Hepatitis B
and
Hepatitis D

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Hepatitis B

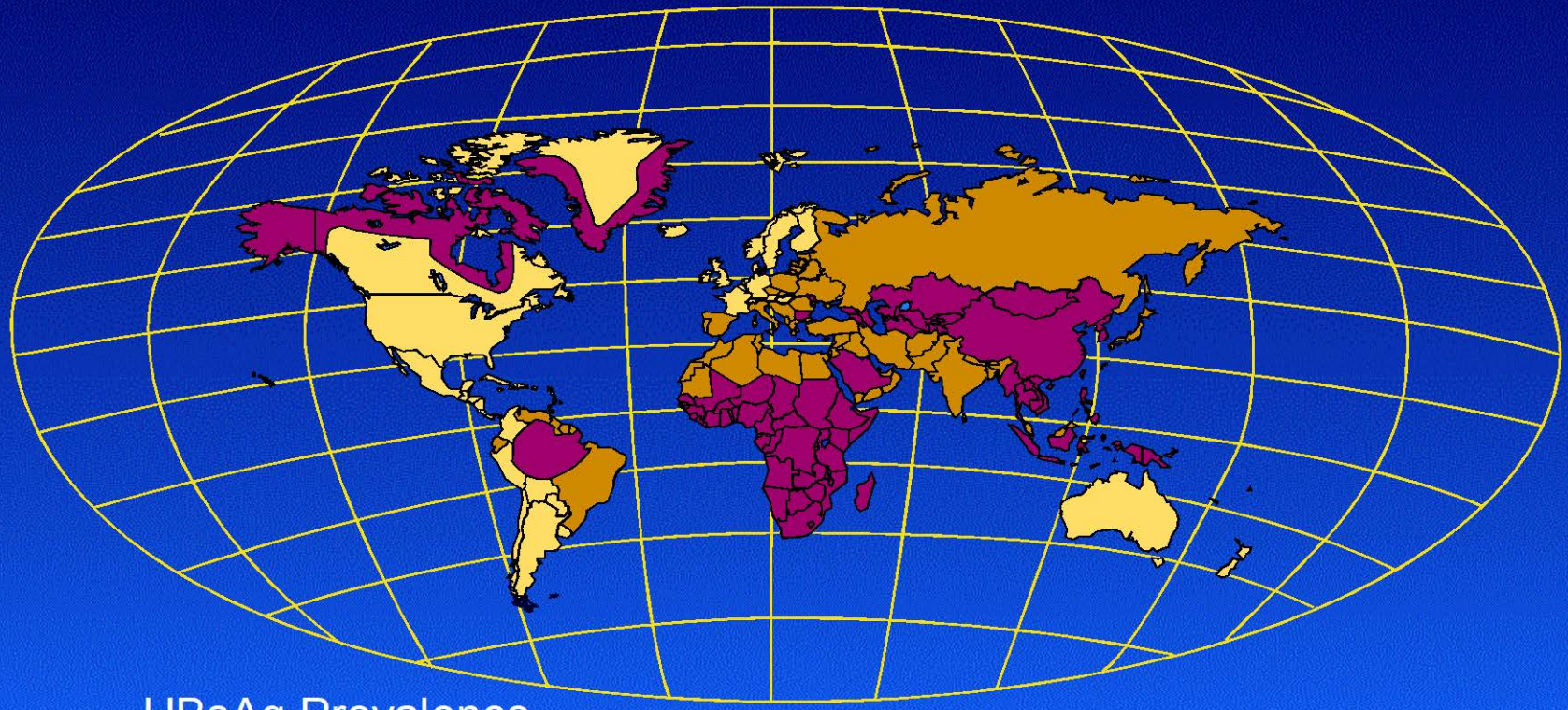
Hepatitis B

- 42 nm, partially double-stranded circular DNA virus.
- 250 million carriers world-wide;
  - causes 500000 to 1 million deaths a year (686,000 in 2013)
- 1.25 million carriers in USA.(0.5 %);
  - > 8% in Alaskan Eskimos.
- Represents 5-10% of liver transplants worldwide.
- New infections: decreasing in frequency
  - 260,000/y in 1980's;
  - now 73,000/y
- Greatest decline among children & adolescents (vaccine effect).

Hepatitis B

- Highest rate of disease in 20 to 49 year-olds
- 20-30% of chronically infected americans acquired infection in childhood.
- High prevalence in:
  - Asian-Pacific with 5-15% HBsAg(+)
  - Eastern European immigrants
- **Transmission**:
  - In USA predominantly sexual and percutaneous during adult age.
  - In Alaska predominantly perinatal.

Global Distribution of CHB Carriers



HBsAg Prevalence

Low < 2%

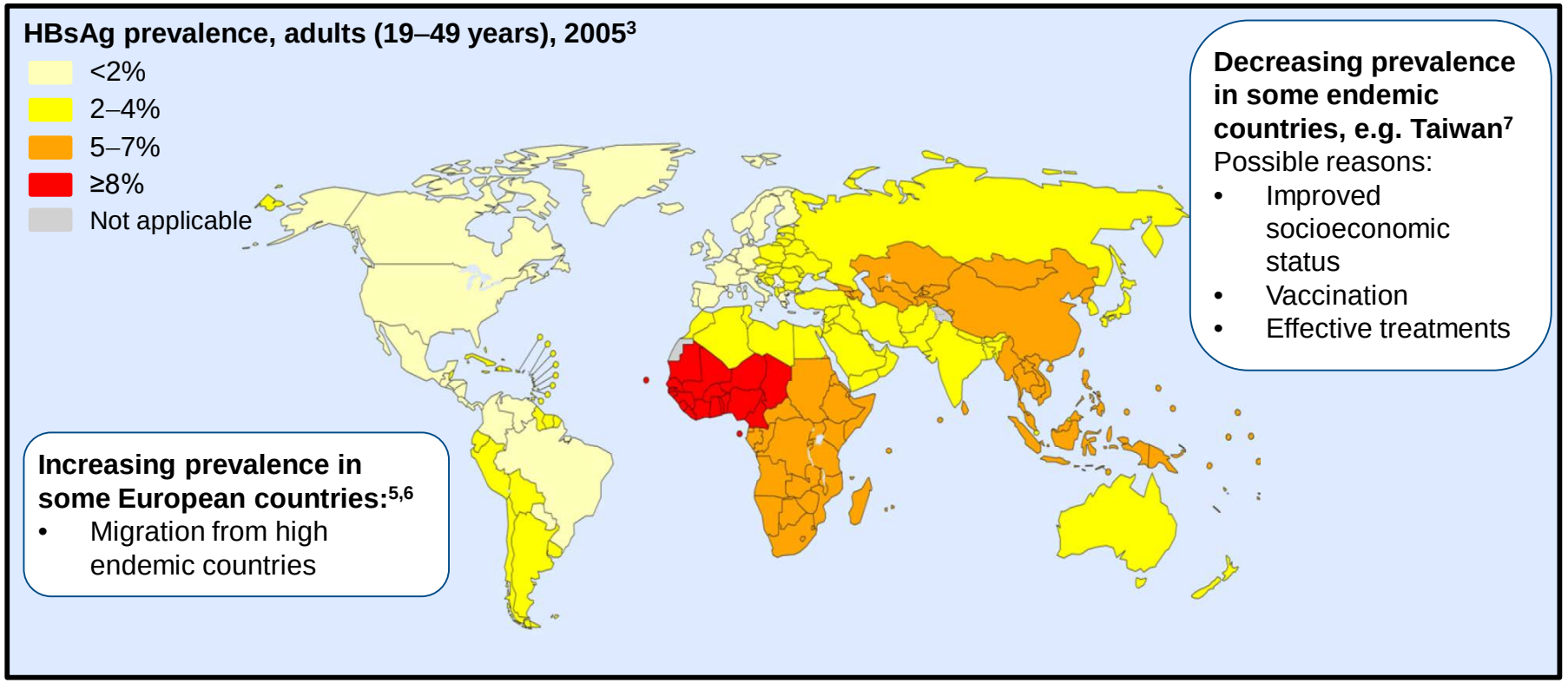
Intermediate 2-8%

High > 8%

Source: World Health Organization / Centers for Disease Control and Prevention.

Epidemiology and public health burden[1]

- Worldwide ≈250 million chronic HBsAg carriers[2,3]
- 686,000 deaths from HBV-related liver disease and HCC in 2013[4]



1. EASL CPG HBV. J Hepatol 2017;67:370–98; 2. Schweitzer A, et al. Lancet 2015;386:1546–55;
3. Ott JJ, et al. Vaccine 2012;30:2212–9; 4. GBD 2013 Mortality and Causes of Death Collaborators. Lancet 2015;385:117–71;
5. Coppola N, et al. Euro Surveill 2015;20:30009; 6. Hampel A, et al. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2016;59:578–83; 7. Chen C-L, et al. J Hepatol 2015;63:354–63.

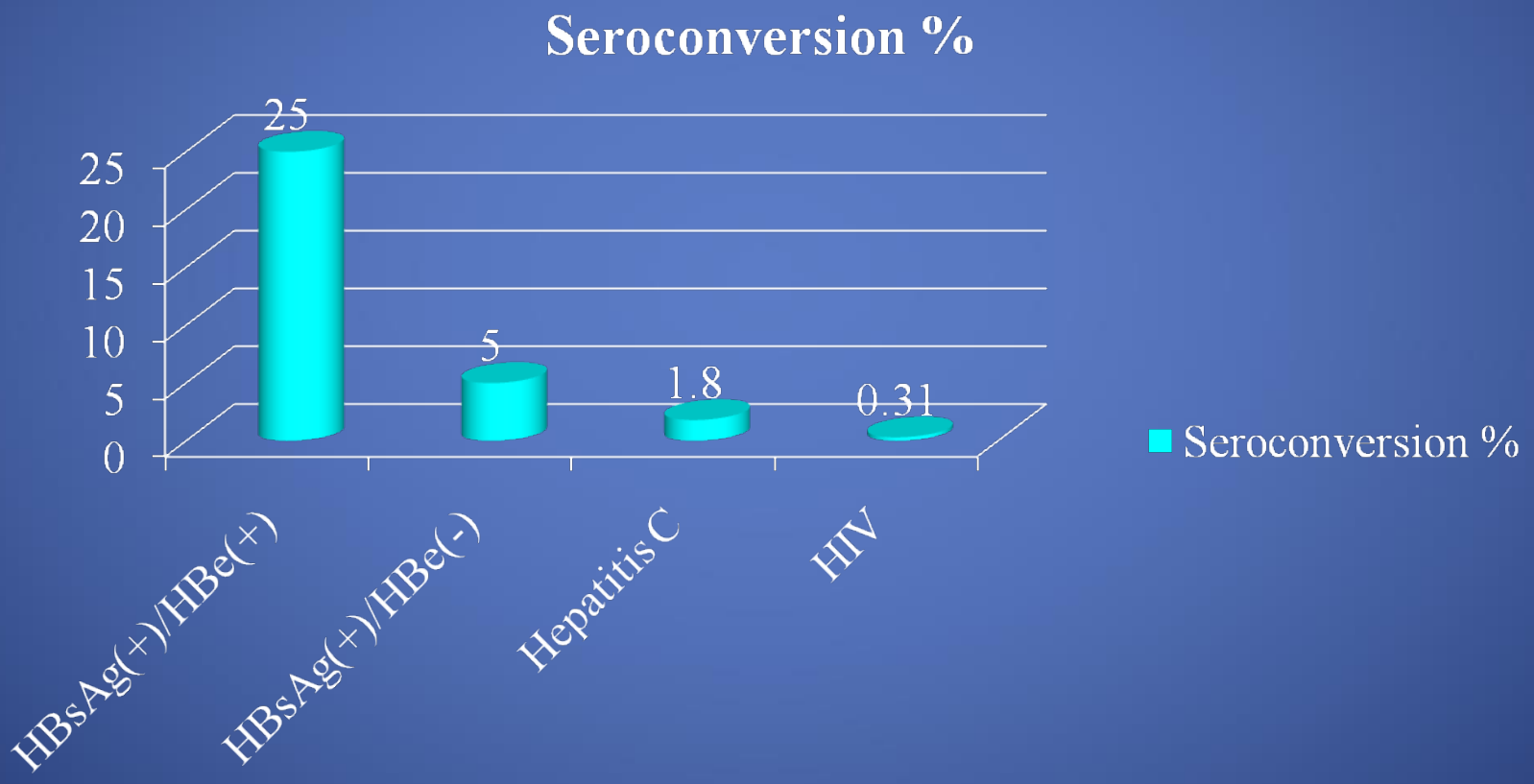
EASL™ The Home of Hepatology

Hepatitis B Transmission

- **Sexual**:
  - Heterosexual in 41% of acute cases.
  - Men having sex with men have 10% risk.
- **Percutaneous** (mostly illicit drug use):
  - 15% of acute HBV cases
- **Perinatal**:
  - 10% of acute cases (mother-child)
- **Transfusion**:
  - 1/63000 transfusions.
- **Other**: organ transplant, tattoo, piercing, acupuncture, …

Risk of Seroconversion after percutaneous exposure to infected source (without prophylaxis)

Epidemiol Rev 1994;16:437-450 & MMWR 1998;47(RR-19):1-39



Seroprevalence of HBV, HCV & HIV

Seroprevalence	HBV	HCV	HIV
General Population	0.42%	1.8%	0.31-0.42%
HCW population	Higher	Same	Same

Risk of Infection by Mode of Exposure to HCWs

	HBV	HCV	HIV
Percutaneous	6-30%	1.8%	0.2-0.5%
Mucosal	Transmission documented	Transmission documented	0.09%
Nonintact Skin	Transmission NOT documented	Transmission NOT documented	< 0.1%
Human Bite	Transmission documented	Transmission documented	Transmission documented

Infective Material Causing HCWs Infection

	HBV	HCV	HIV
Documented	Blood Blood products	Blood Immunoglobulins	Blood Blood products Body fluids
Possible	Semen Vaginal fluid Bloody fluids Saliva	Blood products Bloody fluids Semen Vaginal Fluids	Semen Vaginal fluid Cerebrospinal fluid Breast milk Serosal fluids Amniotic fluid Exudates Saliva in dental exam
Unlikely	Urine Feces	Saliva Urine Feces	Saliva Urine Feces

Postexposure Prophylaxis for Occupational Percutaneous or Mucosal Exposure to HBV

Status of Exposed	HBsAg(+) Source	HBsAg(-) Source	Not tested/ Unknown Source
Unvaccinated	HBIG 0.06 mL/kg or 5mL IM x 1 Vaccinate (0,1,6,12 mo)	Vaccinate	Vaccinate
Vaccine responder	No treatment	No treatment	No treatment
Vaccine non-responder	HBIG 0.06 mL/kg or 5 mL IM x 2, 30 d apart Re-vaccinate	No treatment	If "high risk" source, treat as HBsAg(+)
Vaccinated; unknown response	**Test anti-HBs titer** If > 10 mIU/mL: No treatment If < 10 mIU/mL: HBIG 0.06 mL/kg or 5 mL IM x 1 + Revaccinate x3 dose and test titer	No treatment	**Test anti-HBs titer** If > 10 mIU/mL: No treatment If < 10 mIU/mL: Revaccinate x 3 dose and test titer

Post-Exposure Prophylaxis

Non-Occupational Exposure to HBV

Vaccination and/or antibody response status of exposed person	Treatment when source person is	
	HBsAg-positive/source unknown or not available for testing	HBsAg-negative
Unvaccinated/nonimmune	HBIG × 1; initiate HBV vaccine series	Initiate HBV vaccine series
Previously vaccinated, known responder (anti-HBs > 10 mIU/mL)	No treatment	No treatment
Previously vaccinated, known nonresponder (anti-HBs < 10 mIU/mL)	HBIG × 1 and initiate revaccination or HBIG × 2, 30 days appart	No treatment
Previously vaccinated, antibody response unknown	Single vaccine booster dose	No treatment
If still undergoing vaccination	HBIG × 1; complete series	Complete series

Intra-dermal HBV Vaccination for Vaccine Non-Responders

Levitz RE, Cooper BW, Regan HC. *IC and H Epidemiology 1995;16:88-90. ;*
Fabrizi F, Andrulli S, Bacchini G, Corti M, Locatelli F. Nephrol Dial Transplant. 1997 Jun;12(6):1204-11.

- 1. Week 0: give adult hepatitis B vaccine Engerix B, 0.25cc intra-dermal in forearm
- 2. Week 2: give adult hepatitis B vaccine Engerix B, 0.25cc intra-dermal in other forearm
- 3. Week 4: draw HBsAb (post hepatitis B vaccine)
  - HBsAb > 10 mIU/mL = Immune, no further vaccine
  - HBsAb < 10 mIU/mL = repeat steps 1, 2, 3
- If HBsAb < 10 mIU/mL after second series of intradermal hepatitis B vaccine refer to Employee Health for counseling
  - some protocols give 16 weekly intradermal doses of 0.25 mL Engirex B (80 mcg total).

HBsAg(+) Healthcare Worker

- CDC says:
  - “Those who are HBeAg(+) should not perform exposure-prone procedures without previous counseling and advice from an expert review panel regarding under which circumstances they should be allowed to perform those procedures”.
  - They should notify the patient about their HBV status prior to the procedure.
- In Europe different countries use HBV-DNA varying from 200 IU/mL to < 2000 IU/mL to allow performance of exposure-prone procedures. Monitoring for compliance is needed.

Hepatitis B Transmission in Pregnancy

Hepatitis B
Extent of the Problem

- More than 2000 million infected worldwide
  - 75% in Asia, Western Pacific & sub-Saharan Africa
  - 360 Million with chronic infection (viremia)
  - 600000 deaths per year
- Prevalence:
  - > 8% sub-Saharan Africa, Asia, Amazon Basin;
  - 2-8% Middle East, Eastern Europe, Indian subcontinent;
  - < 2% Western Europe, Australia, Americas

Hepatitis B
Effect of HBV on the Pregnancy

- Prevalence is the same as in general population
- Usually asymptomatic.
- Cirrhosis is uncommon in young childbearing women.
- May increase risk of:
  - perinatal mortality (Safir et al. Liver Intl 2010;30:765-70; Tse KY et al. J Hepatol2005;43:771-5),
  - pre-term birth,
  - low birth weight,
  - gestational diabetes,
  - antepartum hemorrhage

Hepatitis B or C and Perinatal Outcome

Safir A et al. Liver Intl 2010;30:765-70

Characteristics	Odds Ratio (OR)	95% CI	p-value	Adjusted OR	95% CI	p-value
Perinatal Mortality	1.8	1.1-2.9	0.016	1.8	1.1-2.9	1.015
Low birth weight (<2.5 kg)	1.4	1.1-1.7	0.009	1.3	1.1-1.7	0.021
Congenital Malformations	1.4	1.1-1.9	0.011	1.4	1.1-1.9	0.012

Chronic Hepatitis B and Hepatitis C increase the risk of Perinatal mortality, low birth weight, and congenital malformations

Hepatitis B
Effect of the Pregnancy on HBV

- Usually disease remains stable and ALT decreases.
- Exacerbation with liver failure is very uncommon.
- Post-partum, one third will have flare up:
  - More frequent in HBeAg(+) than in HBeAg(-).
  - Frequently associated with increased viral load followed with flare at 15-18 weeks post-partum.
  - Flares sometimes lead to viral clearance but are also occasionally severe and fatal.
  - If in short-term antivirals, 50-60% flare up after discontinuation.
  - No clear evidence of decreasing frequency nor severity of flare ups prolonging post-partum antivirals from 4 to 12 weeks (Nguyen V et al. Aliment Pharmacol Ther 2014;39:1225-34).

Hepatitis B
Mother-to-Child Transmission (MTCT)

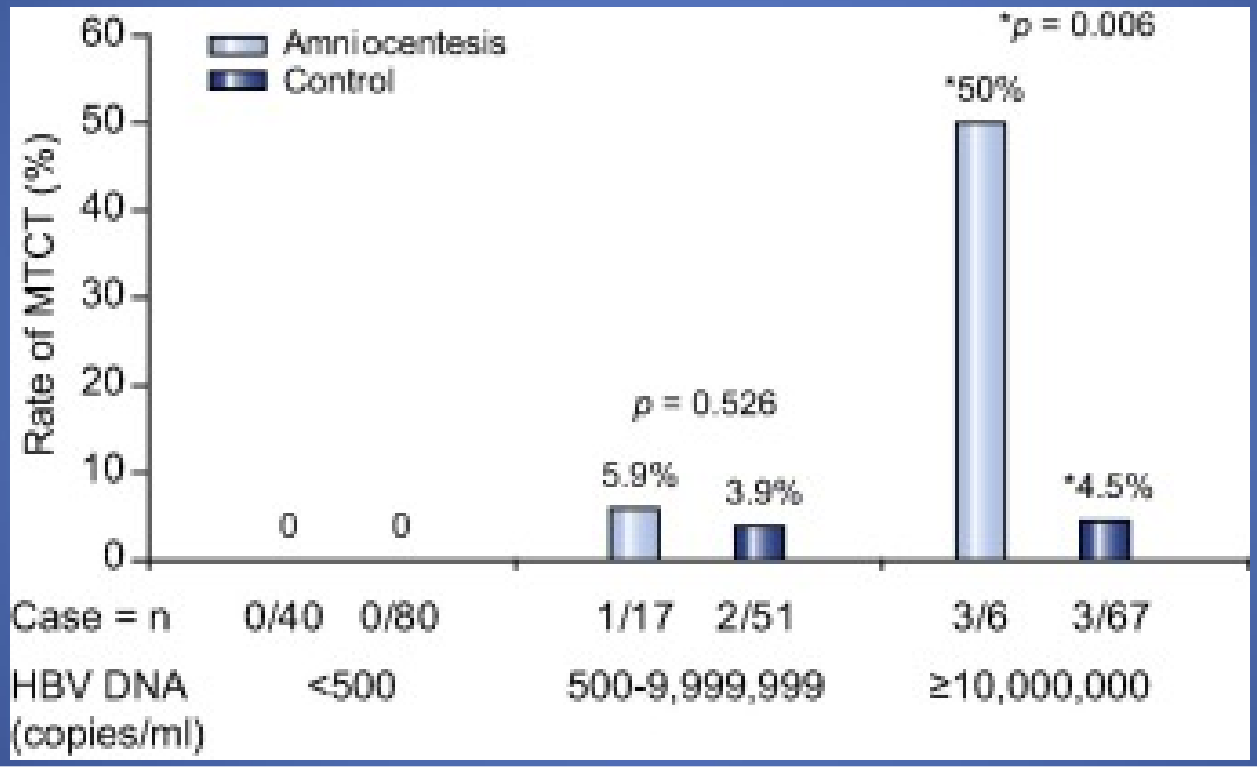
- Risk of MTCT without Post Exposure Prophylaxis (PEP):
  - HBsAg(+)/HBeAg(-): 2-20%
  - HBsAg(+)/HBeAg(+): 90%
    - HBeAg can pass through the placenta and induces T-cell tolerance facilitating chronic HBV in infant.
  - Post-Exposure Prophylaxis (PEP) is extremely effective if HBV-DNA < 10^6 copies/mL (< 200,000 IU/mL) (Pan CQ et al. Clin Gastroenterol Hepatol 2013;11:1349-55)
- In mother with Acute HBV:
  - Highest MTCT is in 3rd trimester infection (68%)
  - Compared with 1st or 2nd trimester infection (1.8%)
- Pre-embryonic infection can occur (HBV present in sperm, oocytes and embryos)
  - Sperm washing and sperm & embryo cryopreservation may reduce risk.

Hepatitis B
Mother-to-Child Transmission (MTCT)

- Intrauterine transmission is rare (3.7-4%).
- Amniocentesis increases MTCT rate (Yi W et al. J Hepatol 2014;60:523-9), especially if:
  - HBV-DNA >/= 10^7 copies/mL or >/= 2 x 10^6 IU/mL (50% vs 4.5%),
  - HBeAg(+), and
  - When amniocentesis is trans-placental.
- Chorionic villous sampling has higher transmission risk than amniocentesis.

Relation of HBV Viral Load (copies/mL) with Risk of MTC Transmission During Amniocentesis

Yi W et al. J Hepatol 2014;60:523-9



Amniocentesis Increases the Risk of Fetal HBV Infection, specially if maternal HBV-DNA is 10 Million copies/mL or more

Hepatitis B
Predictors of MTCT

- Mode of Delivery:
  - Urgent C-section and vaginal delivery are equivalent
  - Elective C-section has very-small benefit over delivery, when both are used with PEP.
    - Elective C-section is not recommended.
- Breast Feeding:
  - No difference in infection in meta-analysis of breast-fed vs formula-fed infants receiving immune-prophylaxis (Shi Z et al. Arch Pediatr Adolesc Med. 2011 Sep;165(9):837-46.)
    - Breast feeding is encouraged.
  - Tenofovir alafenamide fumarate (TAF) will have even lower levels in milk than TDF (T disoproxil F).
- Genetics: no known effect.
- Bathing:
  - Bathing newborn with mild soap solution, to remove contaminated fluids, might decrease risk.
- Father and siblings with HBV:
  - Vaccination + HBIG (dual post-exposure prophylaxis) decreases horizontal transmission.

