity and mortality related to CHB

- **Nucleos(t)ide reverse transcriptase inhibitors**
  - Tenofovir DF
  - Tenofovir AF
  - Entecavir
  - Adefovir, Lamivudine, Telbivudine.

- **Pegylated interferon** (Peg-IFN2a)

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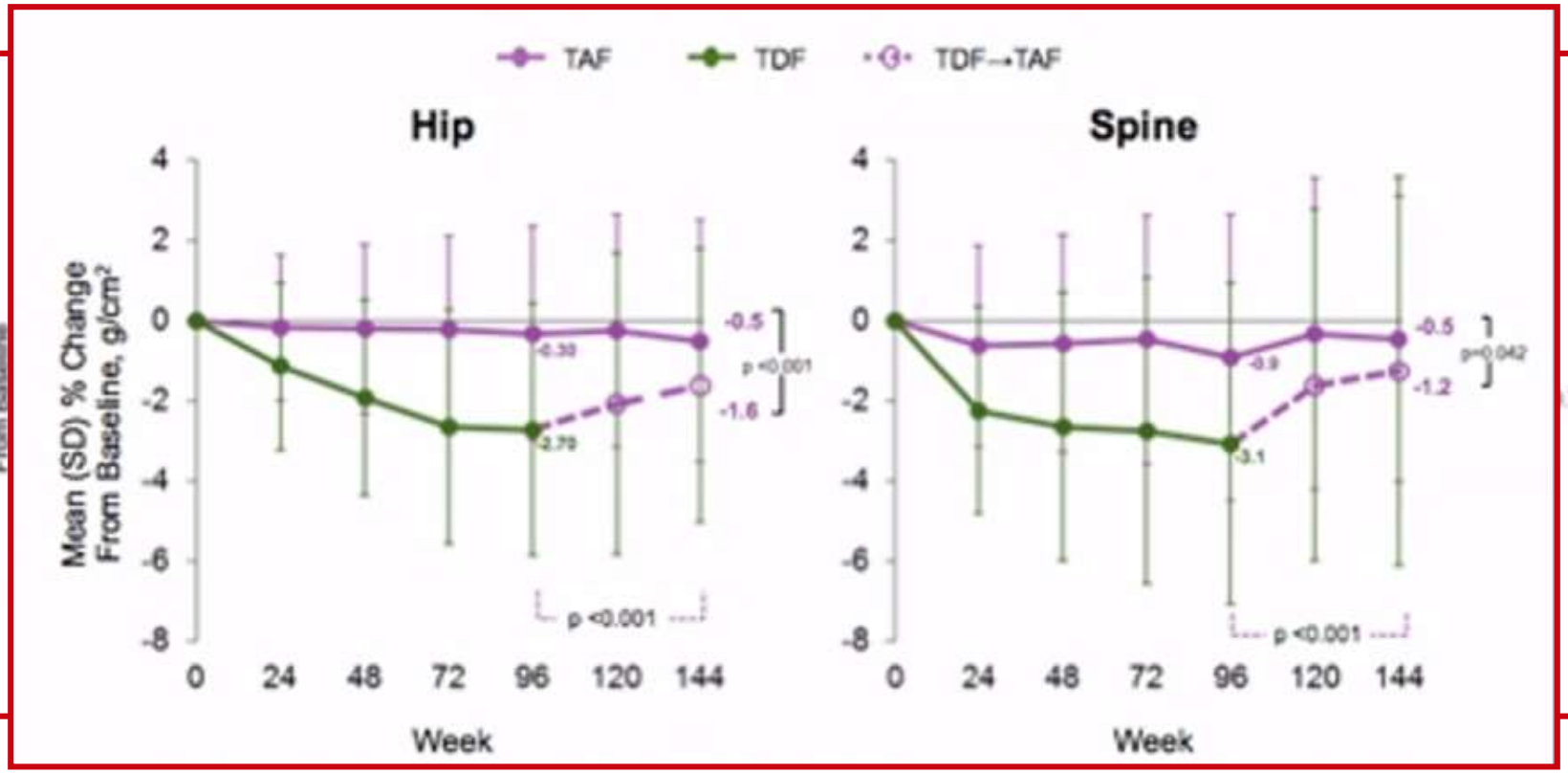
# Treatment options