Hepatitis B
Methods to Prevent MTCT by Post-Exposure Prophylaxis (PEP)

- Vaccination + HBIG to Newborn (dual PEP):
  - **USA Standard for HBV < 200,000 IU/mL**
  - Meta-analysis shows decrease of MTCT with OR: 0.54 compared with vaccine alone (mostly HBeAg(+)).
  - HBIG and Vaccination start within 12 hours from birth
- Third Trimester Antivirals against HBV + Vaccination +/- HBIG:
  - **USA Standard for HBV > 200,000 IU/mL (with HBIG & vaccine within 12 hours from birth)**
  - Antiviral usually starts at week 28-32 of pregnancy, and ends 4 week post-partum, unless mother has medical indication for continuous therapy.
  - HBIG and Vaccination start within 12 hours from birth.

Vaccination Regimens for Newborn from HBV(+) Mother

- Within 12 hours of birth:
  - Single Antigen vaccine (not counted in “true vaccination” schedule) +
  - Hepatitis B Immune Globulin (HBIG) (0.5 mL IM in the anterolateral thigh), followed by “true vaccination”.
- Single Antigen Hepatitis B Vaccine:
  - Recombivax HB or Egerix B: 1, 2, and 6 months, or
- Combination Antigen Vaccines:
  - Pediarix (diphtheria, tetanus toxoids, acellular pertussis adsorbed, hepatitis b and inactivated poliovirus): 2, 4 and 6 months, or
  - Comvax (Haemophilus B + Hepatitis B): 2, 4, and 12 months.
- Test for Response:
  - HBsAg and anti-HBs titer at age 9-15 months, but not before 4 to 8 weeks after last vaccination.
  - Protective titers are > 10 IU/mL (best if > 100 IU/mL)
  - If titer < 10 IU/mL, a second 3-dose series should be offered.

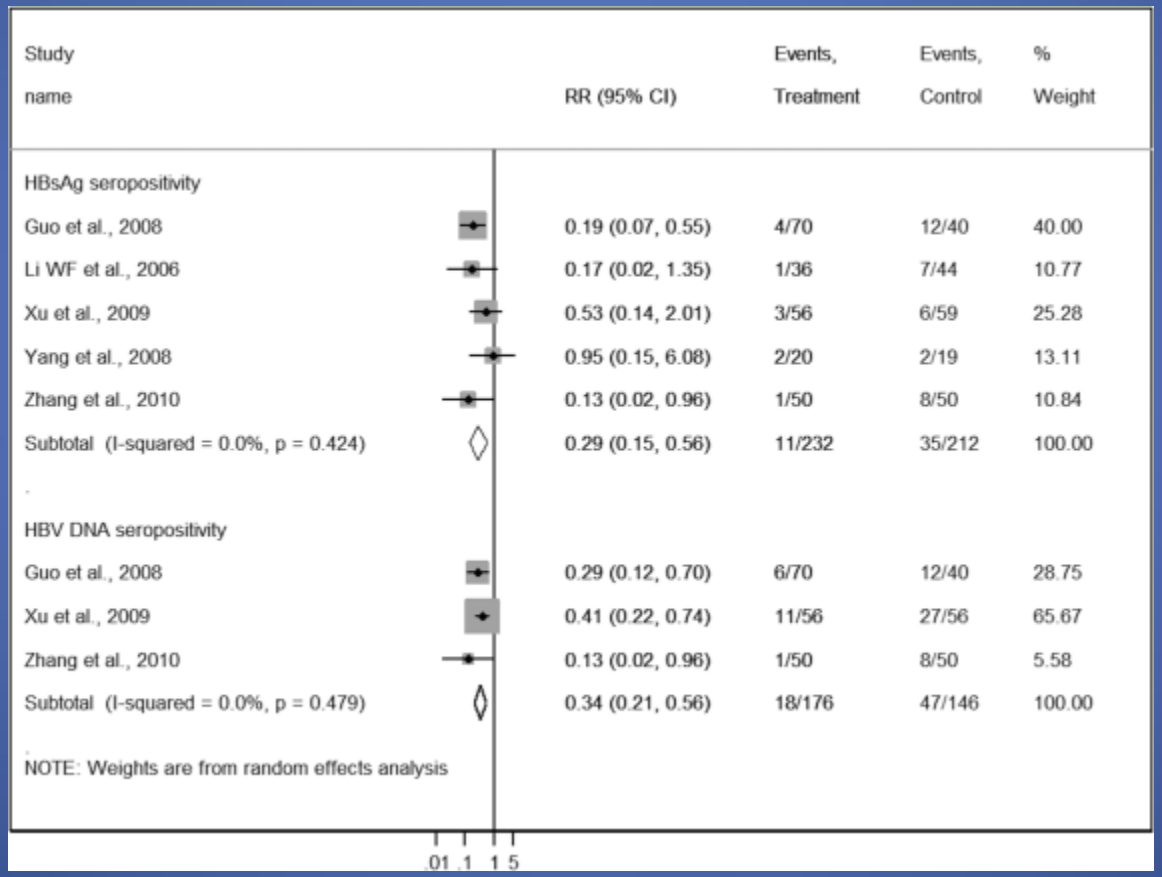
Hepatitis B

Prevention of MTCT by Antivirals + Post-Exposure Prophylaxis (PEP)

- **Choice of Antiviral:**
  - Mother HBV mono-infected and in need of therapy:
    - Tenofovir (category B).
  - Mother HBV mono-infected but without need of therapy other than MTCT:
    - Tenofovir (cat B; preferred agent),
    - Telbivudine (cat B), or
    - Lamivudine (cat C) (only if HBV-DNA is < 2 x 10^7 IU/mL before therapy; (Han L et al. World J Gastroenterol 2011;17:4231-33)
  - Mother with HIV co-infection, in need or not of HBV therapy, but not on HAART:
    - Telbivudine (cat B)
  - Mother with HIV co-infection and in HAART:
    - Tenofovir alafenamide fumarate (TAF) (cat B) as part of HAART
    - Whole-body bone mineral content of Tenofovir exposed infants born to HIV-infected mothers was 12% lower than for unexposed infants.

Effect of Maternal Antiviral Therapy in MTC HBV Transmission at 6-12 months: Meta-Analysis

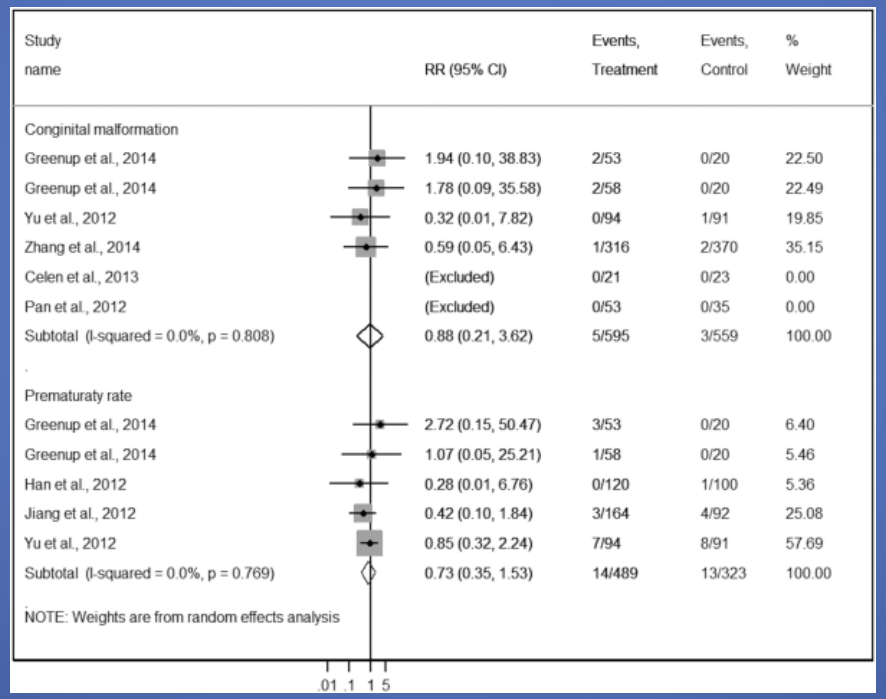
Brown RS et al. Hepatology 63(1): 319-33; 2016



Antiviral Therapy Decreases HBV Transmission to the Neonate

Meta-Analysis: Congenital Malformations and Prematurity in Maternal HBV Therapy vs Control

Brown RS et al. Hepatology 63(1): 319-33; 2016



HBV Antiviral Therapy Does NOT Increase the Rate of Congenital Malformations nor of Prematurity

Hepatitis B

Prevention of MTCT by Antivirals + Post-Exposure Prophylaxis (PEP)

- **MONITORING:**
  - Mother should be monitored for post-partum flare for at least 6 months, if antiviral therapy is discontinued or not given.
  - Mother should have regular HBV control follow up if the treatment was indicated due to mother condition
    - Cirrhosis, or
    - Elevated ALT + HBV-DNA > 2000 IU/mL in HBeAg(-) or HBV-DNA > 20000 IU/mL in HBsAg(+))
  - Mother with risk of liver cancer should be under surveillance with liver ultrasound every 6 months.
  - Child should be checked at age 9-15 months (4-8 weeks after final vaccine) for HBsAg and antibody titer.
    - If child is infected, over a follow up of up to 29 years, up to 2% may develop HCC (Bortoletti et al. Hepatology 2006;43:556-62)

Conclusion

- Testing for HBV should be routine in every pregnancy and before amniocentesis or villous sampling.
- If Hepatitis B is present, a complete evaluation of the patient should follow.
- Neonates with mothers infected with HBV should receive post exposure prophylaxis, starting within 12 hour from birth, and followed by a complete cycle of HBV vaccination and post-vaccination testing.
- If the mother HBV viral load is >/= 200,000 IU/mL, she should receive antiviral therapy to decrease the risk of vertical transmission.
- The choice of agent will depend on: need for the mother for therapy, presence of HIV infection, and presence of anti-HIV HAART therapy.
- The HBV(+) mother should be watch for 6 months after delivery, for flare up of her infection.

HBV & Pregnancy

- Pregnancy is well tolerated by HBV carriers
- HBV reactivation with exacerbation of disease is rare during pregnancy or post-partum.
- Intrauterine transmission of HBV is rare, but may occur during “threatened abortion” by transplacental leakage.
- Transmission by amniocentesis is low (</= 4%).
- If mother is HBeAg(+), risk of vertical transmission is 90% without prophylaxis.
- Post-partum “flare up” is common and due to decrease of cortisol levels. Up to 12-17% may have post-partum “e” seroconversion.

Maternal HBV Viral Load in HBeAg(+) mothers and Risk of Vertical Transmission

Han et al. AASLD Abstr 170, 2011

Viral load (IU/mL)	**< 200,000**	**2×10^5 – $2 \times 10^{5.99}$**	**2×10^6 – $2 \times 10^{6.99}$**	**>/= 2×10^7**
Viral Load (copies/mL)	**< 10^6**	**10^6 – $10^{6.99}$**	**10^7 – $10^{7.99}$**	**>/= 10^8**
# Mothers	174	298	531	239
# Neonates infected	0	9	29	23
% Neonates Infected	**0**	**3**	**5.5**	**9.6**

Neonatal Post-Exposure Prophylaxis is not enough when maternal HBV-DNA is 200,000 IU/mL (1,000,000 copies/mL) or more

HBV & Pregnancy

- If mother has HBV-DNA < 10^8 IU/ml:
  - neonatal immuno-prophylaxis prevents transmission in 95%, when done as follows:
    - HBIG 0.5 mL IM within 12 h of birth +
    - HBV immunization with 1st dose of 0.5 mL IM within 12 h of birth, in a different site from HBIG, and then vaccinate @ 1, 2, and 12 months.
- If mother is "highly infectious" with HBV-DNA > 10^8 IU/mL
  - risk of HBV transmission is 30-40% despite [HBIG + HBV immunization]
- If mother is infected with HBeAg(-) and HBV-DNA > 10^8 IU/mL ("very high load pre-core or core-promoter mutant HBV"):
  - infant is at risk of fulminant hepatitis B during initial 2 to 4 months of life.
- Pre-Partum Decrease of viral load (with antiviral therapy) to < 200,000 IU/mL decreases neonatal risk.

HBV & Pregnancy

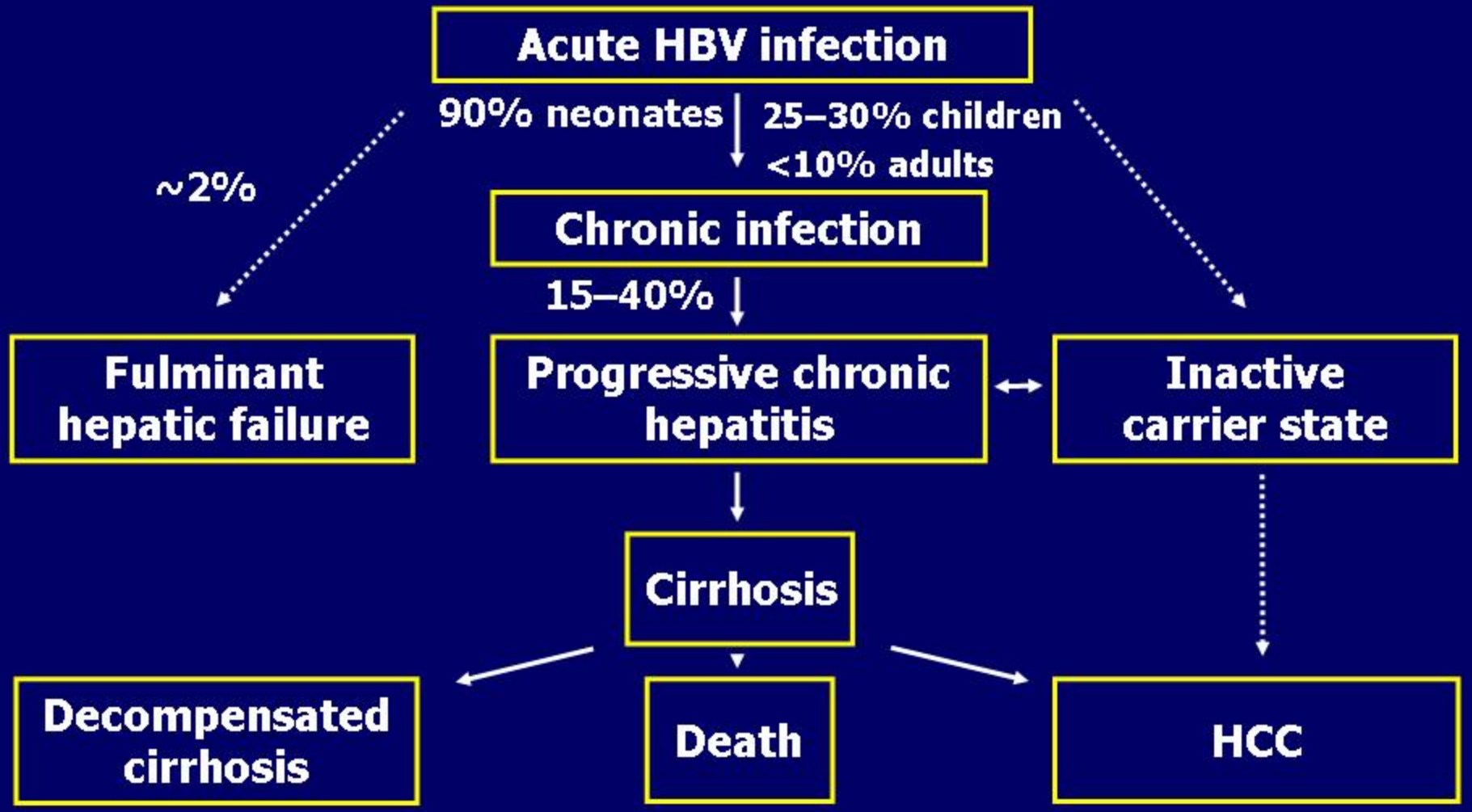
- Treatment, with Telbivudine, of mothers with HBV-DNA > $2x10^6$ IU/mL, starting in wks-24 to 32 and until wk-4 to 12 post-partum,
  - decreases transmission of HBV to the neonate from 8% to 0%.
- AASLD, APASL and EASL recommends to treat mothers, who are not in need of treatment but who have HBV-DNA > 200,000 IU/mL, with Tenofovir, to prevent perinatal transmission.
  - (Lamivudine and Telbivudine are not recommended due to higher risk of inducing resistance).
  - Treat from pregnancy week 24-28 until week 8-12 post-partum (APASL: stop immediately post-partum)
- Mothers should followed for evidence of “flare up” every 3 months, for at least 6 months after delivery or discontinuation of therapy (whichever is last).

HBV & Pregnancy

- Cesarean section decreases vertical transmission rate, but:
  - is not indicated because [HBIG + HBV immunization +/- Antiviral] is very effective.
- Mothers with HBV/HDV co-infection:
  - may vertically transmit both infections to the neonate.
  - HBIG + HBV immunization can protect from both.
- Post-vaccination testing of infant should be done at age 9-15 months.

Hepatitis B in the General Population

Spectrum of Disease



Lok AS, McMahon BJ. Hepatology 2004;39 (3):857-861.
AASLD Practice Guidelines 2003: chronic hepatitis B. Accessed via http://www.aasld.org.

Hepatitis B
High-Risk Groups

- Persons born in high prevalence area >/= 2%
- Active homosexual men
- Promiscuous heterosexuals
- Person with hx of STD
- Healthcare & Public Safety workers
- Attendant/family of institutionalized mentally handicapped
- Person with HCV or HIV
- Person with chronic elevation of ALT or AST.
- Persons undergoing cytotoxic or immunosuppressive therapy.
- Intravenous drug abuser
- Person requiring frequent transfusions
- Inmate in long-term correctional facility
- Hemodialysis patient
- Traveler > 6 months to endemic area
- Sexual partner or household contact of HBsAg(+) person
- All pregnant women
- Persons born in US from parents from areas with prevalence >/= 8%, who were not vaccinated as infants

Hepatitis B Vaccination

- All children and adolescents
- All high-risk groups
- Post-Vaccination testing:
  - **Healthcare & Public-Safety workers (1 month after 3rd dose)**
  - **Infants from HBsAg(+) mother (at age 9-15 months)**
  - **Hemodialysis patients (1 month post 3rd dose, and then yearly).**
  - **Sexual partner of HBsAg(+) persons (1 month after 3rd dose)**

HBV Vaccine in HIV Infected

- If safe, consider delaying until CD4(+) cells are =/> 200 cells/mm^3 or until HIV suppression is achieved.
- Protocol:
  - Double dose vaccine @ 0, 1, 2, and 12 months or
  - Intradermal HBV vaccination for up to 16 doses.

HBV Vaccination for People who Inject Drugs

WHO: July 2012

- Rationale:
  - Evidence shows that both a rapid schedule as well as providing incentives to people who inject drugs helps increase uptake and completion of HBV vaccination.
    - Vaccinations should be provided at a location and time convenient for people who inject drugs.
- Protocol:
  - Rapid schedule at days: 1, 7, and 21

Recommendations for HBsAg(+) Persons

- **PRECAUTIONS**

- Have sexual contacts vaccinated
- Use barrier sexual protection unless partner is immune
- Not share razors, toothbrushes
- Cover open cuts & scratches
- Clean blood spills with detergent or bleach
- Not donate blood, semen, organs.

- **ENCOURAGEMENTS**

- Can participate in all activities, including contact sports.
- Should be included in usual daycare and school activities, without isolation from others.
- Can share food & utensils, and kiss others.
- Breast feeding is recommended if the baby is being immunized with HBIG + vaccine.

Acute HBV

Acute Hepatitis B

- **Incubation**: 1-4 months
- **Prodrome**: arthralgia, arthritis, skin rash
- **Symptoms**: malaise, anorexia, jaundice, nausea, fatigue, low-grade fever, myalgia, change in taste and smell. Tender hepatomegaly in most patients; splenomegaly in 5-15%.
- Infrequently: confusion, edema, coagulopathy, coma (Fulminant Failure in 0.5%)

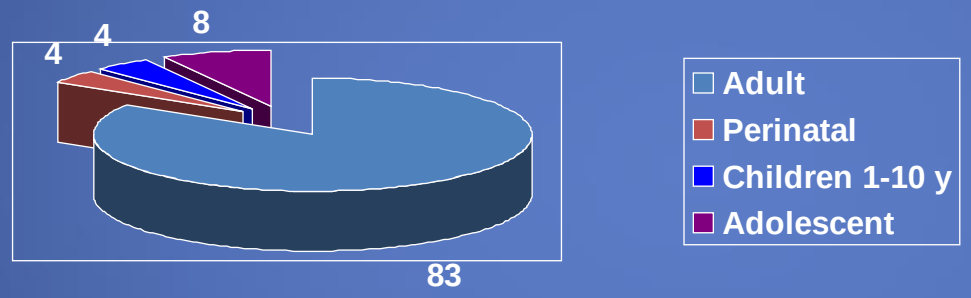
Acute Hepatitis B

- **Diagnosis**:
  - anti-HBc IgM antibody (+) usually with signal/noise ratio > 5.08 (s/n ratio </= 5.08 suggest reactivation of chronic infection);
  - Frequently HBsAg (+) in early phase and anti-HBs(+) in late phase.
  - HBV-DNA usually around 1000 IU/mL (in reactivation of chronic HBV usually >/= 1 million IU/mL)
- **Evolution to Chronicity**:
  - a) Infants: 90%,
  - b) Children 1-5: 25-50% (**30%**) ,
  - c) Adults & older children: 5%

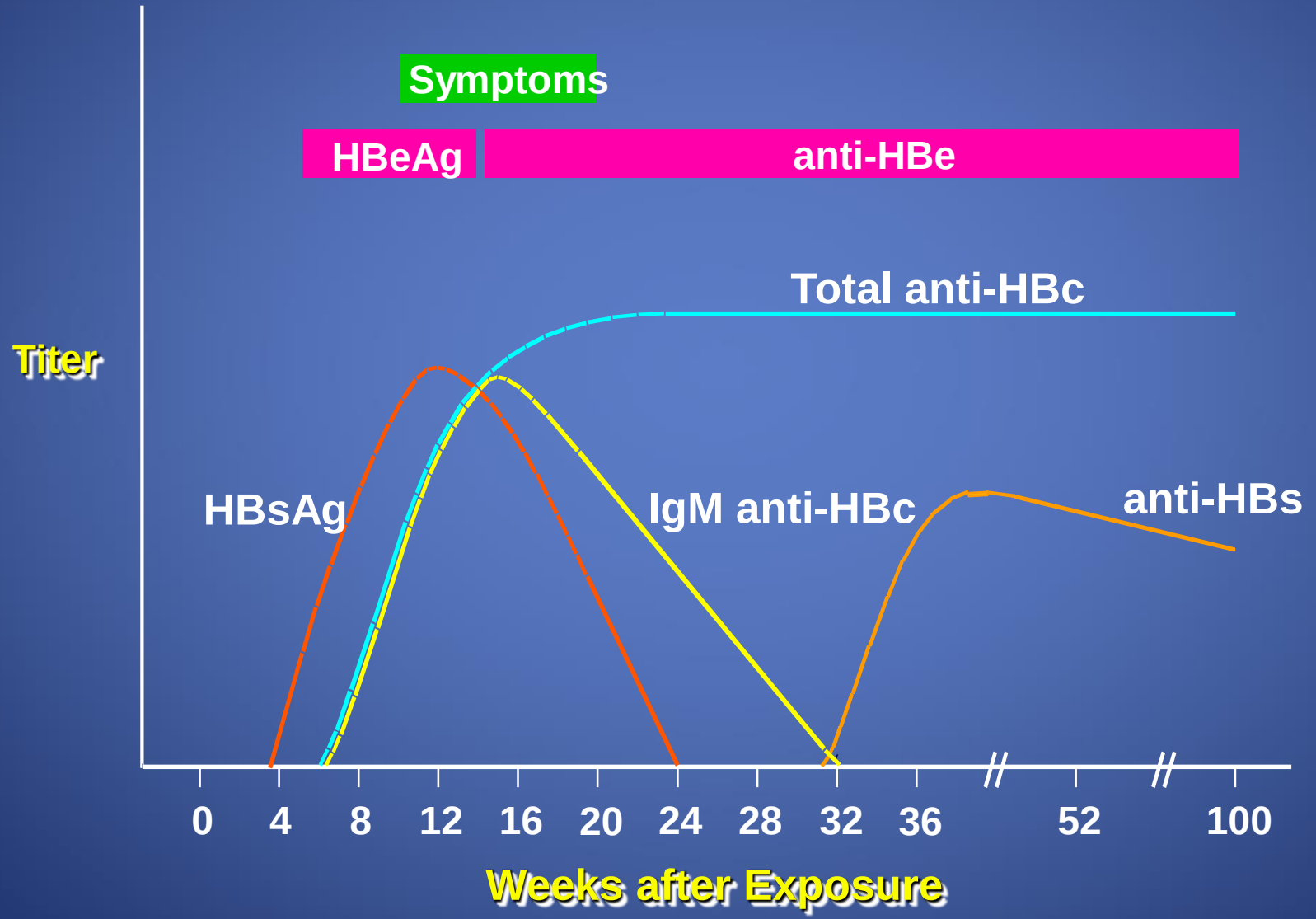
Acute Hepatitis B

- **Treatment**:
  - Supportive;
  - Anti-virals in “protracted hepatitis”, or failure to regenerate/sub-massive necrosis.
    - Lamivudine or Entecavir has been recommended for these cases.
  - In one study of 80 patients with severe acute HBV infection receiving either lamivudine or no therapy, mortality was significantly higher in the control group at 25.0% vs the lamivudine group at 7.5% (*P* = .034)
    - (Dig Dis Sci 2010;55:775-83)
  - Duration:
    - At least 3 months after development of anti-HBs, with HBsAg loss,
    - 12 months after anti-HBe seroconversion without HBsAg loss.

Age of Acquisition of Acute Hepatitis B 1989 estimates



Acute Hepatitis B Virus Infection with Recovery
Typical Serologic Course



Chronic HBV

Chronic Hepatitis B

- In low prevalence areas (USA) 30-50% history of acute hepatitis (rare in high prevalence)
- **Symptoms**: frequently asymptomatic; sometimes RUQ or epigastric pain or acute-like hepatitis episodes.
- **Extrahepatic**: serum-sickness, polyarteritis nodosa, membrano- or membranoproliferative- glomerulonephritis, mixed cryoglobulinemia, IgA nephropathy, papular acrodermatitis.

Extra hepatic Manifestations of HBV

- **Arthritis-Dermatitis**
  - **Manifestations:** fever, arthralgias, rash, angioneurotic edema, and, less commonly, hematuria and proteinuria is seen as a prodromal manifestation of acute hepatitis B and rarely in patients with chronic hepatitis B.
  - **Arthralgia:** proximal interphalangeal joints, knees, ankles, shoulders, and wrists are the joints most commonly affected.
  - **Laboratory:** HBsAg titers in the blood are high and complement levels are low.
    - HBsAg has been detected in synovial membranes, and complement levels in synovial fluid are low.
    - Evidence of activation of the complement system by HBsAg–anti-HBs complexes.

Extra hepatic Manifestations of HBV

- **Polyarteritis Nodosa**
  - As many as 30% of patients with polyarteritis nodosa are infected with HBV.
  - Occurs in less than 1% of patients with HBV infection,
    - after acute or recent hepatitis B or,
    - more commonly, in association with chronic HBV infection.
  - **Manifestations:** arthralgias, mononeuritis, fever, abdominal pain, renal disease, hypertension, central nervous system abnormalities, and rash.
  - **Pathogenesis:** Medium to small arteries and arterioles with fibrinoid necrosis and perivascular infiltration due to deposition of circulating immune complexes that contain HBsAg.
    - No apparent relationship exists between the severity of the vasculitis and the severity of the hepatic disease, and the hepatic disease often is relatively mild despite high levels of viral replication.

Extra hepatic Manifestations of HBV

- **Polyarteritis Nodosa**
  - **Diagnosis:**
    - Arteriography of mesenteric or renal vessels showing cork-screwing and aneurisms.
    - Biopsy of affected organ showing arteritis of medium size arterioles.
  - **Course:** variable, but the prognosis is gravest for patients with substantial proteinuria (>1 g/day), renal insufficiency (serum creatinine > 1.6 mg/dL), gastrointestinal involvement, cardiomyopathy, and involvement of the central nervous system.
  - **Management:** antiviral agents, given alone or in combination with plasmapheresis.

Extra hepatic Manifestations of HBV

- **Glomerulonephritis**
- Most common types:
  - membranous glomerulonephritis and membranoproliferative glomerulonephritis.
- Pathogenesis:
  - Renal biopsy with immune complex deposition and cytoplasmic inclusions in the glomerular basement membrane.
  - The immune complexes activate complement and production of cytokines with a subsequent inflammatory response.
- Manifestations:
  - Nephrotic syndrome is the most common presentation.
  - In affected children, renal failure at presentation is almost always mild, and a history of clinical liver disease is uncommon.
  - Liver biopsy specimens almost always demonstrate varying degrees of chronic hepatitis.

Extra hepatic Manifestations of HBV

- **Glomerulonephritis**
- Diagnosis:
  - serologic evidence of HBV antigens or antibodies, the presence of immune-complex glomerulonephritis in a renal biopsy specimen, and the demonstration of glomerular deposits of one or more HBV antigens, such as HBsAg, HBcAg, or HBeAg, by immunohistochemistry.
  - Most patients have detectable HBeAg in serum and, in addition, demonstrate low serum C3 and occasionally low C4 levels.
- Evolution:
  - Children: The renal disease typically resolves in months to several years. Often, resolution occurs in conjunction with HBeAg seroconversion. Rarely, however, renal failure may ensue.
  - Adults: natural history has not been well defined, but several reports suggest that glomerular disease is often slowly and relentlessly progressive.
- Treatment:
  - Interferon alpha. Linked to long-term control of HBV replication.
  - Therapy with nucleoside analogs has resulted in improved renal function and diminished proteinuria.

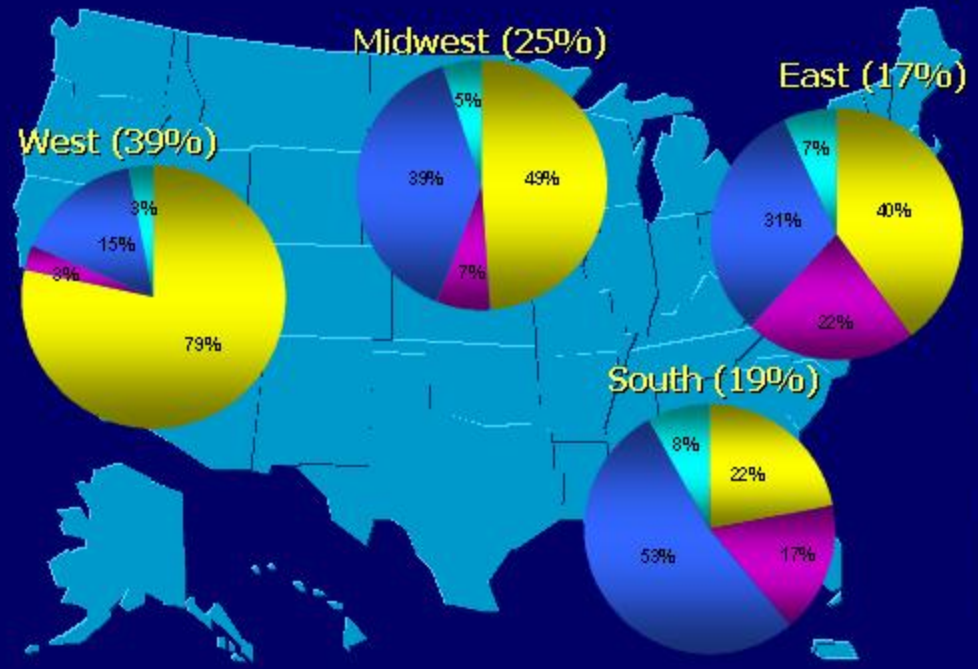
Extra hepatic Manifestations of HBV

- **Cryoglobulinemia:**
- Type II and type III cryoglobulinemia have been associated with hepatitis B, but the association is uncommon.
  - Type II cryoglobulins consist of a polyclonal IgG and monoclonal IgM,
  - Type III cryoglobulins contain polyclonal IgG and rheumatoid factor.
    - Frequency of cryoglobulinemia is higher in with chronic HCV infection (54%) than with chronic HBV infection (15%).
- Manifestations:
  - systemic vasculitis (purpura, arthralgias, peripheral neuropathy, and glomerulonephritis),
  - often paucisymptomatic or asymptomatic.
- Treatment:
  - Interferon has been used successfully to treat symptomatic HBV cryoglobulinemia.
  - Experience with nucleoside analog therapy has not been reported.

Chronic Hepatitis B
Natural History

- Evolution to Chronicity after Acute HBV:
  - 90% of infants infected at birth
  - 30% of children infected at age 1-5 y
  - 6% of infected after age 5 y
- Cumulative cirrhosis risk:
  - 8-20% at 5 y.
- Risk of decompensation in untreated HBV cirrhosis:
  - 20% at 5 y
- Survival for untreated decompensated cirrhosis:
  - 14-35% at 5 y.
- Death from chronic HBV liver disease
  - 15-25% of chronically infected
- Risk of HCC in HBV cirrhosis:
  - 2 – 5% per year.
- USA yearly mortality from HBV
  - 5000 per year

Chronicity of HBV

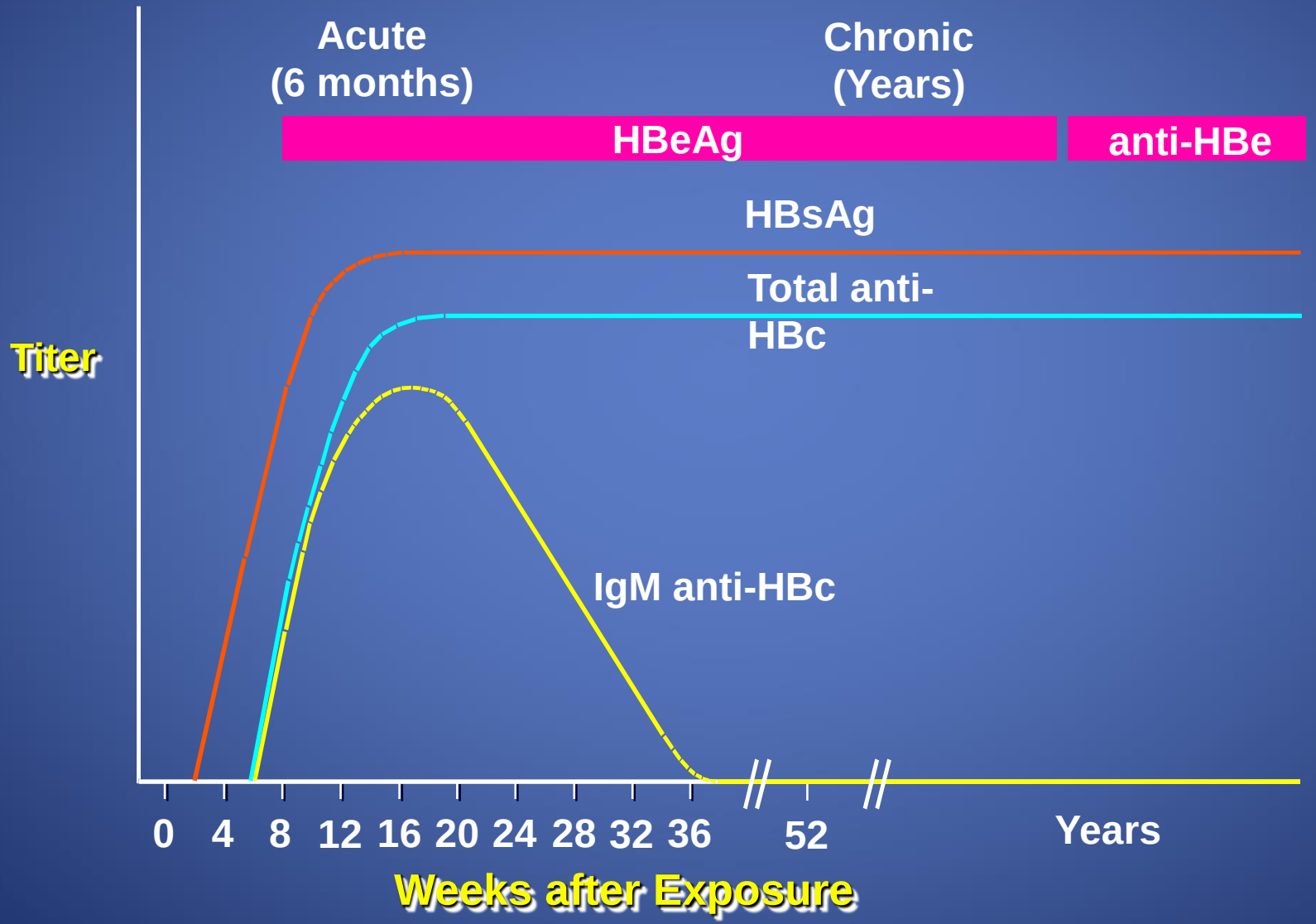


In a survey of 17 liver centers across the US, approximately 56% of HBV carriers were of Asian descent

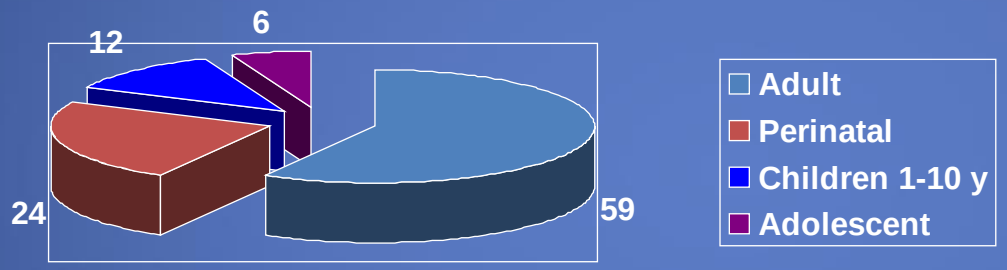
Patient Type	Mode Transmission	Percent Developing Chronic HBV
• U.S.-born	• Sexual, Parenteral	• 2-10%
• Foreign-born (Asia)	• Perinatal (vertical)	• 80-90%

Chu. *Gastroenterology*. 2003;125(2):444-451.

Progression to Chronic Hepatitis B Virus Infection
Typical Serologic Course



Age of Acquisition of Chronic Hepatitis B 1989 estimates



HBV Genotypes

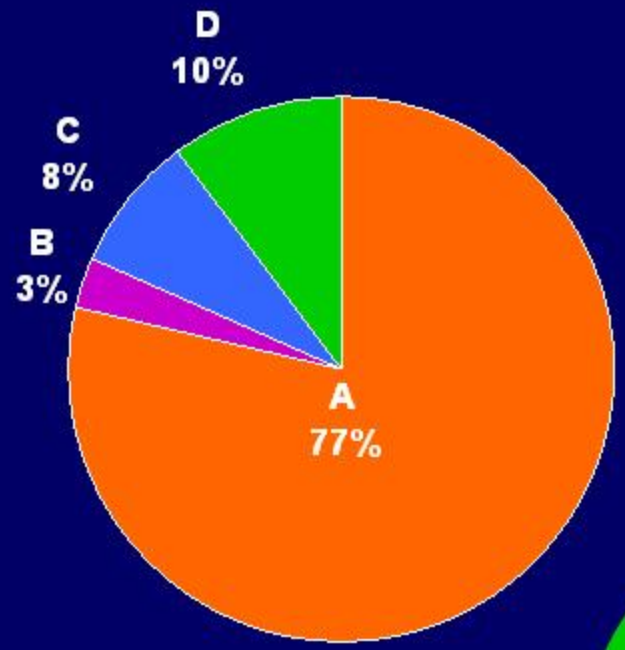
Test genotype with: INNO-LiPA HBV Genotyping

Genotype	Areas of prominence
A	North West Europe, USA, Central Africa
B	Taiwan, Japan, Indonesia, China, Vietnam
C	East Asia, Taiwan, Korea, China, Japan, Vietnam
D	Mediterranean area, India
E	West Africa
F	Central and South America
G	France, USA
H	Mexico, Central and South America

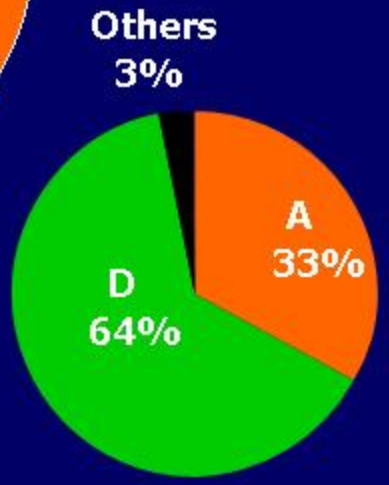
Kao et al. *J Gastroent Hepatol.* 2002.

HBV Genotypes and Place of Birth

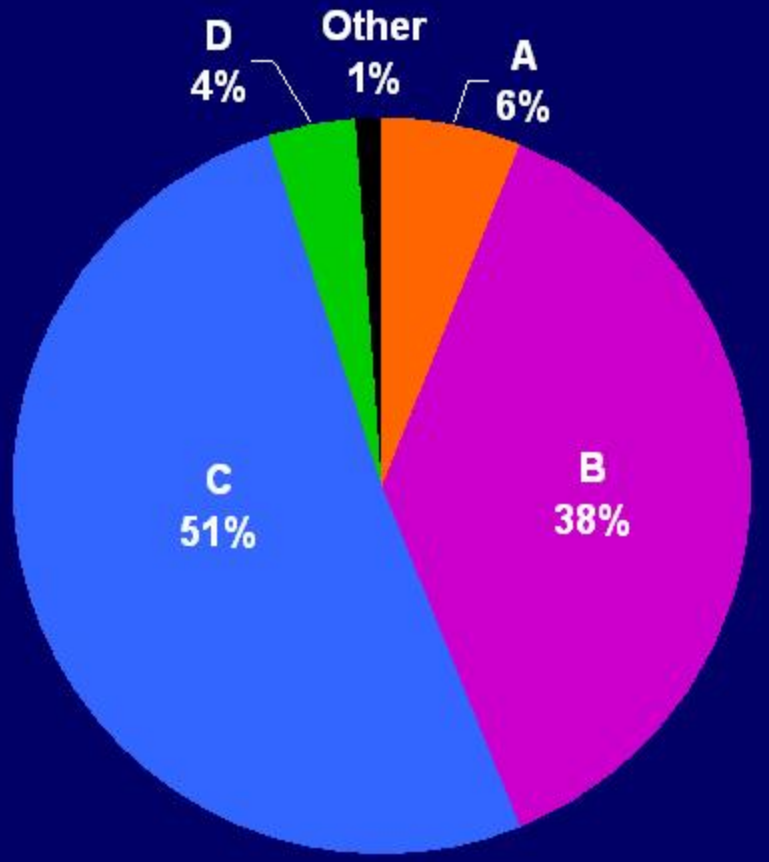
Test genotype with: INNO-LiPA HBV Genotyping



U.S.
n=184



Europe
n=30



Asia
n=284

Chu et al. Gastroenterology. 2003;125:444-451.

Clinical Associations with Genotypes

- Time to HBeAg seroconversion and probability of HBsAg loss:
  - B < C
- Response to treatment with interferon-α:
  - A > B ≥ C > D
- Precore/core promoter mutant frequency:
  - precore mutation not selected with A and F
- Liver disease activity and risk of progression:
  - B < C
- Evolution to chronic liver disease:
  - A < D
- Hepatocellular carcinoma risk:
  - B > C in younger age group in Taiwan, but
  - B < C in older age group in Japan

Characteristics of HBV genotype C

- HBe seroconversion at older age
  - (< 20 vs 48 years)
- Higher rate of HBe reversion, HBe(-) to (+).
- Greater risk of reactivation
- More severe histology
- Higher incidence of HCC
- Lower response to regular IFN

Prognostic Factors For Progression To Cirrhosis

Factors	P-value
Older age	.0001
HBV-DNA persistance	.0001
Virus genotype C	.001
Recurrent acute flares	.001
Histologic Staging	.0002
Alcohol consumption	.001
HCV, HDV co-infection	.001
HIV co-infection	.02

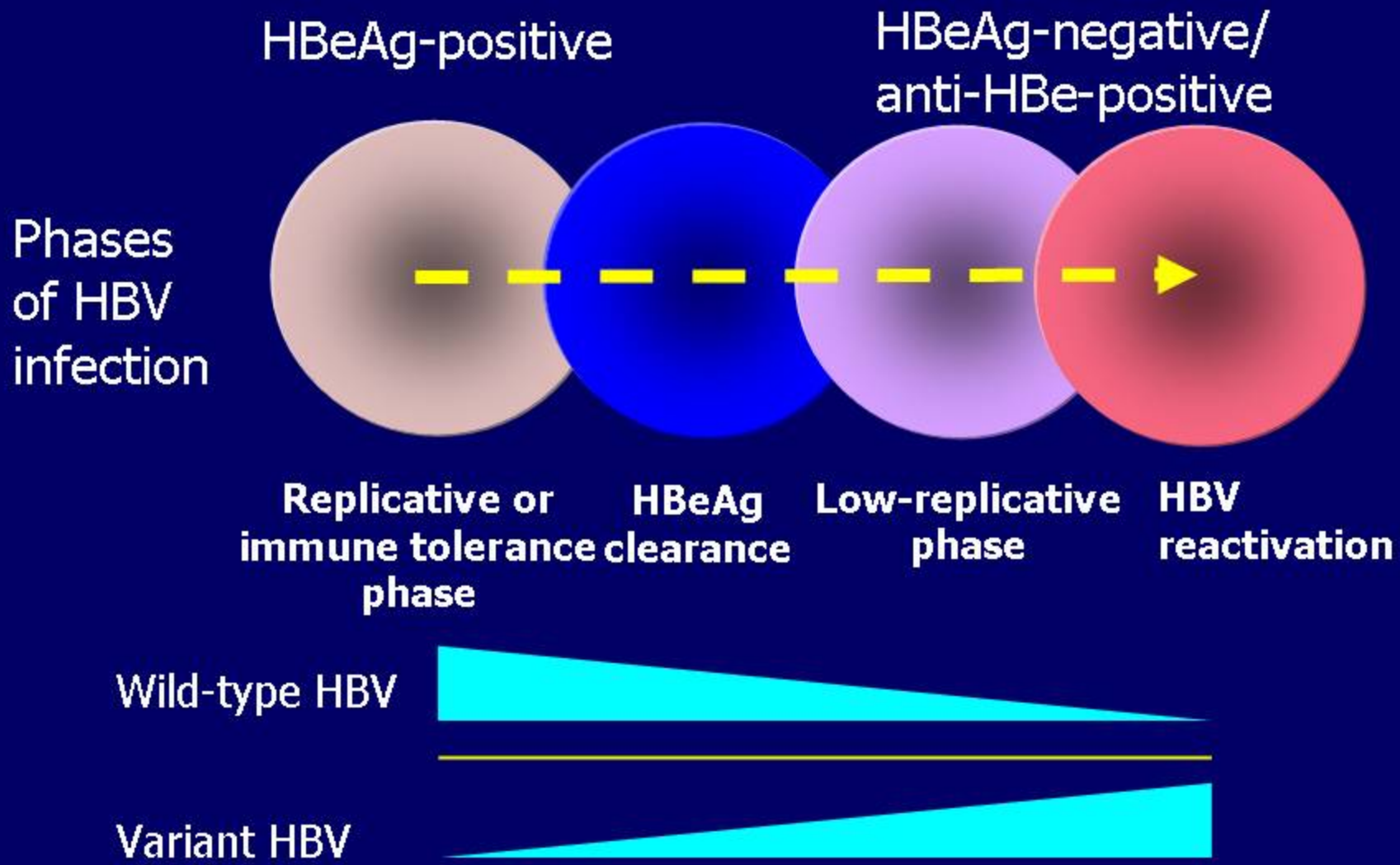
McMahon et al. *Ann Intern Med.* 2001; 135: 759-768.

Development of Pre-Core and Core-promoter Mutants

Meaning of Different HBV Markers

HBeAg(+)	HBV-Genotype	HBV-DNA	Basal Core Promoter (BCP) Mutation	Precore Mutation
-Indicates high viral replication -Risk factor for: chronic hepatitis, cirrhosis, and HCC. -Natural resolution over time (8-10%). -Slower rate of progression of liver disease.	-A responds better to IFN; B & C are intermediate; D has poor response. -B: high risk of HCC in young Taiwanese and old Japanese. -C: higher risk of HCC in BCP mutants	-If > 200000 IU/mL in pregnancy, increase fetal transmission despite vaccination +/- HBIG. -Progression to cirrhosis increases if > 2000 IU/mL. -Risk of HCC increases if > 200000 IU/mL	-Increases disease progression in Genotypes B and C. -Increases HCC risk in Genotype C.	-Most common in HBeAg(-). -Associated with ALT elevation and persistent necro-inflammation at lower HBV-DNA. -Fast progression to liver disease. -No natural resolution over time.

Natural History of HBV: Development of HBeAg-negative CHB



Hadziyannis SJ, Vassilopoulos D. *Hepatol.* 2001;34(4 Pt 1):617-624.

HBeAg-positive vs HBeAg-negative Chronic Hepatitis B

HBeAg (+)

- High HBV DNA
- HBeAg produced
- Less difficult to treat
- Slower rate of progression to liver disease
- Natural resolution over time (8-10%)
- Clinical outcome measures: HBV DNA, ALT, "e" & "s" seroconversion

HBeAg (–)

- Lower HBV DNA
- No HBeAg produced
- Difficult to treat
- Fast rate of progression to liver disease
- No natural resolution over time
- Clinical outcome measures: HBV DNA, ALT normalization

Fung S and Lok A. *Clin Gastro and Hepatology*. 2004;2:839-848.

Prevalence of HBeAg-negative CHB

- Prevalence of HBeAg-negative CHB in HBsAg-positive patients differs according to region and is determined primarily by the infecting genotype[1]
  - **up to 90% in Mediterranean regions**
  - **~30–55% in Asia Pacific**
  - **~30–50% in Northern Europe**
  - **up to 40% in the United States**
- Prevalence of HBeAg-negative CHB is increasing worldwide[2]

[1]Hadziyannis SJ, Vassilopoulos D. Hepatology. 2001;34(4 Pt 1):617-624.
[2]Funk et al. *J Viral Hepat.* 2002.