| Drug | Dose in Adults* | Pregnancy Category† | Potential Side Effects† | Monitoring on Treatment‡ |
|---|---|---|---|---|
| **Preferred** | | | | |
| Peg-IFN-α-2a (adult)<br>IFN-α-2b (children) | 180 mcg weekly | C | Flu-like symptoms, fatigue, mood disturbances, cytopenia, autoimmune disorders in adults, anorexia and weight loss in children | Complete blood count (monthly to every 3 months)<br>TSH (every 3 months)<br>Clinical monitoring for autoimmune, ischemic, neuropsychiatric, and infectious complications |
| Entecavir | 0.5 mg daily‖ | C | Lactic acidosis (decompensated cirrhosis only) | Lactic acid levels if there is clinical concern<br>Test for HIV before treatment initiation |
| Tenofovir dipovoxil fumarate | 300 mg daily | B | Nephropathy, Fanconi syndrome, osteomalacia, lactic acidosis | Creatinine clearance at baseline<br>If at risk for renal impairment, creatinine clearance, serum phosphate, urine glucose, and protein at least annually<br>Consider bone density study at baseline and during treatment in patients with history of fracture or risks for osteopenia<br>Lactic acid levels if there is clinical concern<br>Test for HIV before treatment initiation |
| Tenofovir alafenamide | 25 mg daily | There are insufficient human data on use during pregnancy to inform a drug-associated risk of birth defects and miscarriage. | Lactic acidosis | Lactic acid levels if clinical concern<br>Assess serum creatinine, serum phosphorus, creatinine clearance, urine glucose, and urine protein before initiating and during therapy in all patients as clinically appropriate<br>Test for HIV before treatment initiation |