Testing for HB Pre-core & Core-Promoter Mutant

- Commercial Test: Inno-LiPA HBV PreCore
- Suspect and Test for “mutant” HBV when HBV-DNA is > 2000 IU/mL and patient is HBeAg(-). Patient may have:
  - HBV wild-type in “inactive carrier state” (normal ALT: males =/< 30 U/L, females =/< 19 U/L) : no need to treat, or
  - Precore or Core-promoter mutant HBV in “immunotolerant state” (normal ALT): no need to treat, or
  - Precore or Core-promoter mutant HBV in “immunoactive state” (elevated ALT): **needs treatment**.

Chronic Hepatitis B

- **<u>Diagnosis</u>:**
  - ***HBsAg (+)*** **& HBV-DNA (+) for > 6 months , with**
  - **anti-HBc IgM (-) but anti-HBc total (+) [excludes incubation]**

(1 IU = 5 copies, and 1 pg = 2.86 x 10^5 copies/ml)

States of Chronic Hepatitis B

HBeAg(+) Chronic INFECTION (Immune Tolerant)

HBeAg(+) Chronic HEPATITIS (Immune Active)

(Chronic Hepatitis Immune Clearance)

HBeAg(-) Chronic INFECTION (Immune Control)

HBeAg(-) Chronic HEPATITIS (Immune Escape)

Inactive Disease or Carrier State

Occult Hepatitis B (HBsAg loss) and Immunosuppression Mediated HBV flare-up

Natural History of CHB: New 5 phase model

Chronic infection
High Replicative, Low Inflammatory

- High HBV DNA
- **Trained immunity***
- Normal or low ALT
- HBeAg(+)
- High serum levels of HBeAg & HBsAg
- Mild or no necroinflammation
- No or slow fibrosis progression
- Decreased IL-10, IL-6, IL-8 & TNF-α
- No HBV DNA mutations

Chronic Hepatitis
Immune Clearance

- High changing to low or undetectable HBV DNA
- High decreasing to normal ALT
- Acute or intermittent hepatitis
- Declining HBeAg & HBsAg
- Eventual loss of HBeAg
- High changing to minimal necroinflammation
- Emergence of core and precore mutations

Chronic Hepatitis
HBeAg(-) Chronic

- Moderate to high HBV DNA
- High but fluctuating ALT
- Low HBsAg levels
- Persistent hepatitis
- Necroinflammation
- Progressive liver disease
- Immune clearance attempts ineffective

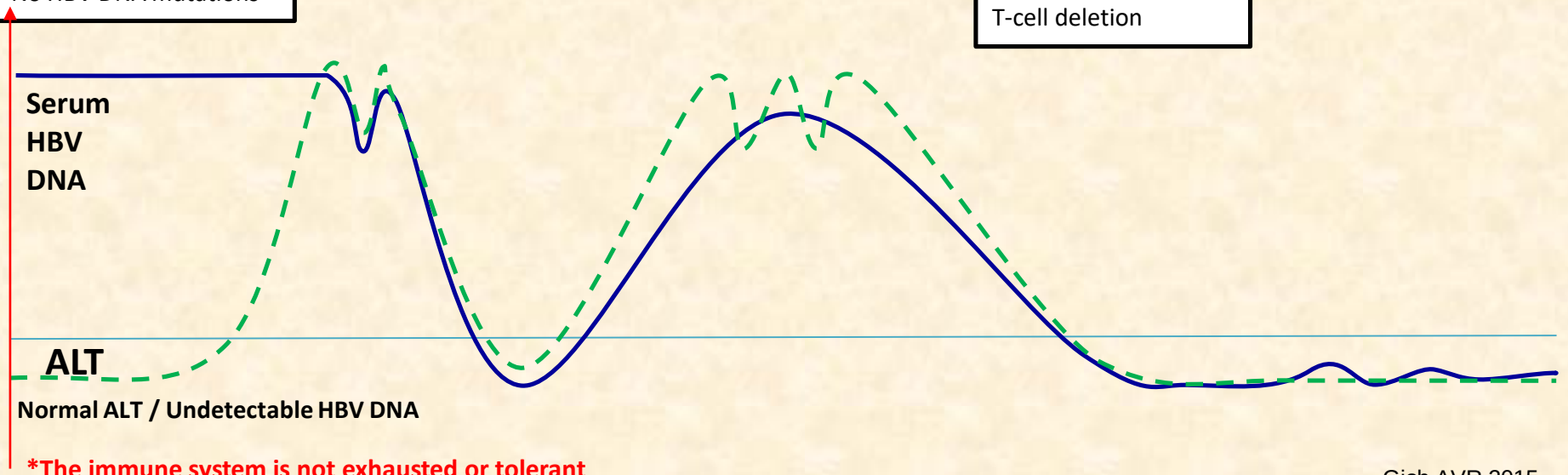
Chronic Infection
Immune Control Inactive Dz Non-Replicative

- Low or undetectable HBV DNA
- HBeAg(-)
- Very low HBsAg levels
- Normal ALT
- May be seen after Immune clearance T-cell deletion

HBsAg(-) Loss/Occult Hepatitis B

- Serum HBV DNA phases, alternating undetectable and very low but detectable
- Detectable HBV DNA in the liver
- Intrahepatic replication-competent HBV genomes such as HBV cccDNA
- Integrated HBV DNA

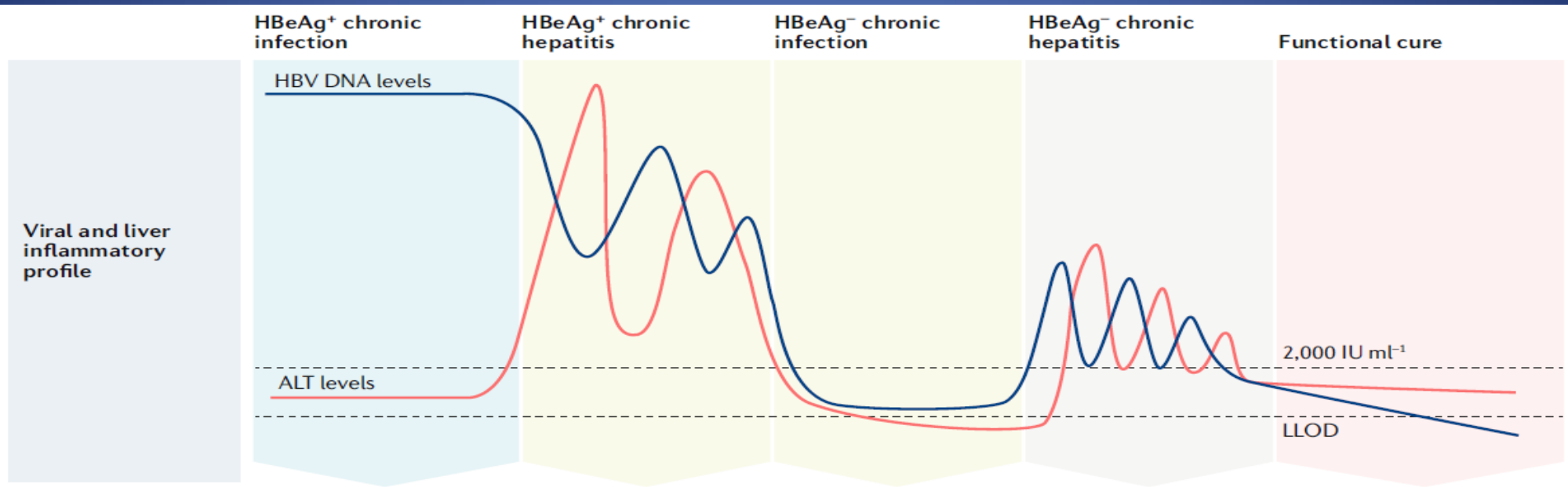
Resolved infection



*The immune system is not exhausted or tolerant

Gish AVR 2015

Natural History of Hepatitis B



	HBeAg⁺ chronic infection	HBeAg⁺ chronic hepatitis	HBeAg⁻ chronic infection	HBeAg⁻ chronic hepatitis	Functional cure
Viral and liver inflammatory profile					
Serum HBsAg	+++++	++++	+	++	–
cccDNA	+++++	+++++	++	+++	+
Fibrosis	Minimal fibrosis	Variable degree of fibrosis (progressing)	Variable degree of fibrosis (progressing)	Moderate to severe fibrosis (resolving)	Variable fibrosis (sequelae of previous phases)
Liver inflammatory infiltrate	Absent	High	Absent/moderate	Moderate	Absent
Profile of adaptive immunity	T cells • HBs –/+ • HBc –/+ • HBp –/+	T cells • HBs –/– • HBc –/+ • HBp –/+	T cells • HBs –/– • HBc –/+ • HBp –/+	T cells • HBs –/– • HBc –/+ • HBp –/+	T cells • HBs –/– • HBc –/+ • HBp –/+
	B cells • HBs –/– • HBc +	B cells • HBs –/– • HBc + +	B cells • HBs –/– • HBc + +	B cells • HBs –/– • HBc +	B cells • HBs + • HBc +

Fanning, G.C., Zoulim, F., Hou, J. et al. Nat Rev Drug Discov 18, 827–844 (2019)

HBV Disease Progression

~ 2 people per minute will die from complications associated with HBV

Chronic Infection

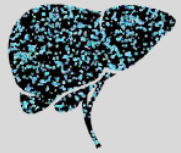
>250 million chronically infected worldwide

8% diagnosed

<1% receive treatment

1%-3% of those receiving treatment with current options achieve functional cure

Cirrhosis/HCC



20%-30%

Surgery, chemotherapy, and liver transplant

Death

~1 million people/year

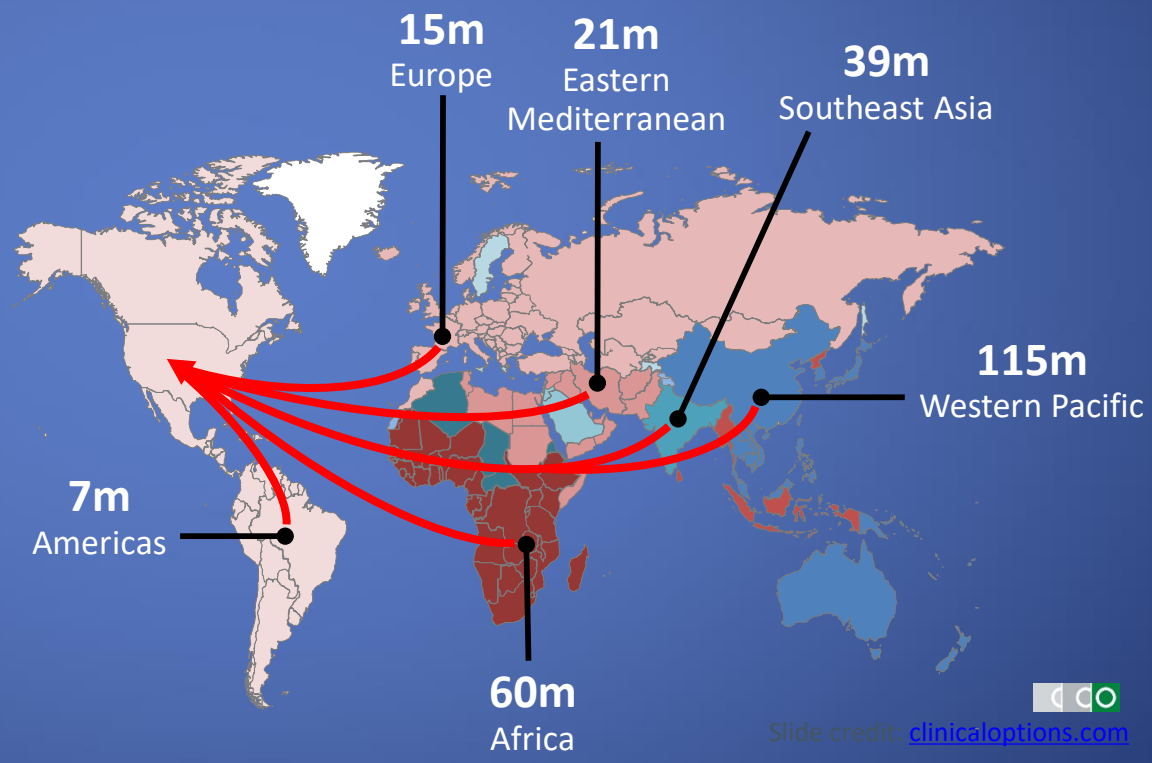
2 people/minute

Estimated Prevalence of CHB

- **US Prevalence of CHB in Foreign-Born Persons in 2009[1]**

Birth Country	Total (M)	Midrange CHB Prevalence (%)
All regions	**38.4**	**3.5**
Asia	10.6	7.3
Central America	14.4	< 1.0
Caribbean	3.4	4.5
South America	2.6	1.3
North America	0.8	< 1.0
Oceania	0.19	4.8
Africa	1.5	10.3
Europe	4.9	2.0

- **Global Prevalence of CHB in 2015: 257 Million[2]**



Slide credit: clinicaloptions.com

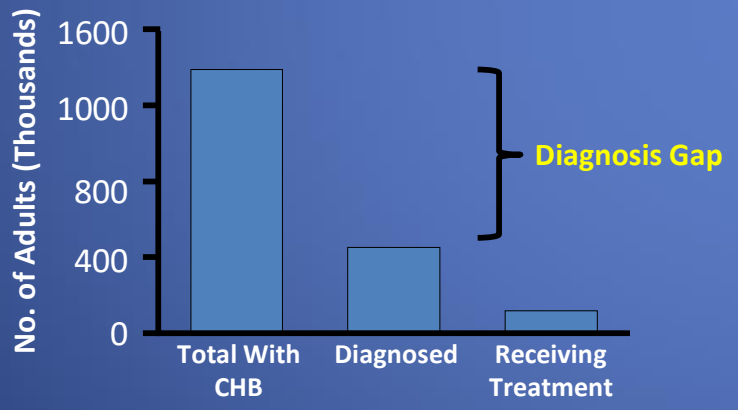
1. Kowdley. Hepatology. 2012;56:422. 2. WHO. Global hepatitis report, 2017.

Prevalence of CHB in the United States

Including foreign-born persons, **850,000 to 2.2 million people in the US** are living with CHB,[1] including **400,000 to 800,000 Asians**[1,2]

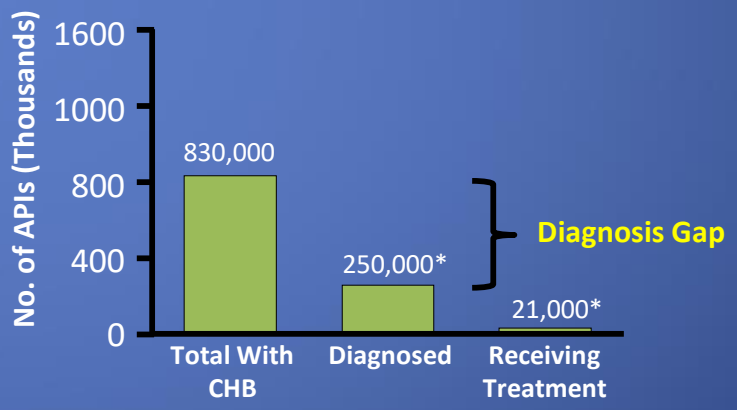
- 2013-2016 estimated CHB prevalence in **US** was 0.7%[3]

Diagnosis and Treatment Gaps in US Population[3]



- 2007 CHB prevalence among foreign-born **APIs in US** was 8.9%[4]

Diagnosis and Treatment Gaps in US API Population[4,5]



*Estimates established by applying percentage of persons with CHB diagnosed and treated in total population to number of APIs with CHB.

1. Harris. MMWR. 2018;67:541.
2. Kowdley. Hepatology. 2012;56:422.
3. Zhou. Clin Gastroenterol Hepatol. 2019. Epub.
4. Cohen. J Viral Hepat. 2008;15:12. 5. Cohen. J Viral Hepat. 2011;18:377.

Prevalence of Chronic Hepatitis B Infection in the U.S.

Estimated prevalence of 1.59 million persons (range 1.25-2.49 million)

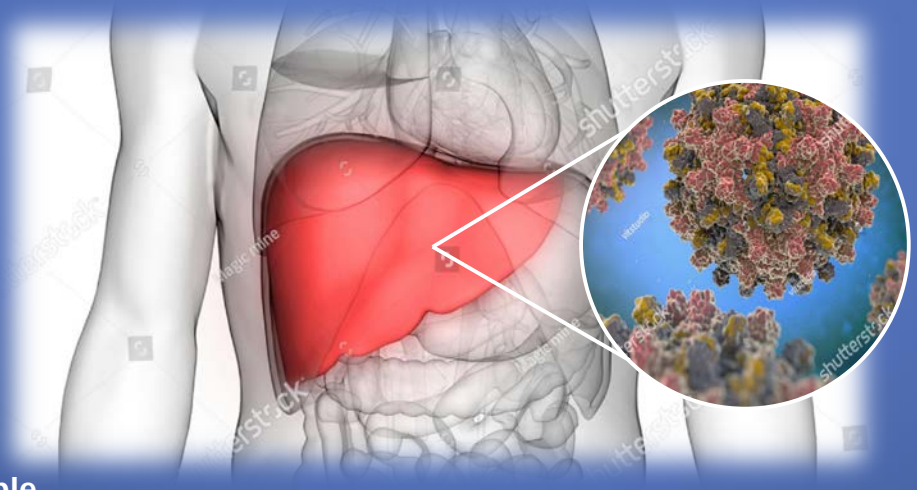
Individuals at-risk for HBV are those who are unvaccinated, fall into high-risk groups or are foreign-born and immigrating from HBV endemic regions (e.g. Asia, Africa),

Veterans
0.3[1] – 0.84%[2]

Healthcare Professionals
0.1-8.1%[3]

Prisoners
0.9-11.4%[4]

Homeless People
0.4[5]-1.17%[6]



Men Who Have Sex with Men
Prevalence unknown

People Who Inject Drugs
11.8%[7]

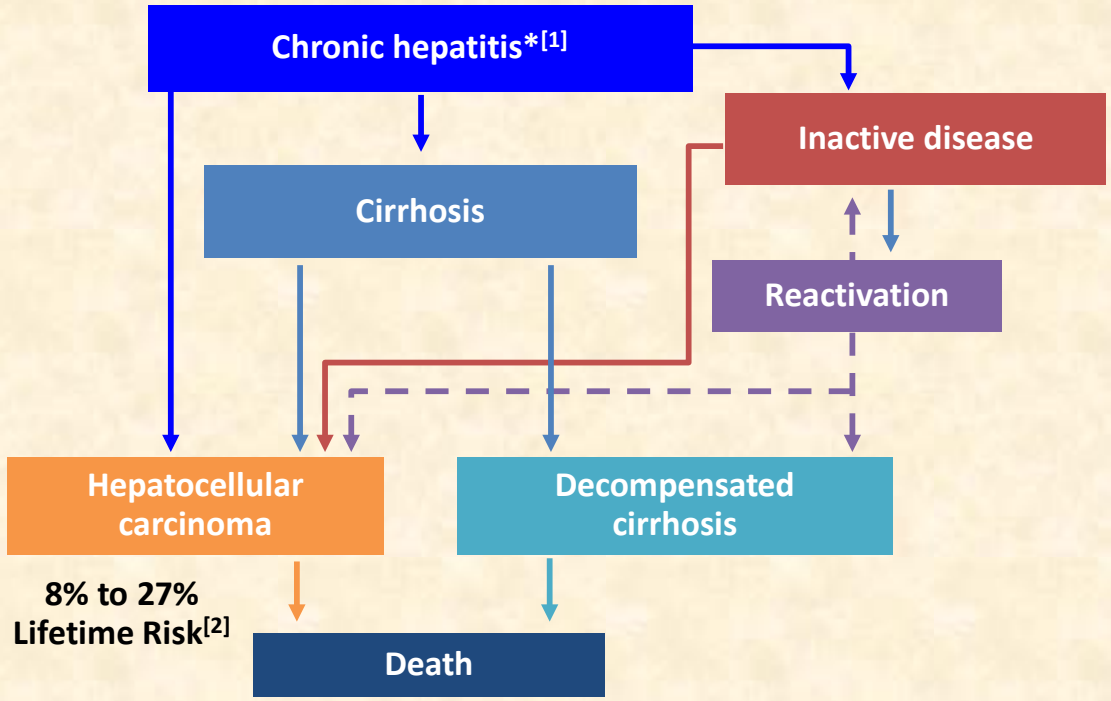
Patients with HIV Coinfection
0.7-5.8%[8-12]

Patients HCV Coinfection
3.0-8.4%[13-15]

Newborns Born to HBV-Infected Mothers
3.84%[16]

AJG 2020 Lim in press

Hepatitis B Disease Progression and Impact



*Failure to clear HBsAg 6 mos after acute infection.

- Up to 40% of persons with CHB develop significant clinical consequences, including cirrhosis, liver failure, and HCC[3]
- 25% of persons with CHB will die prematurely from complications[4]

1. The elimination of hepatitis B. In: Buckley. Eliminating the public health problem of hepatitis B and C in the United States: Phase One Report. 2016.

2. Huang. JCO. 2011;29:3643.

3. Lok. NEJM. 2002;346:1682.

4. Harris. MMWR. 2018;67:541.

Slide credit: clinicaloptions.com

HBV Viral Load Conversion

- 1 pg = 2.86 x 10^5 copies/mL
- 1 pg = 5.72 x 10^4 IU/mL
- 1 copy = 0.2 IU
- 1 IU = 5 copies
- 2000 IU = 10000 copies = 0.035 pg
- 20000 IU = 100000 copies = 0.35 pg

Viral Load and ALT Thresholds to Consider Treatment

- The likelihood of hepatic injury is determined by the presence of:
  - elevated liver enzymes (ALT > 1-2 X the ULN),
  - Moderate to severe necro-inflammation or fibrosis,
  - by a meaningful elevation of HBV-DNA.

- For treatment purposes normal ALT values are:
  - **Males up to 30 U/L**
  - **Females up to 19 U/L**

Viral Load and ALT Thresholds to Consider Treatment

- The threshold of HBV-DNA viral load which is likely to be associated with tissue damage (meaningful elevation) is different according to AASLD with “Wild Virus” (HBeAg(+)) and in pre-core or core promoter “Mutant Virus” (HBeAg(-)).

- For treatment purposes, meaningful HBV-DNA values are:
  - **Wild-type HBeAg(+): 20,000 IU/mL (2000 IU/mL EASL)**
  - **Mutant HBeAg(-): 2,000 IU/mL**

Viral Load and ALT Thresholds to Consider Treatment

- When a patient is HBeAg(-) and has an HBV-DNA > 2,000 IU/mL but less than 20,000 IU/mL:
  - check for the presence of pre-core or core-promoter mutations because the infection with a “mutant” virus may need treatment if ALT is elevated or if ALT elevates in the future.

Viral Load and ALT Thresholds to Consider Treatment

- Exceptions to ALT & HBV-DNA rules:
  - **CIRRHOSIS:** In patients with cirrhosis, liver damage may continue in absence of ALT elevation and even with relatively low viral replication (> 2000 U/L vs any detectable > 60 U/L) (EASL: any detectable HBV-DNA)
  - **AGE 40 or OLDER:** In patients older than 40, liver damage may occur with viral load > 2000 U/L even in absence of ALT elevation, hence liver biopsy is recommended on them to directly asses presence or absence of liver injury.
    - (EASL: age > 30, or Family hx of cirrhosis or HCC; If HBeAg(-) with HBV-DNA 2000 to <20000 do not need immediate Bx.)

Chronic Hepatitis B states

Inactive State

- **Inactive or Carrier State**

- ***Normal ALT and***
  - **HBe(+) or "Wild-type":**
  - **HBV-DNA < 20,000 IU/mL, (EASL: < 2000)**

  - **Mutant-HBe(-):**
  - **HBV-DNA < 2,000 IU/mL,**

  (in HBe(-): if HBV-DNA > 2000 IU/mL but < 20000 IU/mL, needs testing for PreCore or Core-promoter mutation to classify, but management will not change)

Chronic Hepatitis B states

Inactive State

- **Follow-up of Inactive State**

- Repeat ALT every 3 months x 1 year; then every 6-12 months. After age 40, add HBV-DNA every year.
  - If HBeAg(-), qHBsAg titer < 1000 IU/mL the interval may be longer (supports inactive state with s/s 71% & 85%)
- If ALT elevates > ULN and HBV-DNA remains low: investigate cause & consider liver Bx
- If ALT elevates > ULN (male > 30 U/L, female > 19 U/L) & HBV-DNA increases to > 20,000 IU/mL: treat
- If ALT remains normal but HBV-DNA elevates > 2,000 IU/mL:
  - Liver Bx if older than 40 (EASL: > 30);
  - otherwise observe (Immune Tolerant state).

Chronic Hepatitis B States

Infection State

- **HBeAg(+) INFECTION or Immune-Tolerant State**

- ***Persistently Normal ALT and***
  - **HBe(+) or Wild-type:**
  - **HBV-DNA > 20000 IU/mL, (EASL > 2000)**

- **HBeAg(-) INFECTION or Immune-Control State**

- ***Persistently Normal ALT and***
  - **Mutant-HBe(-):**
  - **HBV-DNA > 2000 IU/mL**

NOTE:
AASLD: Consider Liver Bx in older than 40 years & HBV-DNA > 2000 IU/mL, (May be HEPATITIS STATE)
EASL: Consider liver Bx after age 30, or if family history of cirrhosis or HCC; If HBe(-), no need for Bx unless HBV-DNA > 20000
Is in HEPATITIS STATE if Liver biopsy shows chronic hepatitis with moderate or severe necro-inflammation (>/= A3) and with or without fibrosis

Chronic Hepatitis B States

Infection State

- **Follow-up of Infection State**

- **ALT every 3-6 months**
- **If ALT elevates > ULN** (male > 30 U/L, female > 19 U/L) **& HBV-DNA still > 20000 IU/mL (> 2000 in HBeAg(-)): consider liver Bx and/or treat**
- **If person is or reaches age =/> 40: consider liver Bx to asses histologic activity and decide about treatment**

Liver biopsy or noninvasive test results showing no fibrosis (< F2) and minimal inflammation (< A2)

Chronic Hepatitis B states

Hepatitis State

- **HBeAg(+) HEPATITIS or Immune-Active State**

- *Persistently or Intermittently Elevated ALT (> ULN)*
  - **HBe(+) or Wild-type:**
  - **HBV-DNA > 20000 IU/mL (EASL: > 2000)**
- *Treat*

- **HBeAg(-) HEPATITIS or Immune-Escape State**

- *Persistently or Intermittenrly Elevated ALT and*
  - **Mutant-HBe(-):**
  - **HBV-DNA > 2000 IU/mL**
- *Treat*

Liver biopsy or noninvasive test results show chronic hepatitis with moderate or severe necro-inflammation (>/= A2) and with or without fibrosis

Quantitative HBsAg (qHBsAg)

- qHBsAg reflects BOTH cccDNA and intrahepatic DNA levels, it also measures HBsAg that arises from integrated DNA, thereby reducing its specificity as a biomarker for viral replication.
- qHBsAg levels vary by genotype (higher in A) and by presence of preS/S mutants or host immune control (inverse correlation with both).
- qHBsAg is higher in HBeAg(+) patients.
- Higher qHBsAg levels are associated with progression to Cirrhosis and HCC.
- In HBeAg-negative patients, low qHBsAg (< 1000 IU/mL) and low HBV-DNA (< 2000 IU/mL) suggest inactive HBV (a qHBsAg < 100 IU/mL increases the specificity but decrease the sensitivity to 35%).
- In HBeAg(-) with low HBV-DNA < 2000 IU/mL, low qHBsAg < 1000 IU/mL, predicts HBsAg clearance.

Quantitative HBsAg (qHBsAg) during Therapy

- **In PEG-IFN therapy of HBeAg(+):**
  - If qHBsAg is < 1500 by week 12, 57% will seroconvert to HBe(-) and 18% will loose HBsAg.
  - If qHBsAg does NOT decline by week 12, patient is unlikely to seroconvert to HBe(-) or to reach HBV-DNA < 2000 IU/mL after EOT.
  - In genotype B or C, if qHBsAg > 20,000 at week 12 and 24, they will NOT seroconvert to HBe(-).
- **In PEG-IFN therapy of HBeAg(-):**
  - In genotype D, if by week 12 qHBsAg does not decline and HBV-DNA decline is < 2 log, no patient will reach sustained response of HBV-DNA < 2000 IU/mL after full 6 months therapy.
- In Nucleotide Analog Therapy of HBeAg(-):
  - A decline of qHBsAg > 1 log predicts higher probability of HBsAg clearance.
  - A qHBsAg < 100 IU/mL during therapy is associated with a sustainable off-treatment response following 3 years or more of consolidation therapy.

Management of Patients in “Gray Zone”

(Expert Opinion)

EVALUATION

Risk Factor	Partial Score
Age >/= 40	1
Male gender	1
Male ALT > 30 U/L Female ALT > 19 U/L	1
BCP Mutation	2
HCC in 1st degree relative	3
Albumin < 3.5 g/dL or Platelets < 130K	3

DECISSION

Total Added Score	Action
< 3	Monitor without therapy
>/= 3 & HBV-DNA</= 2000 IU/mL	Monitor without therapy
>/= 3 & HBV-DNA > 2000 IU/mL	Treat

Occult Hepatitis B

- **Definition:** HBV-DNA in liver and/or serum in absence of HBsAg
  - may be anti-HBc(+), anti-HBs(+), or be negative for both (20%).
- **Causes:**
  - a) Persistent HBV cccDNA in hepatocyte nucleus after "clearance" of clinical infection, with viral control mediated by:
    - 1) T-cell mediated immune surveillance, or
    - 2) Viral interference (i.e.: co-infection with HCV or schistosoma), or
    - 3) Epigenetic mechanisms like transcriptional repression.
  - b) Infection with virus with antigenically modified S protein or with mutation inhibiting S gene expression: **"a" determinant mutant** virus (most common G145R mutation)

Occult Hepatitis B

- **Highest risk groups for occult HBV:**
  - Natives from highly HBV-endemic areas,
  - chronic HCV co-infected,
  - HIV co-infected,
  - hemodialysis patients,
  - hemophiliacs,
  - former/current IV drug abusers

Occult HBV Infection/Viremia and Occult HBV

- Occult HBV infection/viremia
  - Presence of HBV DNA in the liver (± detectable serum HBV DNA) of individuals testing HBsAg negative by currently available assays, most patients are anti-HBc positive
- Occult HBV is the preferred term when the level of infectivity can not be established
  - Detection of HBV DNA does not always correspond to infectivity or to the number of progeny viruses released from hepatocytes
  - Prevalence varies significantly between geographic regions, various patient populations tested, and type of routine screening assay used
  - Detection requires assays with a lower limit of detection of <10 IU/L for HBV DNA and <0.1 ng/mL for HBsAg
  - Relatively common among HCV-infected patients
  - Transmission via solid organ transplantation or transfusion has been reported
  - Reactivation can occur with immunosuppression or intensive cytotoxic chemotherapy

Torbenson M, et al. *Lancet Infect.* 2002;2:479-486.
Hollinger FB, et al. *J Viral Hepat.* 2010;17:1-15.

Occult Hepatitis B

- **Clinical Relevance:**
  - a) Transmission of infection by blood transfusion (seen in Taiwan and India),
  - b) Reactivation due to immunosuppression:
    - Rituximab, Alemtuzumab, Infliximab, liver transplant, hematological malignancies, HIV infection, stem cell transplantation, chemotherapy, kidney or heart transplantation,
  - c) Acceleration of liver damage in chronic HCV and cryptogenic liver disease,
  - d) Increased risk of HCC
- **Prevention of Transmission of Occult HBV**
  - Test donated blood for HBV-DNA in highly endemic areas.
    - Do not use blood if HBV-DNA is (+).

Summary of HBV-Reactivation Prophylaxis

AGA 2015

Risk	Agent	Clinical Situation	Action
High HBV Reactivation > 10%	-**B cell depleter**: Rituximab, ofatumumab	-**Anti-HBc(+);** -HBsAg (+) or (-)	Prophylaxis with Entecavir or Tenofovir, until 12 months after end of B cell depletion or 6 months for other agents.
	-**Anthracyclines**: Doxorubicin, epirubicin -**Corticosteroids:** Prednisone 10 long term, or Pred > 20mg >/= 4 weeks	**-HBsAg(+)**	
Moderate HBV Reactivation 1-10%	-**Cytokine/Integrin inh**: etanercept, adalimumab, certolizumab, infliximab, abatacept, ustekinumab, natalizumab, vedolizumab, -**Tyrosine kinase inh**: imatinib, nilotinib	**-Anti-HBc(+);** -HBsAg (+) or (-)	Prophylaxis with Entecavir or Tenofovir, until 6 months after end of therapy.
	-**Corticosteroids:** <10 mg prednisone daily or equivalent corticosteroids for duration of 4 weeks; >20 mg prednisone daily or equivalent corticosteroids daily for 4 weeks; **-Anthracyclines:** doxorubicin, epirubicin	**-HBsAg(+)**	
Low HBV Reactivation < 1%	-**Traditional Immunosuppressors:** azathioprine, 6-mercaptopurine, methotrexate -**Corticosteroids:** Intra-articular, or any systemic dose < 1 week	**-Anti-HBc(+);** -HBsAg (+) or (-)	No Prophylaxis
	-**Corticosteroids:** < 10 mg Prednisone equivalent > 4 weeks	**-HBsAg(-) but anti-HBc(+)**	

Prevention of HBV Reactivation by Immunosuppression

- **Management of Pre-Immunosuppression HBV markers:**
  - Test for HBsAg & anti-HBc before immunosuppression;
    - **If HBsAg(+):**
      - Risk of reactivation, even when HBV-DNA is negative, is 40%
      - Investigate checking HBV-DNA quantitation and ALT;
        - » If HBV-DNA is (+): treat accordingly with Entecavir or Tenofovir (Lamivudine OK if HBV-DNA < 2000 IU/mL)
        - » If HBV-DNA is (-): Any oral anti-HBV antiviral can be an option.
      - Continue antiviral until 12 months after end of therapy.
      - Monitor HBV while immunosuppressed to detect evidence of resistance.

Prevention of HBV Reactivation by Immunosuppression

- **Management of Pre-Immunosuppression HBV markers:**
  - Test for HBsAg & anti-HBc before immunossuppression;
    - **If only HBc(+):**
      - Risk of reactivation with anti-HBc(+) and HBV-DNA(-), is 4%.
      - Investigate checking HBV-DNA quantitation;
        - » If HBV-DNA is positive, treat with Entecavir or Tenofovir (Lamivudine OK if HBV-DNA < 2000 IU/mL)
        - » If HBV-DNA is (-):
          - **A)** Start pre-immunosuppression prophylaxis with Lamivudine or other anti-HBV drug and continue antiviral until 12 months after end of therapy, or
          - **B)** monitor while on immunosuppressive therapy q 1-3 months for reappearance of HBsAg or HBV-DNA; If HBV reactivates, treat.

Treatment of HBV

Chronic Hepatitis B
Treatment Candidates

- **Cirrhotic:**
  - **Any ALT value**
  - **HBV-DNA > 2000 IU/mL (EASL: any detectable HBV-DNA) even if HDV (+).**
- **Non-cirrhotic with HBsAg(+) > 6 months, and:**
  - **ALT > ULN, or Liver Bx with moderate or severe activity,** plus
    - **a)** Wild **HBe(+):** HBV-DNA > 20000 IU/mL (EASL > 2000)

      or
    - **b)** Mutant-**HBe(-):** HBV-DNA > 2000 IU/mL

Therapeutic Strategies in HBeAg-negative CHB

- Treatment course of limited duration
  - off-therapy sustained responses
  - best achieved with IFN-based treatment
  - long-term clinical benefit without need of continuous medication
- Long-term maintenance therapy
  - effective HBV suppression maintained as long as the patient is on-therapy
  - best achieved with NAs
  - high rates of relapse once treatment is stopped
  - long-term suppression of HBV DNA can lead to increased survival benefit, but is compromised by risk of drug resistance

Lok et al. *Hepatology* 2004;39 (3):857-861.
AASLD Practice Guidelines 2003: chronic hepatitis B. Accessed via http://www.aasld.org.

Chronic Hepatitis B
Treatment Options

- **Interferon**:
  - non-cirrhotic, and
  - ALT > 2 x ULN, and HBV-DNA < 12 x 10^6 IU/mL (200 pg/mL, or 57 x 10^6 copies/mL)

- **Peg-IFN**:
  - non-cirrhotic, and
  - HBV-DNA < 3.6 x 10^9 IU/mL (EASL: < 2x 10^8 IU/mL)
  - ALT > 1 x ULN (EASL: ALT > 2-5 X ULN)
  - Genotype A > B >/= C > D
  - Older age
  - Liver Bx with Activity >/= A_2

Chronic Hepatitis B
Treatment Options

- **Entecavir or Tenofovir :**
  - They are preferred due to “high barrier” for viral resistance, needing several viral mutations before resistance develops.
  - Given if patient is a not candidate for interferon but is a candidate for treatment, or because of physician/patient preference.
  - Lamivudine , Telbivudine, Emtricitabine, and Adefovir have a low barrier for resistance and/or lower antiviral activity. For these reasons they are not first-line therapies.

Chronic Hepatitis B
Treatment Options in Special Groups

- **In Pregnancy:** in the following order
  - Tenofovir
    - category B & conditionally safe for lactation depending on dose or patient-group.
  - Telbivudine
    - category B & possibly unsafe for lactation.
  - Lamivudine
    - category C & unsafe for lactation
- **In Patients with HIV co-infection:**
  - All HBV patients should be check for HIV before therapy.
  - If CD_4 > 500/mL, only use Peg-IFN, Adefovir, or Telbivudine unless the anti-HBV drug is being use as part of HAART.
  - If on HAART: Tenofovir + (Emtricitabine or Lamivudide)
  - Use of other HBV drugs, as monotherapy, may facilitate HIV resistance.

Chronic Hepatitis B
Treatment Options in Special Groups

- Woman in child-bearing age wishing to eradicate virus before pregnancy:
  - Peg-Interferon
- Renal Insufficiency:
  - Entecavir
- Decompensated Cirrhosis:
  - Entecavir
    - 1 mg/d (not 0.5 mg/d); risk of lactic acidosis if MELD > 20.
  - Tenofovir may be considered.

Chronic HBV
Goals of Therapy

- **Ideal**:
  - Clear HBsAg and cure disease; (infrequently reached).

Chronic HBV
Goals of Therapy

- **Practical**:
  - **HBe(+):** Convert to “inactive carrier state” with:
    - HBV-DNA < 20000 IU/mL and
    - sero-conversion to HBe(-)/anti-HBe(+), confirmed 1-3 months later;
    - ideally < 20 IU/mL (complete response)
  - **Mutant-HBe(-):** Convert to “inactive carrier state” with:
    - HBV-DNA < 2000 IU/mL
    - ideally < 20 IU/mL (complete response)
  - **Cirrhotic:** Convert to:
    - HBV-DNA < 2000 IU/mL
    - ideally < 20 IU/mL (complete response)

Chronic HBV Therapy
Points to Keep in Mind

- **Sustained loss of HBeAg requires:**
  - to confirm seroconversion by a second test 1-3 months post-seroconversion.
  - to continue oral agent for at least 6 months (EASL: 12 months) after confirmation of the loss of HBeAg and development of anti-HBe.
- **Long therapy with oral agents increases frequency of drug-resistance.**
- **If patients were HBe(-) pre-treatment, therapy will be life-long or until patient looses HBsAg.**

Definitions of Virological Response to Interferon / Peg Interferon

- Primary Non-Response:
  - Not well defined
- Virological Response:
  - HBV-DNA < 2000 IU/mL at any time.
  - Evaluated during therapy at 6 & 12 months.
  - Evaluate after EOT at 6 and 12 months.
- Sustained Off-treatment Virological Response:
  - HBV-DNA < 2000 IU/mL >/= 12 months after EOT.
- Use of HBsAg titer to predict response to Peg-IFN:
  - **HBeAg(+):** If week 12 HBsAg titer is > 20000 IU/mL the NPV is 84-100%; consider discontinue therapy (?)
  - **HBeAg(-):** In genotype D, if HBsAg titer decline is < 0.5 log and HBV-DNA decline < 2 log, NPV is 90%; discontinue (?).

Definitions & Management for Treatment with Oral Antivirals

- **Primary non-response**: drop of HBV-DNA < 1 log after 12 wks of therapy or < 2 log after 24 weeks of therapy.
  - Check for viral resistance (INNO-Lipa HBV DR v2).
  - May be compliance issue, or host pharmacologic effect.
  - Change to more potent drug or **add second drug without cross-resistance**.
- **Partial Response**: HBV-DNA drop > 1 log, with HBV-DNA > 2000 IU/mL, after 24 weeks of therapy.
  - Predicts high risk for resistance. (Resistance risk is low if HBV-DNA is < 200 IU/mL).
  - Change or **add second drug without cross-resistance**.
- **Complete On-therapy Response:**
  - HBV-DNA < 20 IU/mL

Definitions for Treatment with Oral Antivirals

- **Virologic Breakthrough**:
- a) Increase of HBV-DNA > 1 log from nadir, at any time, while on therapy, or

  b) Reappearance of HBV-DNA(+) after 2 negative HBV-DNA, at least 1 month apart, while still on therapy.
  - Check for viral resistance (INNO-Lipa HBV DR v2).
  - May be compliance problem.
  - Change to more potent drug or **add second drug without cross-resistance**.
- **Virologic Relapse:**
  - Increase in serum HBV-DNA > 1 log IU/mL after discontinuation of therapy, on at least 2 determinations 4 weeks apart.

Definitions for Treatment with Oral Antivirals

- **Sustained Virological Response:**
  - Persistence of clinical response 12 months after end-of-therapy, to a predefined goal (like HBV-DNA < 2000 IU/mL in HBeAg(-) or < 20000 IU/mL in HBeAg(+)).
- **Complete Off-Therapy Response:**
  - SVR plus loss of HBsAg
- **Histological Response:**
  - Decrease in necro-inflammation by =/> 2 Ishak or HAI score without worsening of fibrosis.
- **Commercial Test for Drug Resistance:**
  - Inno-LiPA HBV DR v2 (Lamivudine, Telbuvidine, Emtricitabine and Adefovir)

Drug Cross-Resistance Profile

(reverse transcriptase mutations)

Zoulim F et al. J of Hepatology 2008;48: S2-S19

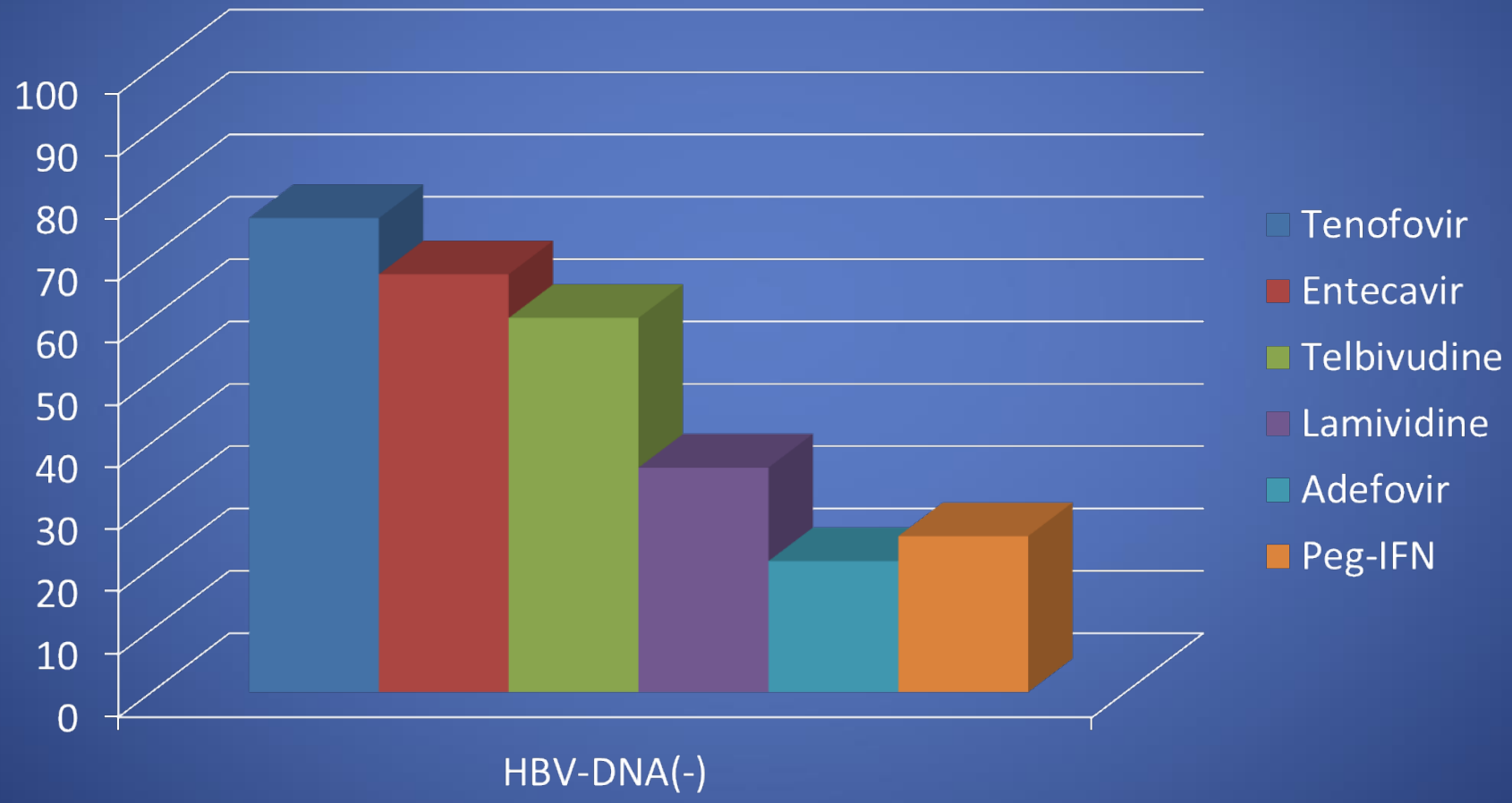
	Lamivudine	Telbivudine	Entecavir	Adefovir	Tenofovir
Wild	S	S	S	S	S
M204I	R	R	R	S	S
L180M + M204V	R	R	I	S	S
A181T/V	I	S	S	R	S
N236T	S	S	S	R	I
I169T + V173L + M250V	R	R	R	S	S
T184G + S202I/G	R	R	R	S	S
I233V				Resistance ?	
A194T					Resistance ?