# TAF vs TDF

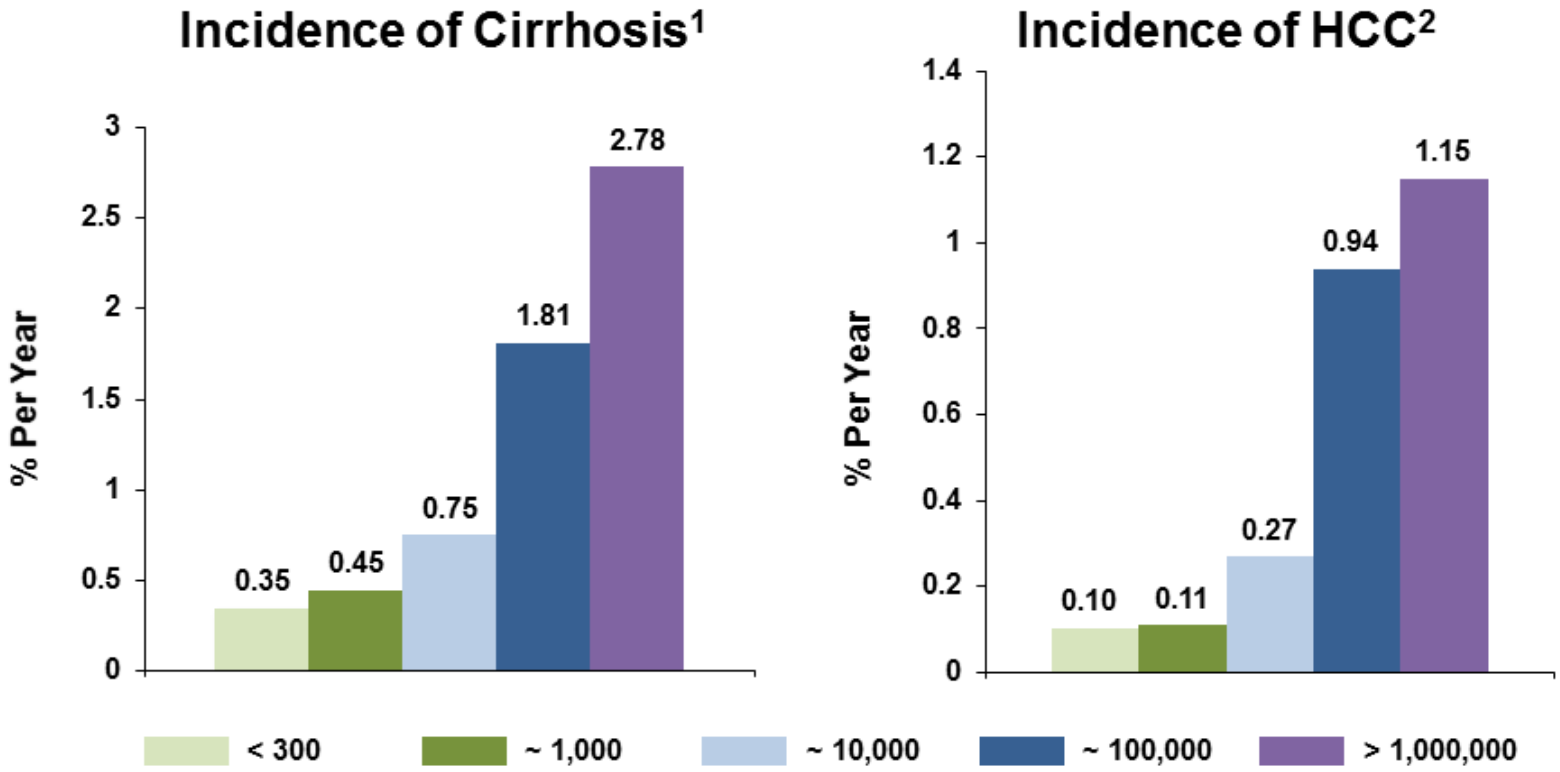
- Resist rapid metabolism in the plasma, more efficient.




1. Agrawal. EASL, 2017
2. Pan. Hepatology, 2017

# Why it is important?

- High VL is associated with cirrhosis and HCC




1. Iloeje UH, et al. *Gastroenterology*. 2006;130:678-686.
2. Chen C-J, et al. *JAMA*. 2006;295:65-73.

# Special Tx groups

- Decompensated cirrhosis:[1]
  - High resistance barrier NA. Interferon is contraindicated.
- Liver transplant Recipient :[2]
  - Hepatitis B immunoglobulin (HBIG) plus NA
  - Monoprophylaxis with a potent NA
  - HBsAg-negative patients receiving anti-HBc positive livers: NA
- HIV coinfected:[3]
  - ART irrespective of CD4 cell count
  - TDF/TAF based ART regimen
- HDV coinfected:[4]
  - PegIFNa for at least 48 weeks
  - Consider NA