Management of NA Resistance

Antiviral Resistance by Genotypic	Testing Switch Strategy (Preferred)	Add Strategy: 2 Drugs Without Cross-Resistance
Lamivudine resistance	Tenofovir* (TDF or TAF)	Continue lamivudine; add tenofovir (TDF or TAF) (or alternative emtricitabine-tenofovir)
Telbivudine resistance	Tenofovir* (TDF or TAF)	Continue telbivudine; add tenofovir (TDF or TAF)
Adefovir resistance	Entecavir or Tenofovir* (TDF or TAF)	Continue adefovir; add entecavir
Entecavir resistance	Tenofovir* (TDF or TAF)	Continue entecavir; add tenofovir (TDF or TAF) or alternative emtricitabine-tenofovir
Tenofovir resistance	Entecavir*	Continue tenofovir (TDF or TAF) and add entecavir
Multidrug resistance	Tenofovir	Combined tenofovir (TDF or TAF) and entecavir*

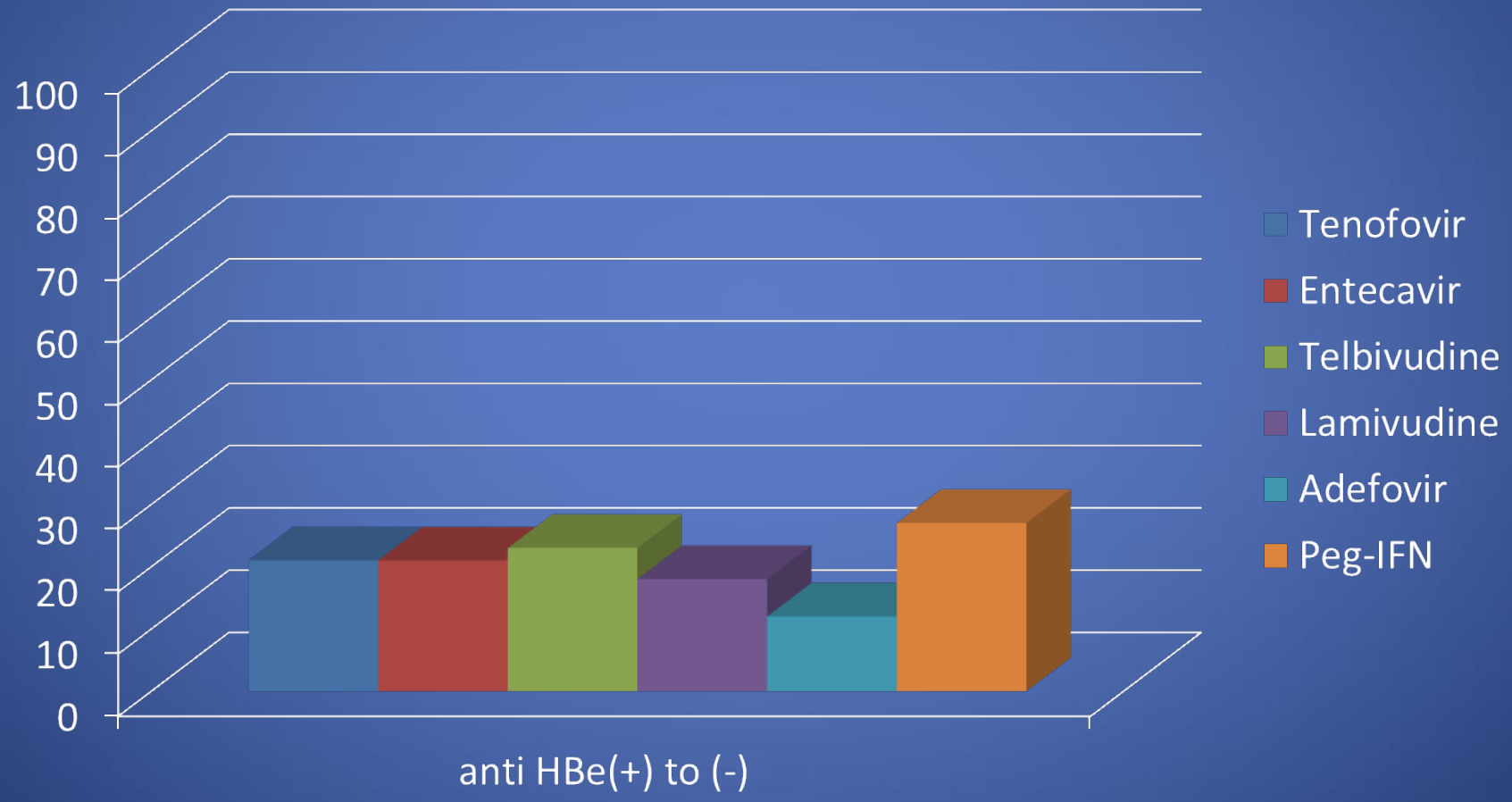
Undetectable HBV-DNA at 1 year

HBeAg(+) Patients



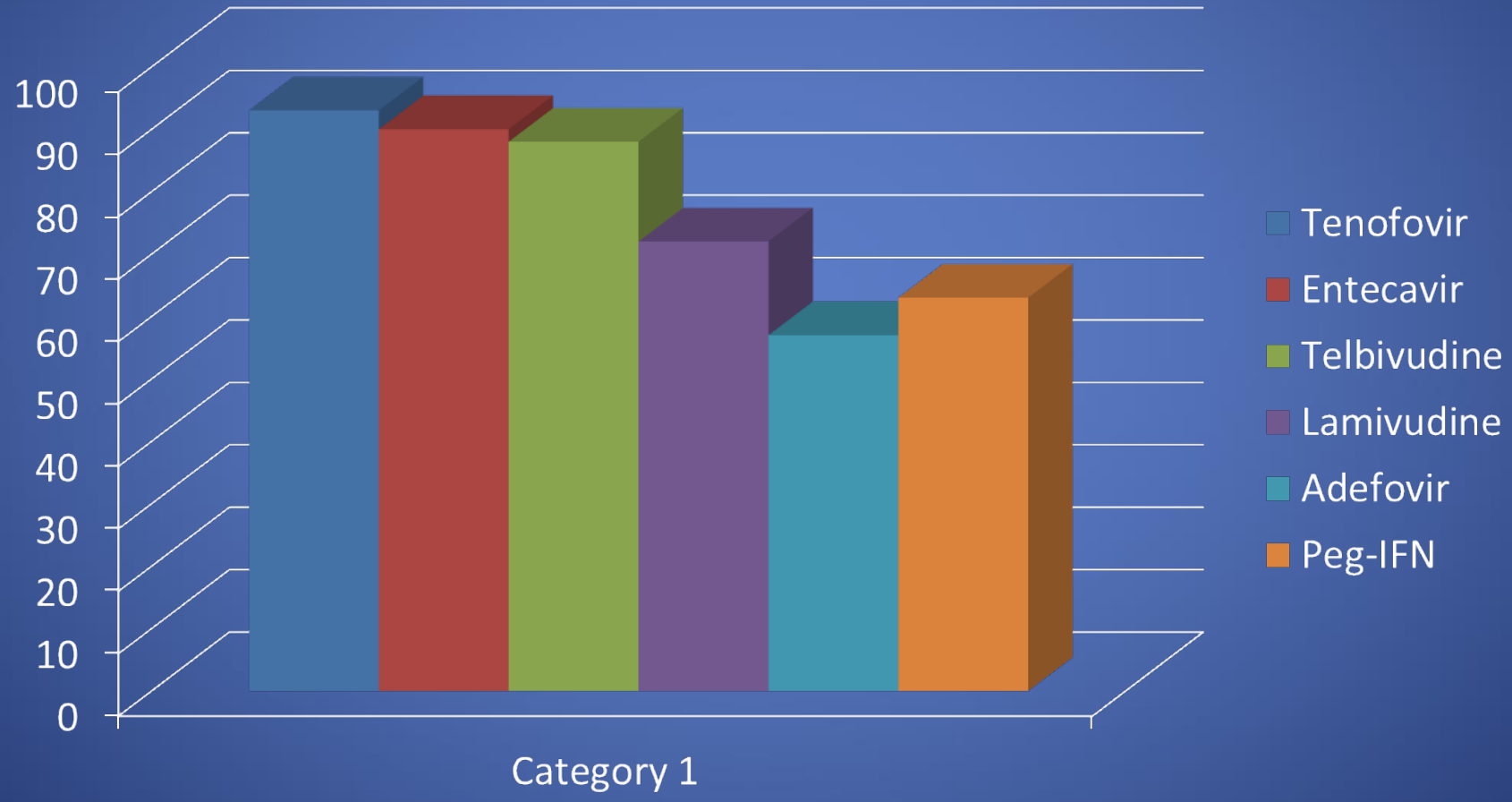
Seroconversion to anti-HBe at 1 year

HBeAg(+) Patients

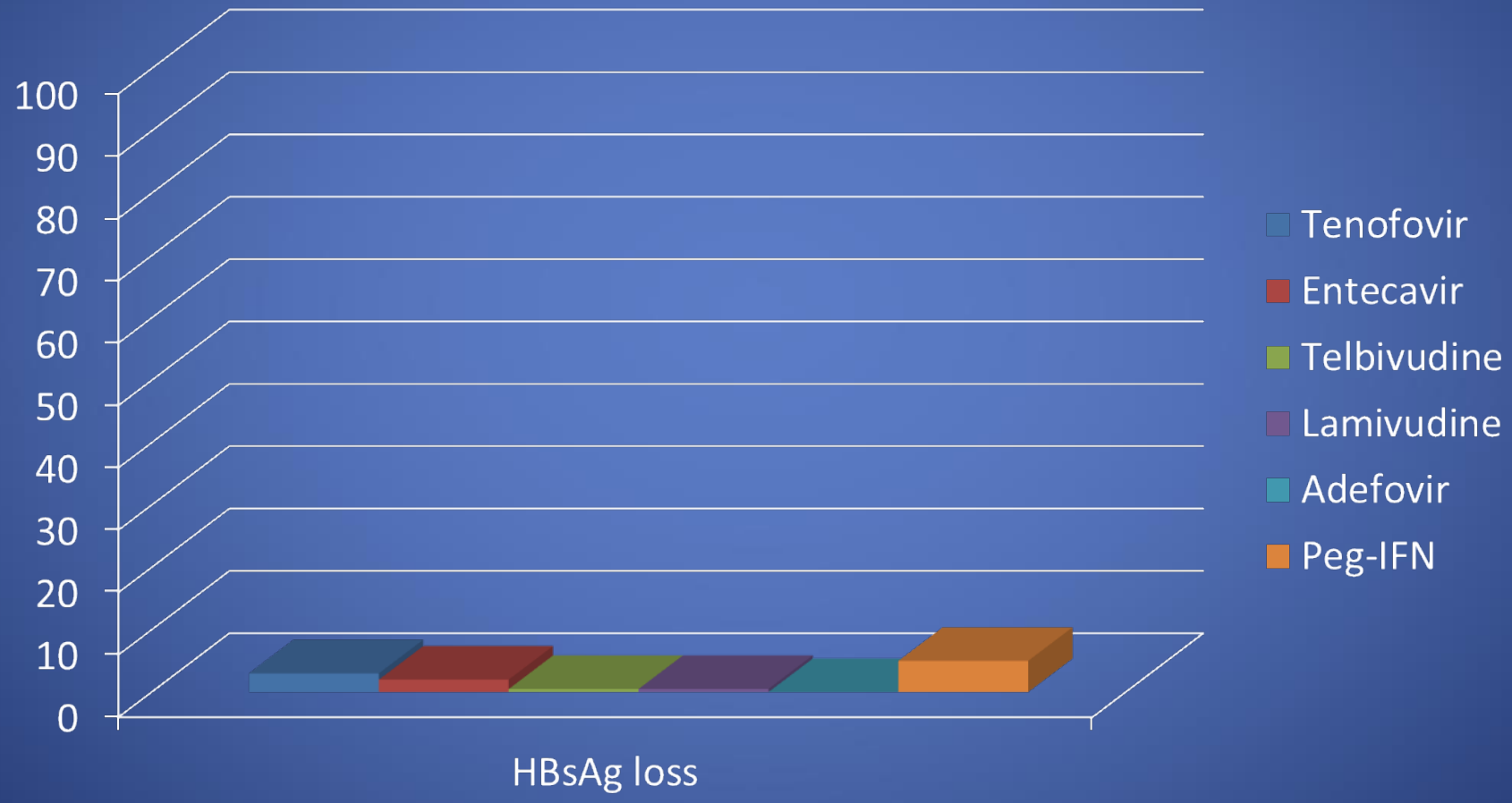


Undetectable HBV-DNA at 1 year

HBeAg(-) Patients

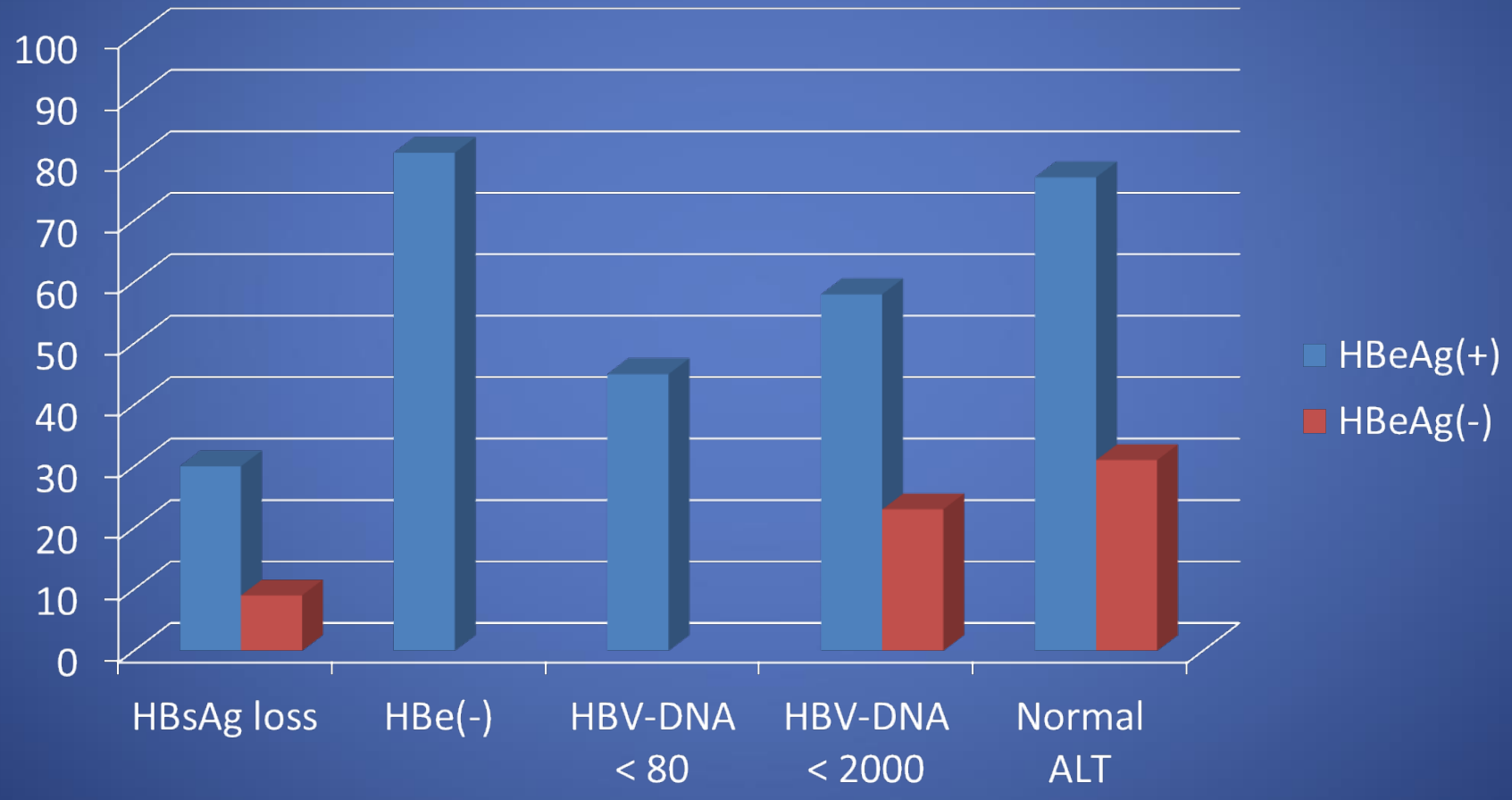


Loss (%) of HBsAg after 1 year of Different Therapies



3 year F/U after Virological Response* with Peg-IFN

HBeAg(+) & HBe(-) Patients

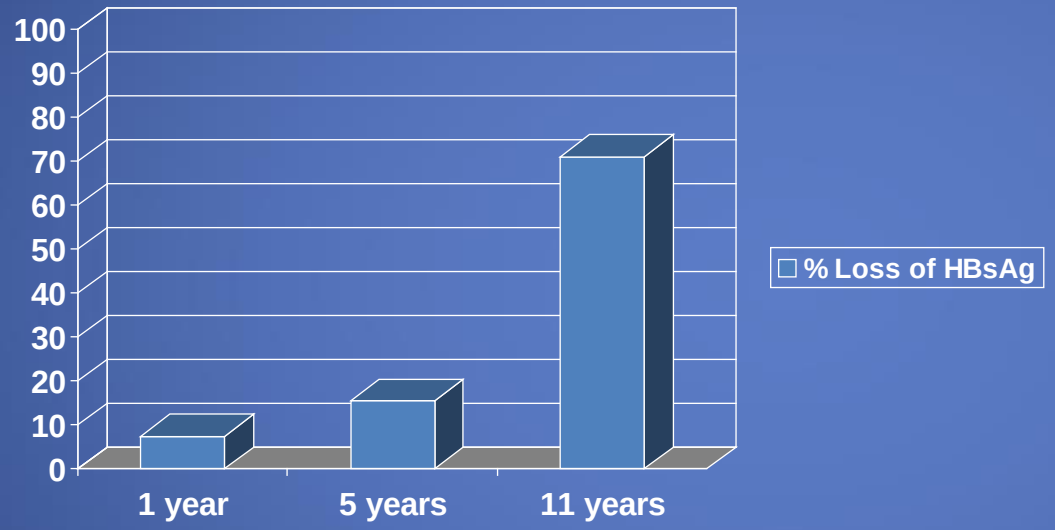


* Within 6 months after EOT

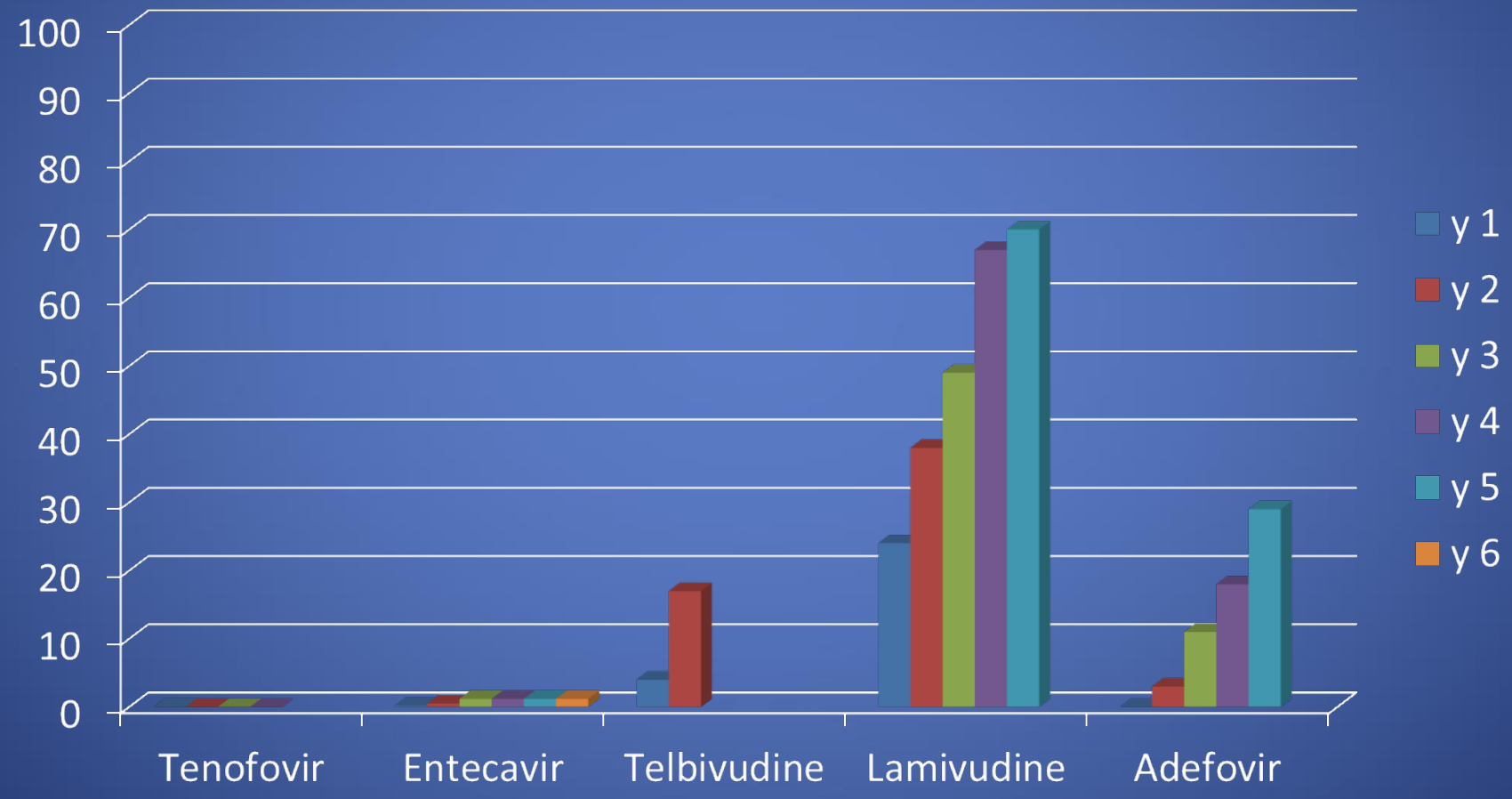
Long term F/U of Interferon Responders

Loss of HBsAg after HBe seroconversion (Europeans & Americans)

Gut 2000;46:715-718, Am J Gastroenterol 1998;93:896-900, Gastroenterology 1997;113:1660-1667



Rates of Antiviral Resistance



Peg-IFN

- Approved in 2002 for adults.
- Immunomodulatory therapy.
- Dose Peg-IFN alpha 2a: 180 mcg/week x 48 weeks, SQ.
- For both HBeAg(+) and (-).
- Does not induce viral resistance
- May cause transient and potentially severe ALT elevations
- Best candidates:
  - Viral load < 2 x 10^8 IU/mL
  - Genotypes A > B >/= C > D
  - ALT > 2 x ULN; ideal if > 5 x ULN
  - Females > males
  - Older age

Peg-IFN

- Contraindicated:
  - Decompensated cirrhosis
  - Pregnancy
  - Autoimmune disorder
  - Post organ-transplant
- Side effects:
  - Very Common (> 10%): anorexia, malaise, arthralgia, myalgia, alopecia
  - Common (1-10%): anxiety, depression, neutropenia, infections, thyroid disease, visual disorder
  - Uncommon (< 1%): Suicidal ideation, pancytopenia, peripheral neuropathy

Hepatitis B Therapy and ALT Flares

- Exacerbations of hepatitis during hepatitis B therapy
  - Characterized by transient and potentially severe increases in serum ALT
- Transient acute exacerbations of hepatitis B (ALT elevation >10-fold higher than the upper limit of normal) were observed
  - HBeAg negative: 12% and 7% during and after treatment
  - HBeAg positive: 18% and 12% during and after treatment
- Marked transaminase flares while on PEGASYS therapy have been accompanied by other liver test abnormalities
  - Dose reduction should be considered in patients experiencing transaminase flares
  - If ALT increases are progressive despite reduction of PEGASYS dose or are accompanied by increased bilirubin or evidence of hepatic decompensation, PEGASYS should be immediately discontinued

PEGASYS® (Peginterferon alfa-2a) [package insert]. Nutley, NJ: Hoffmann-La Roche Inc.; 2005.

Entecavir

- Oral deoxyguanidine nucleoside analog approved in 2005
- Active in wild, HBe(-), and YMDD
- **Dose**: - 0.5 mg/d in HBe(+) or (-);
  - 1 mg/day in YMDD mutant and in decompensated cirrhosis;
  - modify in renal impairment.
- No interaction with Lamivudine, Adefovir, nor Tenofovir.
- Should be taken in empty stomach.
- In HIV co-infection, may induce HIV drug resistance; OK to use while in HAART.
- In Lamivudine- or Telbivudine- resistant HBV, these drugs must be discontinue when Entecavir is initiated.

Entecavir

- Side Effects:
  - Lactic acidosis (highest risk with MELD > 20),
  - severe hepatomegaly
  - **Headache, fatigue, nausea.**
- **Viral Response after 1 y therapy**:
  - HBe(+) = 82%,
  - HBe(-) = 48%
- **Resistance:**
  - YMDD mutant (Lamivudine resistant): 7% @ 1 y, 26% @ 3y, & > 50% @ 5y.
  - In Naïve: 1.2% @ 5 y.
  - Resistance to Lamivudine increases risk of resistance to Entecavir, Telbivudine, and Emtricitabine; do not give them together.

Tenofovir Disoproxil

- Oral adenosine nucleotide analog; approved in 2008.
- Dose: 300 mg/day; adjusted by renal function
- Effective in: wild and YMDD mutant; HBeAg(+) and (-)
- Causes 4-5 log drop HBV-DNA @ 48 weeks
- No resistance in up to 4 years
- Side Effects:
  - Lactic acidosis
  - Severe hepatomegaly
  - Osteomalacia, decreased mineral density
  - Renal insufficiency, Fanconi Syndrome (both rare)

Comparison of Entecavir & Tenofovir

Lok A. Hepatology 2010: 52(2):743-747

	ENTECAVIR	TENOFOVIR
HBe(+) 1y HBV-DNA log drop	6.9	6.2
HBe seroconversion	21%	21%
HBsAg loss	2%	3%
HBe(-) 1 y HBV-DNA log drop	5	4.6
HBsAg loss	< 1%	0%
Genotypic resistance Nucleoside-Naive	1.2% (year 5)	0% (year 3)
Lam-experienced	51% (year 5)	N/A
Safety in Pregnancy	Class C	Class B
Adverse Events	None	Osteopenia, nephrotoxicity

Telbivudine (LdT)

- Telbivudine: specific inhibitor HBV polymerase; approved in 2006.
- Oral beta-L-deoxynucleoside of thymidine
- Causes 2-3 log HBV-DNA drop by wk 4; not effective in YMDD mutant.
- Dose: 600 mg/d
- Side Effects:
  - Lactic acidosis,
  - Severe hepatomegaly,
  - CPK elevation with myopathy,
  - Peripheral neuropathy (especially if combined with Peg-IFN)
- Resistance to Lamivudine increases risk of resistance to Entecavir, Telbivudine, and Emtricitabine; do not give them together.

Lamivudine

- Nucleoside analogue; Approved in 1998.
- Dose: 100 mg/day (300 mg/d in HIV-HBV co-infection); correct by creatinine clearance.
- Side effects:
  - Lactic acidosis,
  - Severe hepatomegaly
  - Mild increase in ALT
- High rate of resistance.

Adefovir Dipivoxil

- Oral adenosine nucleotide analog.
- Moderately active in wild, HBe(-), and YMDD mutant.
- Good choice for HBe(-) mutant, and as second drug for YMDD mutant, and as monotherapy in HIV co-infection.
- Decreases levels of intrahepatic cccDNA.
- Used together with Peg-IFN, increases rate of HBe seroconversion and of HBsAg loss.
- Dose 10 mg/day; correct by renal fx.
- Escape mutants are sensitive to Lamivudine.
- Nephrotoxic in 1%; creatinine raise and waste of phosphate & glucose (Fanconi)
- When changing from Lamivudine to Adefovir, continue both long term to decrease resistance to adefovir.

HBV prevention Post-OLTx

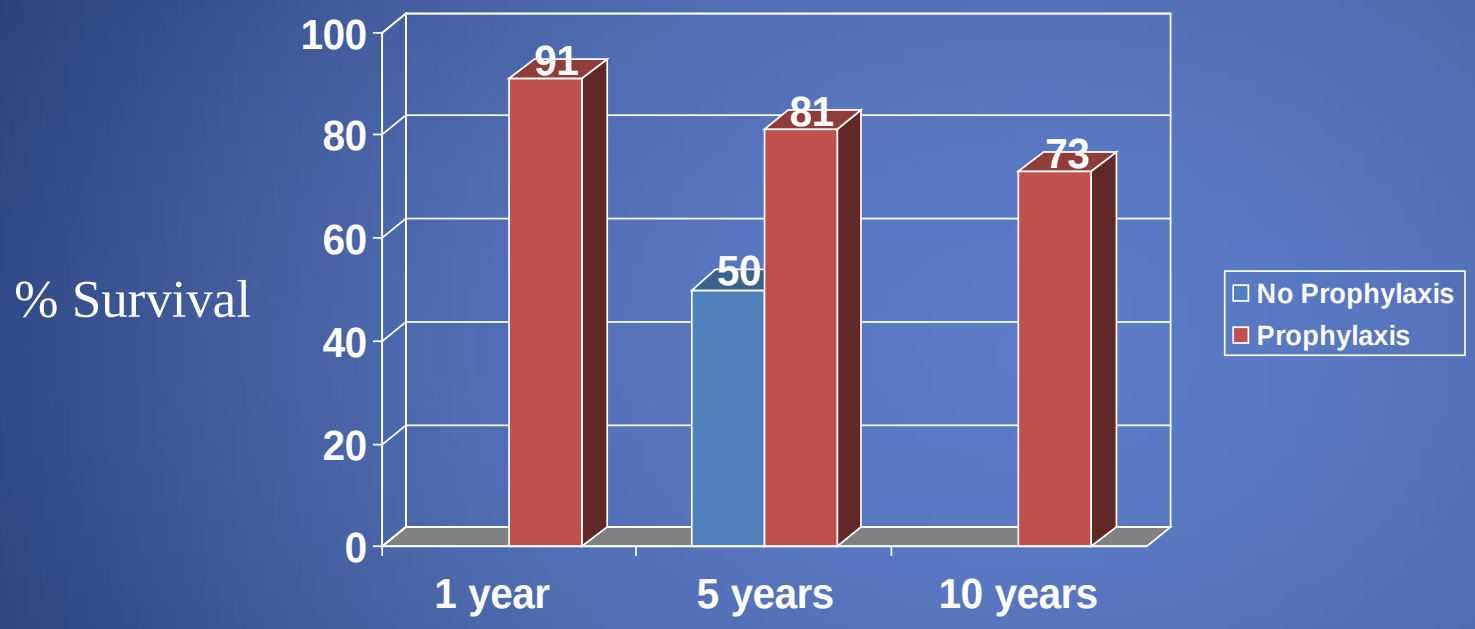
HBsAg(+) Recipient

Prophylaxis for HBsAg(+) Liver Recipient

Prophylaxis Choice in HBsAg(+) Recipient	Long-term HBIG Plus Indefinite NAs	Perioperative Only or No HBIG Plus Indefinite NAs
Patient factors	Questionable adherence	Adherent High share of cost for medications
Virological factors	Presence of drug resistance or HBV-DNA high at time of LT HIV coinfection HDV coinfection	No drug-resistant variants Undetectable to low (< 100 IU/mL) HBV-DNA at time of LT
Other	Access to HBIG Lack access to entecavir or tenofovir (TDF or TAF)	Access to entecavir or tenofovir (TDF or TAF)

Benefits of HBIG Prophylaxis

HBsAg(+) Recipients



Benefits of HBIG Prophylaxis HBsAg(+) Recipient

- Anti-HBs titer goals post-OLTx (in HBIG monotherapy):
  - a) first week: >500 IU/L,
  - b) week 2-4: >500 IU/L in high-replic; >100-150 in low-replic
  - c) day 28-180: >250 IU/L in high-replic; >100-150 in low-replic
  - d) thereafter: > 100-150 IU/L
- Escape occurs b/o:
  - a) “inadequate anti-HBs titer”, or
  - b) “pre-S/S mutation” causing reduced binding of anti-HBs.

Definitions for Oral Antivirals
Pre-OLTx anti-HBV Therapy

- **High replicators** > 10^4 copies/mL or > **2000 IU/mL**:
  - high risk for graft re-infection and death;
  - all cirrhotics with > 10^4 copies/mL (2000 IU/mL) need therapy with "high resistance-barrier agent" (Tenofovir, Entecavir, or Lamivudine+Adefovir).
- **Low replicators** < 10^4 copies/mL (**< 2000 IU/mL**):
  - moderate/low risk re-infection & death;
  - if < 10^2 copies/mL, may be candidates for post-OLTx [short-term HBIG + oral agent], or [oral "high resistance-barrier" agent monotherapy].

Combination HBIG + Oral agent

Low replicators (</=10^4 copies/mL or < 2000 IU/mL), Fulminant HBV, and HBV+Delta

Angus PW. Liver Transpl 2000;6:429-433; Gane EJ. Gastroenterology 2007;132:931-937

- **Anhepatic phase**: HBIG 936 IU IM (3 mL Nabi-HB)
- Start/continue oral agent post-OLTx: Either (Adefovir + Lamivudine), Entecavir, or Tenofovir, or the combination that was effective before transplant. Continue oral agent **for life**.
- **First week**: daily 936 IU HBIG (3 mL Nabi-HB) IM x 7 days.
- **Thereafter**: HBIG 936 IU IM q month (3 mL Nabi-HB)
- If pre-OLTx HBV-DNA was < 10^4 IU/mL, and after 1 year HBV-DNA is still "non-detectable", consider to discontinue HBIG after vaccination + boosters (40mcg @ 0,1,2 & 6 mo) x 1-3 courses, if patient responds with anti-HBs > 100 mIU/mL.
- **Monitoring**:
  - HBsAg, HBe Ag & Ab, and HBV-DNA quant q month x 3; then
  - HBsAg, HBe Ag & Ab, and HBV-DNA quant q 3 months for life.

Combination HBIG + Oral agent

High Replicators (> 10^4 copies or > 2000 IU/mL)

- **Anhepatic phase**: HBIG 10000 IU IV
- Continue effective oral agent, with high resistance barrier, post-OLTx **for life**. Give either (Adefovir + Lamivudine), Entecavir, Tenofovir, or combination regimen that was effective pre-Tx.
- **First week**: daily 10000 IU HBIG IV x 6 days
- **Thereafter: 936** IU IM q month (3 mL Nabi-HB), starting on day 7 post-op.
- **Monitoring**:
  - HBsAg, HBe Ag & Ab, and HBV-DNA quant q month x 3; then
  - HBsAg, HBe Ag & Ab, and HBV-DNA quant q 3 months for life.

UofL Protocol: HBsAg (+) Liver Transplant Recipient

Terrault N. Am J Gastroenterol 2013;108:949-951; Cholongitas E. *American Journal of Transplantation 2013; 13: 353–362*

Recipient's viral load	Anhepatic Phase	First week	Thereafter	Monitoring
HBV-DNA < 100 IU/mL Good Adherence No Drug-Resistance HBV No HDV coinfection No HIV Coinfection	HBIG 4992 IU (16 mL Nabi-HB, IM, or 16 mL HepaGam B IV)	HBIG 4992 IU (16 mL Nabi-HB, IM or 16 mL HepaGam B, IV) X 5 days + Daily Entecavir or Tenofovir	Entecavir, or Tenofovir **for life**	HBsAg, HBe/anti-HBe, HBV-DNA quantitation q month x 3, and then q 3 months for life
HBV-DNA < 1000 IU/mL No Drug-Resistance HBV No HDV coinfection No HIV Coinfection	HBIG 4992 IU (16 mL Nabi-HB, IM, or 16 mL HepaGam B IV)	HBIG 4992 IU (16 mL Nabi-HB, IM or 16 mL HepaGam B, IV) X 7 days + Daily Entecavir, or Tenofovir	HBIG 936 IU (3 mL Nabi-HB), IM q month for >/= 6 months. Immunize after 6 months, and if anti-HBs response > 100 IU/L, d/c HBIG Entecavir, or Tenofovir **for life**	HBsAg, HBe/anti-HBe, HBV-DNA quantitation q month x 3, and then q 3 months for life
HBV-DNA > 1000 IU/mL Drug Resistant HBV HDV Coinfection HIV Coinfection Questionable Adherence	HBIG 4992 IU (16 mL Nabi-HB, IM, or 16 mL HepaGam B IV)	HBIG 936 IU (3 mL Nabi-HB), qd IM, x 7 days + Daily Entecavir, or Tenofovir,	HBIG 936 IU (3mL Nabi-HB), q month IM **for life**. (could consider vaccination after 18 months of HBIG and D/C HBIG if anti-HBs > 100 IU/L but 5-6% relapse if HBIG is discontinued) Entecavir, or Tenofovir **for life**	HBsAg, HBe/anti-HBe, HBV-DNA quantitation q month x 3, and then q 3 months for life

Anti-HBc(+) organ

given to HBsAg(-) Recipients

Window Time Before (+) NAT Test after Infection Acquisition

Agent	Days
HIV	HIV-RNA: 5-6
HCV	HCV-RNA: 3-6
HBV	HBV-DNA: 20-22

Anti-HBc(+) organ donors

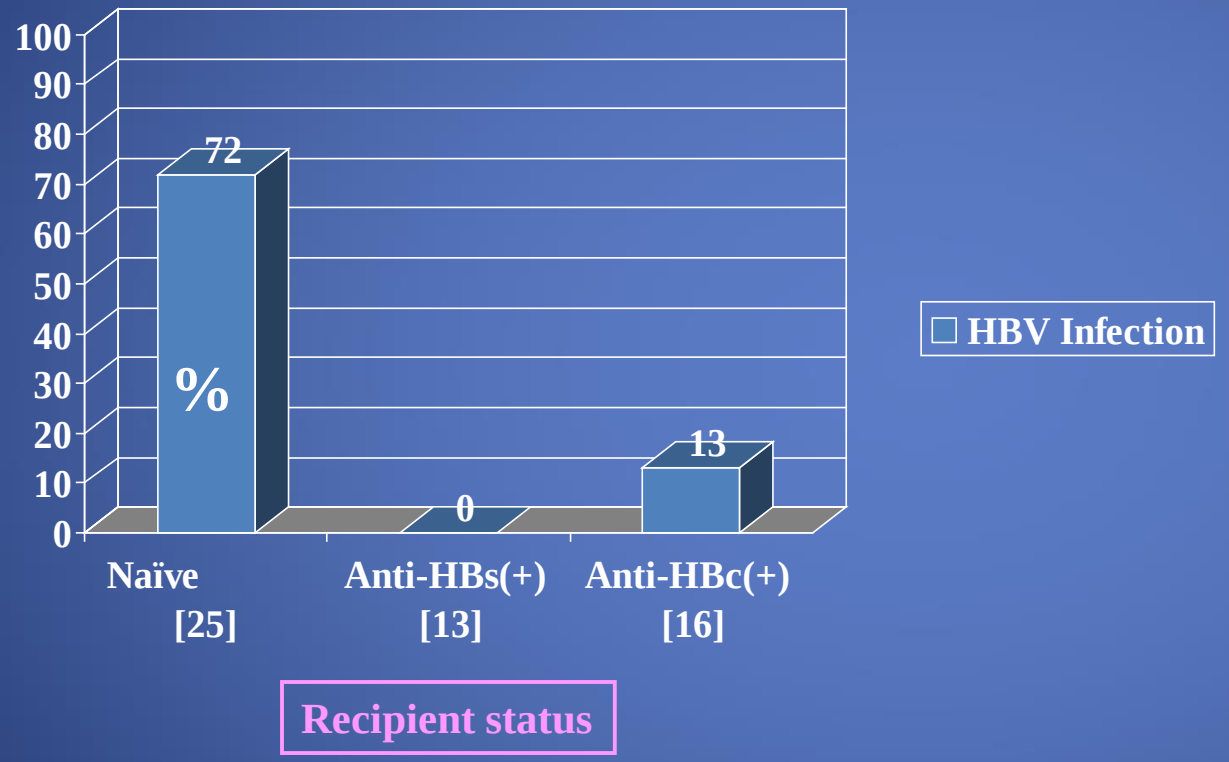
Risk of HBV acquisition

- Anti-HBc (+) or anti-HBs (+) donors:
  - Overall 33-100%
- Anti-HBc(+) organ given to:
  - HBV naïve recipient: 30-72%.
  - Anti-HBc(+) recipient: 13%.

Anti-HBc(+) Organ Donors

Risk of HBV Infection

Dodson et al. Transplantation 1997

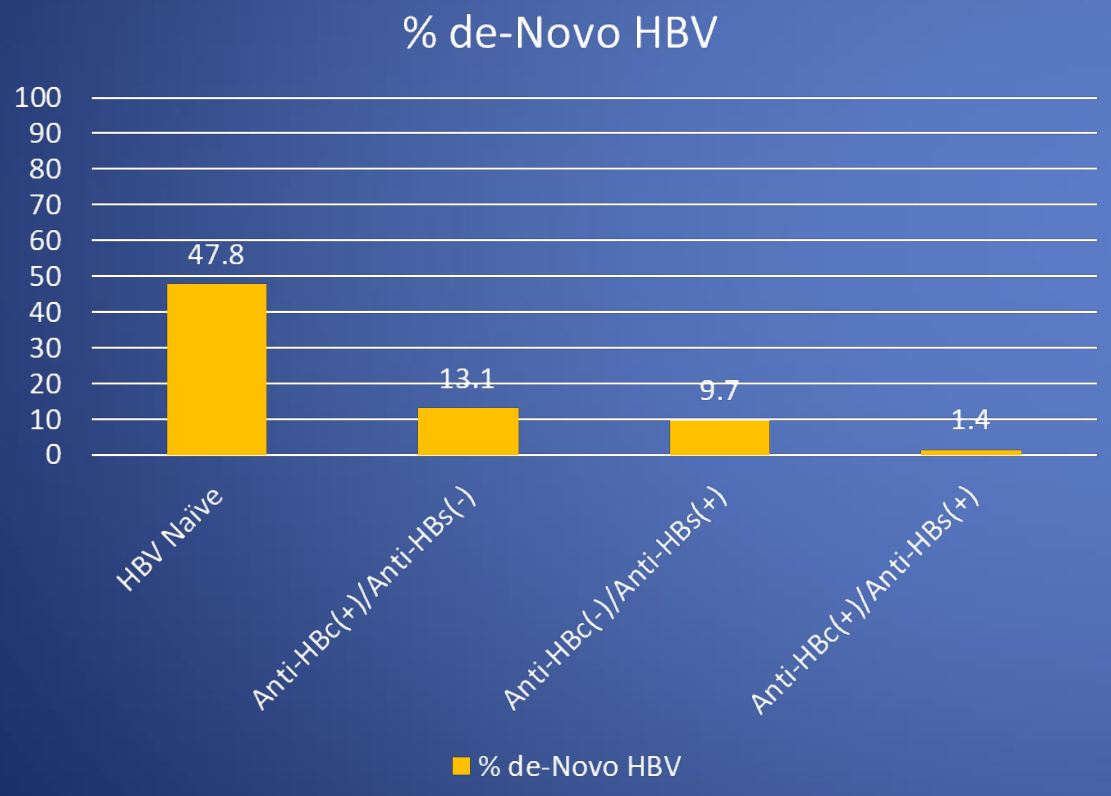


No HBV prophylaxis was given

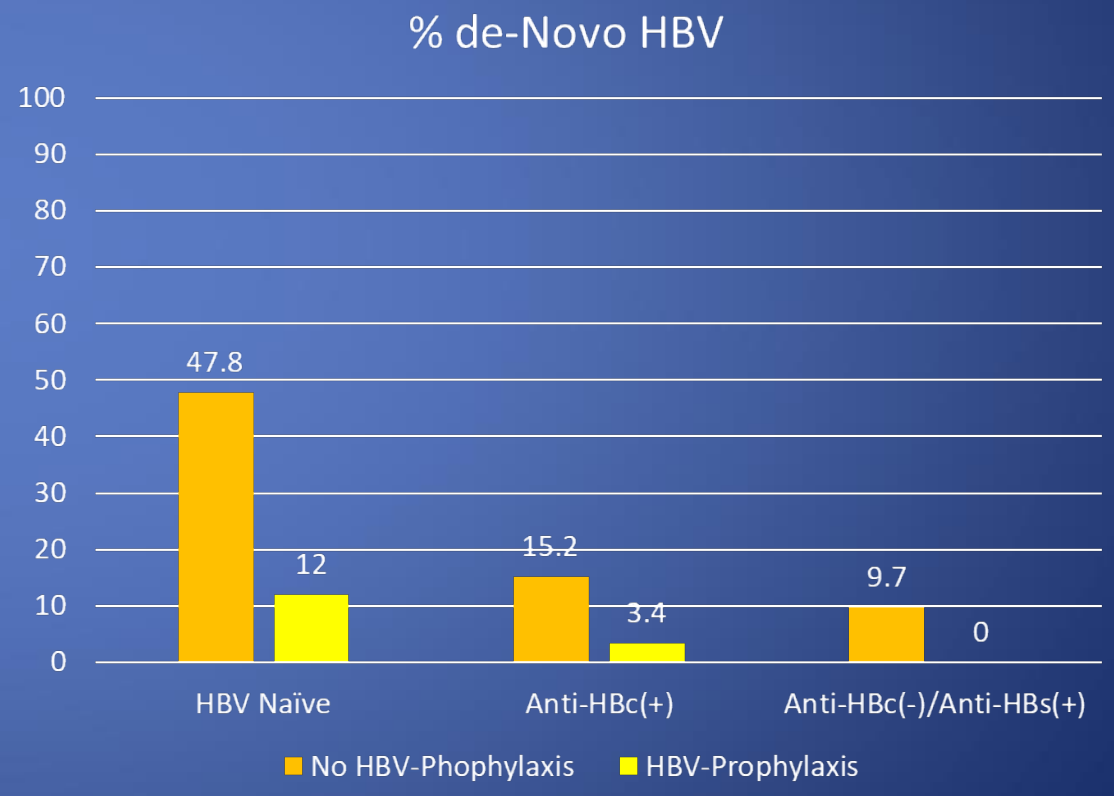
Risk of HBV infection from Anti-HBc(+) Liver Donor by Recipient Status

Cholongitas E J Hepatol 2010; 52:272-279

No HBV Prophylaxis



HBV Prophylaxis vs No Prophylaxis

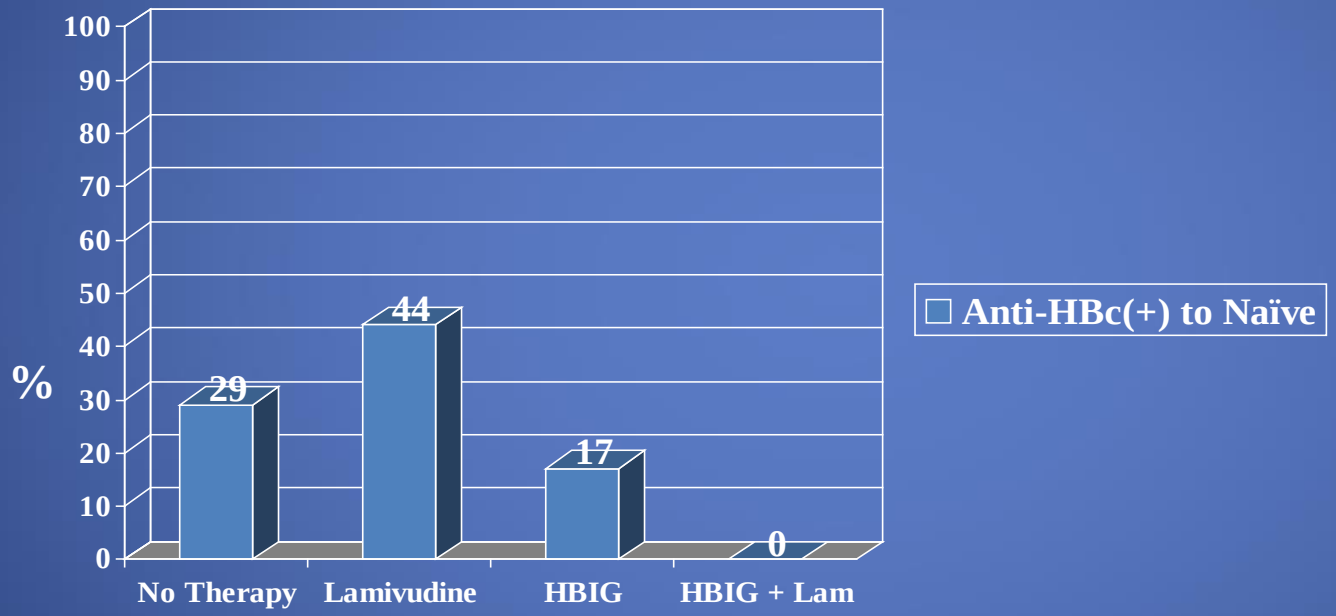


Anti-HBc(+) Donor To Naïve Recipient

Effect of Prophylaxis

UCLA Experience

Ghobrial RM ; Transplant Hepatology CAQ Course - 2006



Anti-HBc(+) organ donors

- **Primary candidates:**
  - **HBsAg(+) recipients**

– Follow protocols for Low, or High Replicators as described in previous section (“HBsAg(+) Recipient”).

Anti-HBc(+) organ donors

- **<u>Secondary candidates</u>:**
- **1)** anti-HBs(+) recipients (with titer > 10 IU/L),
- **2)** anti-HBc(+) recipient, and
- **3)** critically ill.

– **Before OLTx or other Tx:**

- Order HBV-DNA in donor's serum (to detect "pre-S/S mutant virus" = HBsAg(-) mutant), and
- Check or order recipient's "peak" anti-HBs titer (if not known, obtain pre-op anti-HBs titer)

Anti-HBc(+) organ donors

– **Secondary candidates management:**

- **Donor's serum HBV-DNA(+) & any Recipient's peak anti-HBs titer (**despite absence of HBsAg) **:**
  - Highly active oral agent (Lamivudine+Adefovir combination, or Tenofovir or Entecavir, **for life**);
  - Booster Vaccinate after 1 year [if HBV-DNA(-)] (40mcg @ 0,1,2 & 6 mo) x 1-3 courses, until anti-HBs > 100 IU/mL (but continue oral agent for life)

Anti-HBc(+) organ donors

– **<u>Secondary candidates management</u>:**

– **Donor's serum HBV-DNA (-) & Recipient's peak anti-HBs titer > 100 IU/L :**
  - Lamivudine 150 mg BID (until anti-HBs > 100 mIU/mL, or for life).
  - Booster vaccinate x 1 dose, after 1 year, and check anti-HBs.
  - Discontinue oral agent after if good anti-HBs response is maintained (> 100 mIU/mL) ?

– **Donor's serum HBV-DNA (-) & Recipient's peak anti-HBs titer is < 100 IU/L :**
  - Lamivudine 150 BID (until anti-HBs > 100 mIU/mL, or for life).
  - Booster Vaccinate after 1 year [if HBV-DNA(-)] (40mcg @ 0,1,2 & 6 mo) x 1-3 courses, until anti-HBs > 100 mIU/mL.
  - Discontinue oral agent if good anti-HBs response is achieved (> 100 mIU/mL) ?

Anti-HBc(+) liver donors

– **Secondary candidates management**:

– **Choice of oral agent**:
  - If donor HBV-DNA in serum is (+) give Tenofovir or Entecavir.
  - If donor HBV-DNA in serum is negative, give Lamivudine 150 mg BID (corrected by renal function).

– **Monitoring**:
  - HBsAg, HBe Ag & Ab, and HBV-DNA quant q month x 3; then
  - HBsAg, HBe Ag & Ab, and HBV-DNA quant q 3 months for life.

Anti-HBc(+) liver/other organ donors

- **Tertiary candidates:**

- **HBV naïve patients [anti HBc(-) & anti-HBs(-)]**
  - Before OLTx, check/order HBV-DNA in donor's serum.
  - **If Donor's serum HBV-DNA is (+) :**
    - High resistance barrier oral agent (Entecavir, or Tenofovir) **for life**; [to give HBIG will not help if donor's HBsAg was (-)]
    - Vaccinate after 1 year [if HBV-DNA(-)]; Independently of response, give oral agent for life.
  - **If Donor's serum HBV-DNA is negative**:
    - Lamivudine 150 mg BID (until anti-HBs > 100 mIU/mL, or for life)
    - Vaccinate after 1 year [if HBV-DNA(-)], with 40mcg @ 0,1,2 & 6 mo x 1-3 courses, until anti-HBs > 100 mIU/mL.
    - Discontinue oral agent if good anti-HBs response is achieved (> 100 mIU/mL) ?

Anti-HBc(+) liver donors

- **Tertiary candidates:**

– **Choice of oral agent**:
  - If HBV-DNA in serum is (+) give Tenofovir or Entecavir.
  - If HBV-DNA in serum is negative, give Lamivudine.

– **Monitoring**:
  - HBsAg, HBe Ag & Ab, and HBV-DNA quant q month x 3; then
  - HBsAg, HBe Ag & Ab, and HBV-DNA quant q 3 months for life.