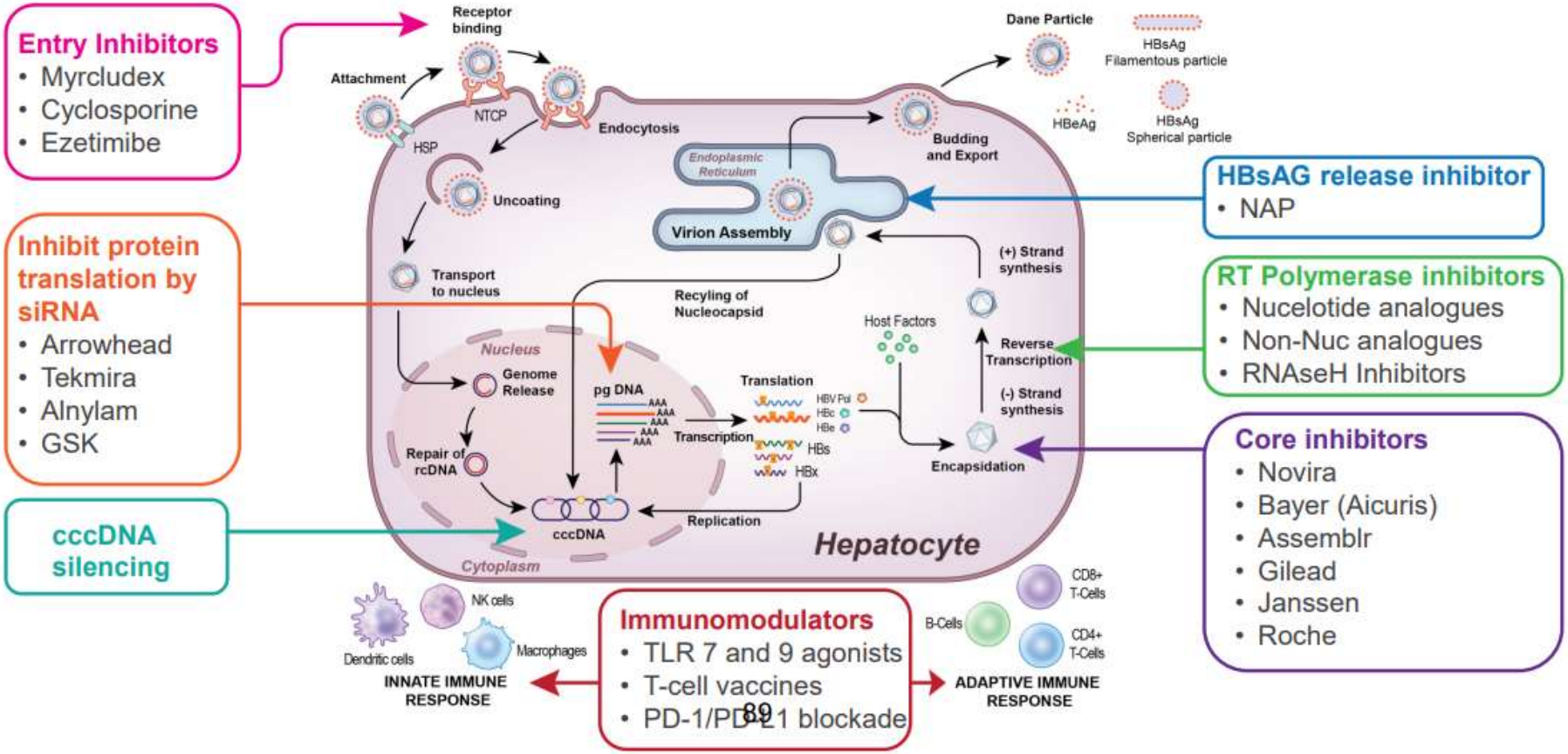
1. Wang, Sci Rep, 2016
2. Fox. J Hepatol, 2012
3. European AIDS Clinical Society. Treatment Guidelines 2016
4. Heidrich. Hepatology, 2014

# Special Tx groups

- Pregnancy:[1]
  - Screen all pregnant women.
  - Pregnant with cirrhosis or already on NA or High DNA VL (>200k) start TDF
  - Breast feeding not contraindicated
- IS or chemotherapy:[2]
  - HBsAg-positive > NA prophylaxis until week 12 post DAA
  - HBsAg-negative, anti-HBc positive > NA prophylaxis if high risk
- Extrahepatic manifestations:[3]
  - Tx with NA, PegIFN CI
  - Consider other IS

1. Chen. Hepatology, 2015
2. Reddy. Gastroenterology, 2015
3. De Virgilio.. Autoimmun Rev, 2016

# New targets






1. Ghany, AASLD meeting 2017

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# Thank you