UofL Protocol: Anti-HBc(+) organ given to HBsAg(-) Recipient

Recipient Status	Donor Status	Oral Agent (adjust dose by renal function)	Immunization	Monitoring
Peak anti-HBs > 10 mIU/mL, or anti-HBc(+)	**Serum HBV-DNA(+)**	High "barrier-resistance", [(Adefovir+Lamivudine), Entecavir, or Tenofovir] **for life.**	HBV-vaccine 40 mcg @ 0,1,2,6 mo x 1-3 times until anti-HBs > 100 mIU/mL	HBsAg, HBe/anti-HBe, HBV-DNA quantitation q month x 3, and then q 3 months for life
Peak anti-HBs > 100 mIU/mL	Serum HBV-DNA(-)	Lamivudine 150 BID, until anti-HBs > 100 mIU/mL, or for life	HBV-vaccine 40 mcg, until anti-HBs > 100 mIU/mL	HBsAg, HBe/anti-HBe, HBV-DNA quantitation q month x 3, and then q 3 months for life
Peak anti-HBs 10-99 mIU/mL, or anti-HBc(+)	Serum HBV-DNA(-)	Lamivudine 150 BID, until anti-HBs > 100 mIU/mL, or for life	HBV-vaccine 40 mcg @ 0,1,2,6 mo x 1-3 times until anti-HBs > 100 mIU/mL	HBsAg, HBe/anti-HBe, HBV-DNA quantitation q month x 3, and then q 3 months for life
anti-HBs < 10 mIU/mL, and anti-HBc(-)	**Serum HBV-DNA(+)**	High "barrier-resistance", [(Adefovir+Lamivudine), Entecavir, or Tenofovir], **for life.**	HBV-vaccine 40 mcg @ 0,1,2,6 mo x 1-3 times until anti-HBs > 100 mIU/mL	HBsAg, HBe/anti-HBe, HBV-DNA quantitation q month x 3, and then q 3 months for life
anti-HBs < 10 mIU/mL, and anti-HBc(-)	Serum HBV-DNA(-)	Lamivudine 150 BID, until anti-HBs > 100 mIU/mL, or for life	HBV-vaccine 40 mcg @ 0,1,2,6 mo x 1-3 times until anti-HBs > 100 mIU/mL	HBsAg, HBe/anti-HBe, HBV-DNA quantitation q month x 3, and then q 3 months for life

Hepatitis D

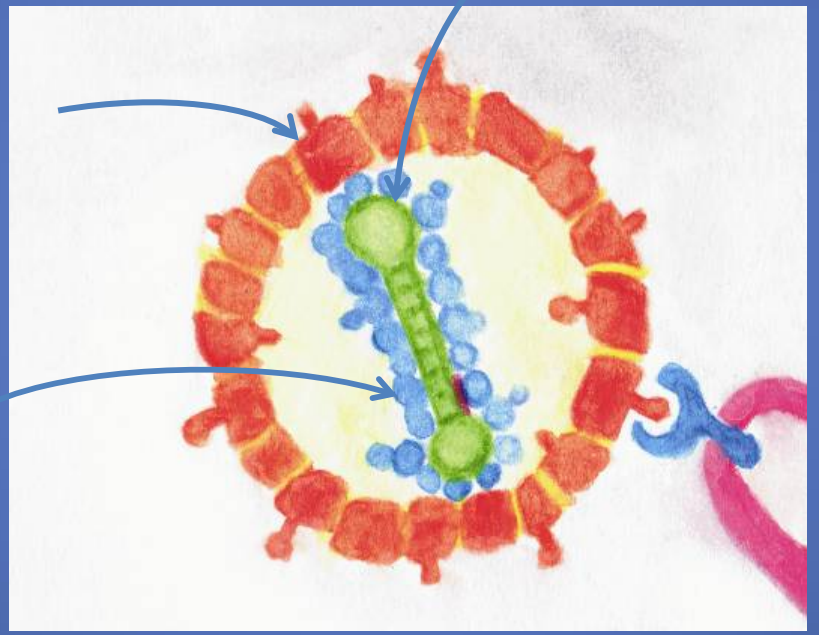
Delta Virus Hepatitis

- 36-43 nm Deltavirus with negative-stranded circular RNA which depends on HBV to propagate
- **Virion**: outer lipoprotein envelope made of the HBsAg and an inner ribonucleoprotein structure in which the HDV genome resides.
- **HDV genome**: single stranded RNA folded as a rod-like structure through internal base-pairing
- Causes cytopathic damage in acute infection, and immune-mediated liver injury in chronic infection;
- Anti-HBs is protective; anti-HD is not protective.
- Can be acquired as **Co-infection** (HBV + HDV together) or as **Super-infection** (HDV over chronic HDV)
- **Prophylaxis**: HBV vaccination.

The Hepatitis Delta Virus and Interaction with HBV

HDV-RNA

HBsAg



HDAg

- The smallest of all animal viruses
- Highly paired – rod like structure
- No native viral enzymes but Ribozymes
- Only encodes S-HDAg

- HBsAg particles can self assemble
- HBV: 1 virion x 10^3-10^6 particles

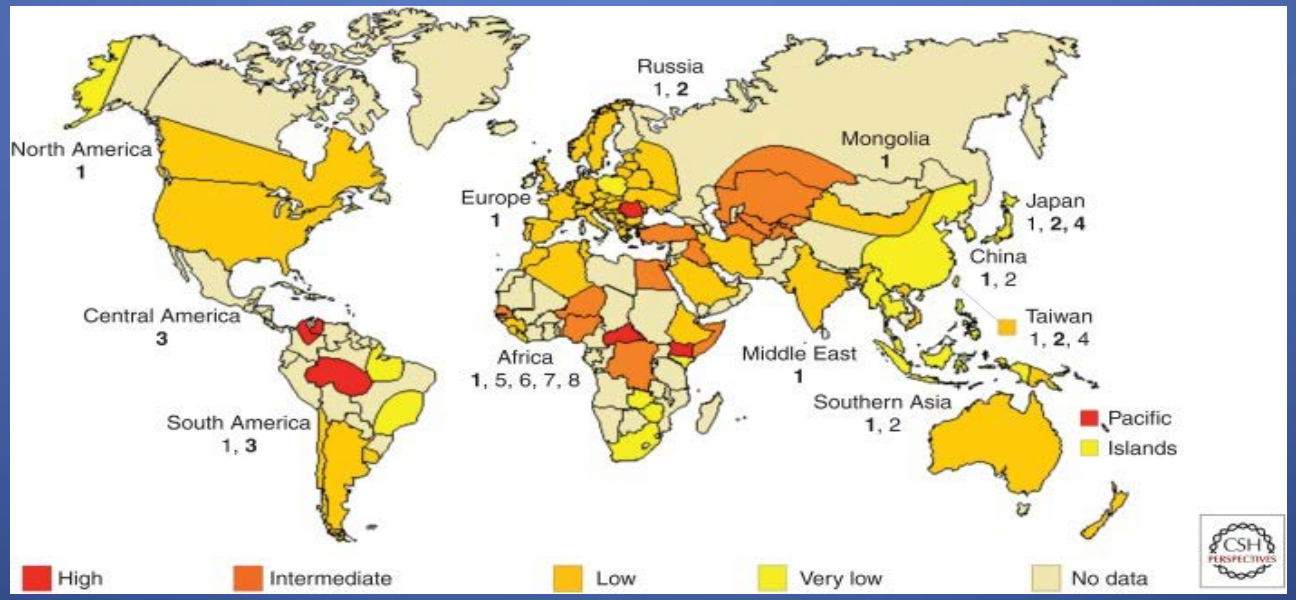
- 2 forms: Small-HDAg and Large-HDAg
  - S-HDAg (mRNA): ↑ replication
  - L-HDAg (template directing transcription): ↑ assembly (↓ replication)

Calle Serrano, Manns & Wedemeyer, Seminars in Liver Disease 2012

Introduction

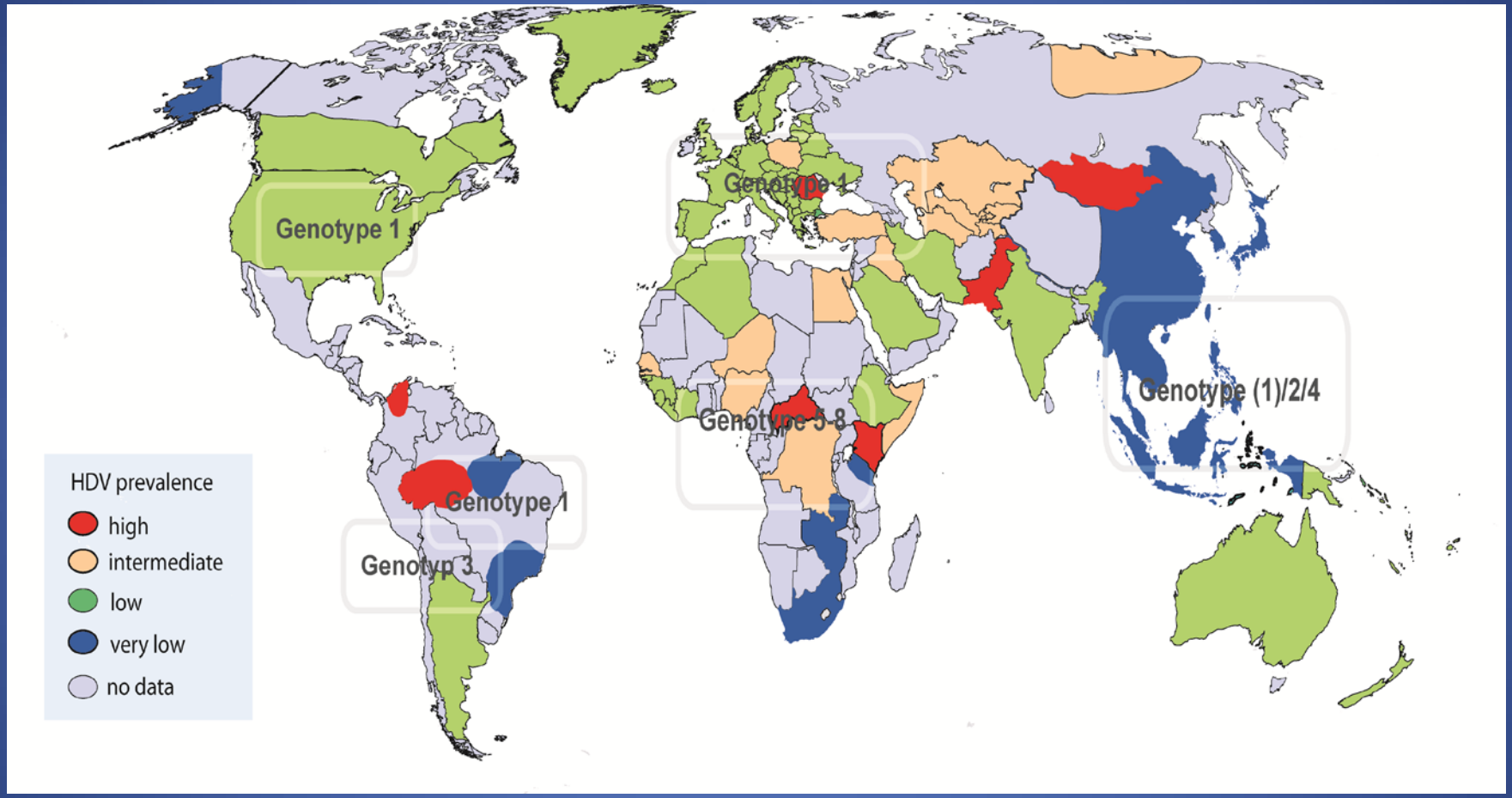
Epidemiology of HDV:

- Approximately 5% of patients with HBV have delta infection; however, any recent prevalence data is largely lacking due to very low-level testing
- Estimates vary depending on risk factors and location:
  - Some high-risk populations such as IVDU with rates as high as 50% vs 1-2% in low risk HBV populations
  - In patients with chronic HBsAg hepatitis, the pooled prevalence of HDV was **47.36% in Somalia, 24.37% in Egypt, and 8.15% in Saudi Arabia**.



Ahn J, Gish RG. Hepatitis D Virus: A Call to Screening. Gastroenterol Hepatol (N Y). 2014;10(10):647–686.
Rizzetto M. Hepatitis D Virus: Introduction and Epidemiology. Cold Spring Harb Perspect Med. 2015;5(7):a021576. Published 2015 Jul 1. doi:10.1101/cshperspect.a021576

Prevalence of Hepatitis Delta by Genotype



15-20 million patients with chronic hepatitis D (delta):
100 to 150 K US, 200+ K EU, 2 M China

Delta Virus Hepatitis

HBV/HDV Co-Infection

- Suspect in protracted acute HBV, in IV drug users, and in person fro endemic country.
- Severity similar to acute HBV but less chronicity (5% vs 2%). Fulminant mostly with genotype III
- Most patients very symptomatic and jaundiced.
- Classically two bouts of elevated ALT/AST a few weeks apart.
- **DX**:
  - anti-HBcIgM(+) & HDV-RNA(+) +/- transient anti-HD IgM (+), followed 4 weeks later with anti-HD IgG(+).
  - If evolves to chronicity, high titers anti-HD IgG and anti-HD IgM will persist.

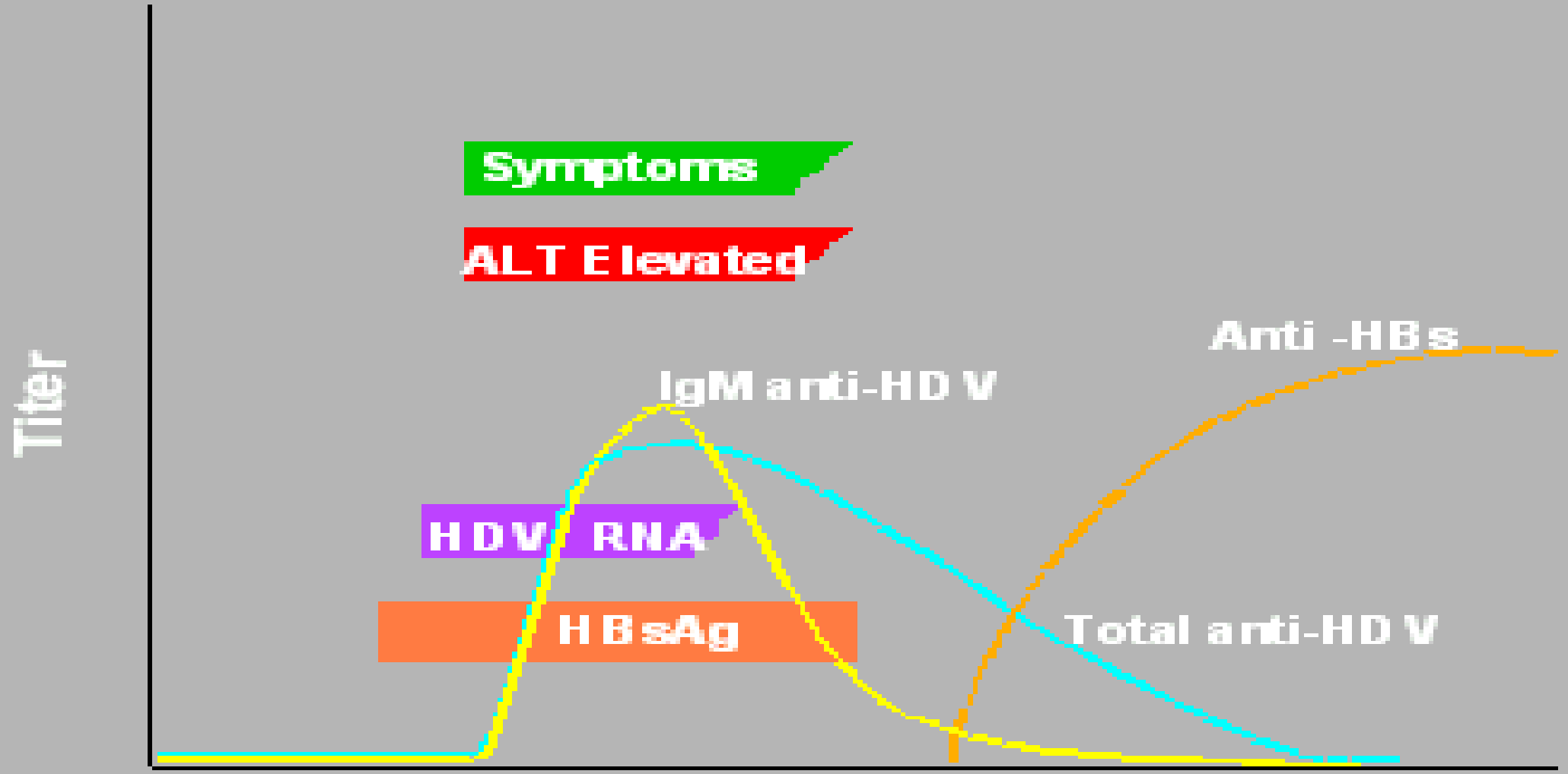
HBV/HDV Superinfection

- Presents as HBV ”flare up” or Acute-on Chronic Liver Failure.
- Evolves to chronic HBV+HDV in 80%; FHF in some; the rest clears HBV & HDV.
- Most patients evolve to cirrhosis over a decade; 15% benign course; few have rapid progression to cirrhosis in < 2 years.
- **DX**:
  - HBsAg(+), anti-HBcIgM(-), and HDV-RNA(+); HBV-DNA will be low or non-detectable.
  - If evolves to chronicity (most patients), persistent HDR-RNA and high titer anti-HD IgM(+) and anti-HD IgG(+).

All patients with stable Chronic HBV should be tested once with anti-HD IgG
Periodic retesting in persons who inject drugs, men who have sex with men, and those at risk for sexually transmitted diseases

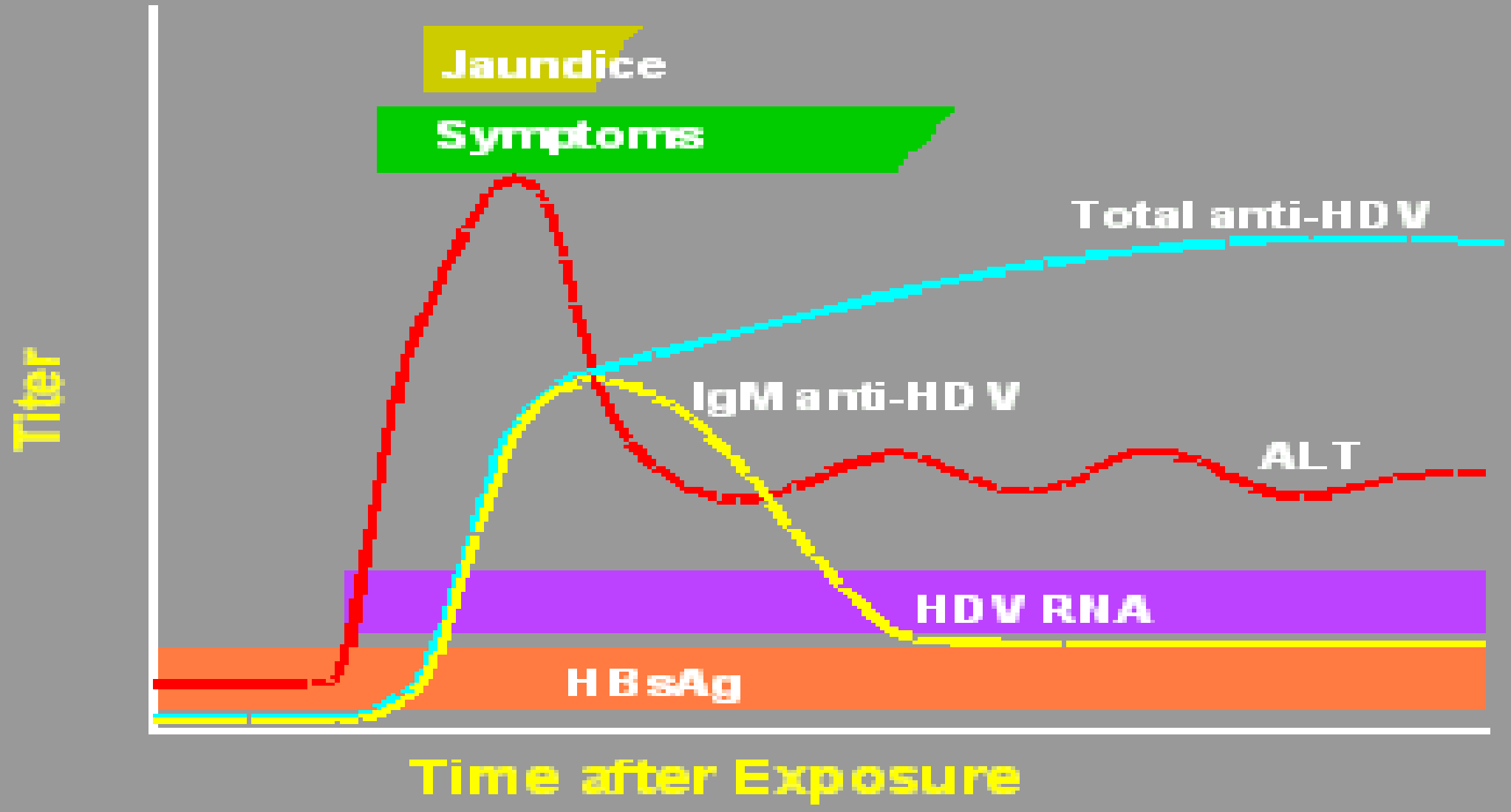
HBV – HDV Coinfection

Typical Serological Course

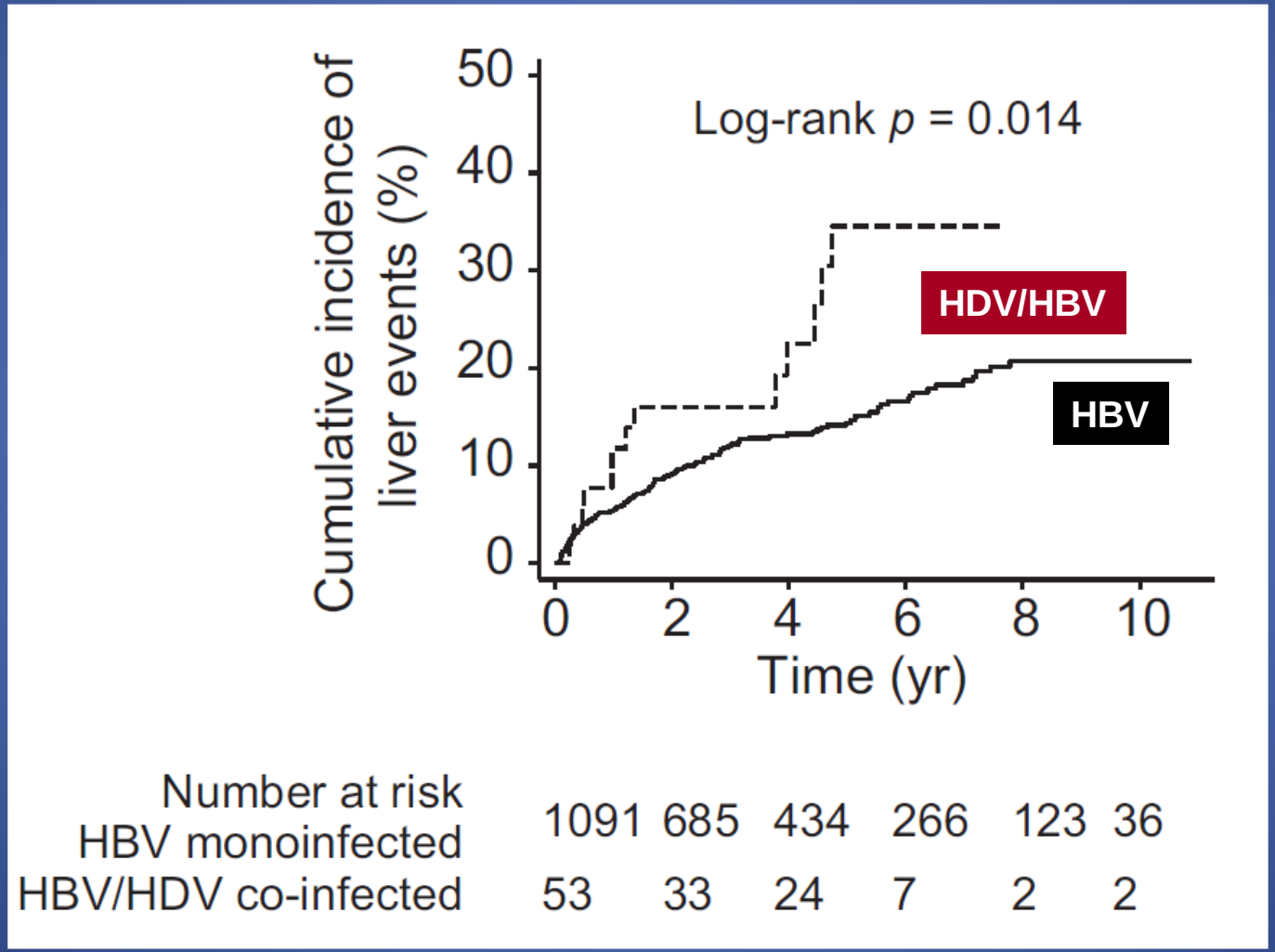


HBV – HDV Super-infection

Typical Serological Course

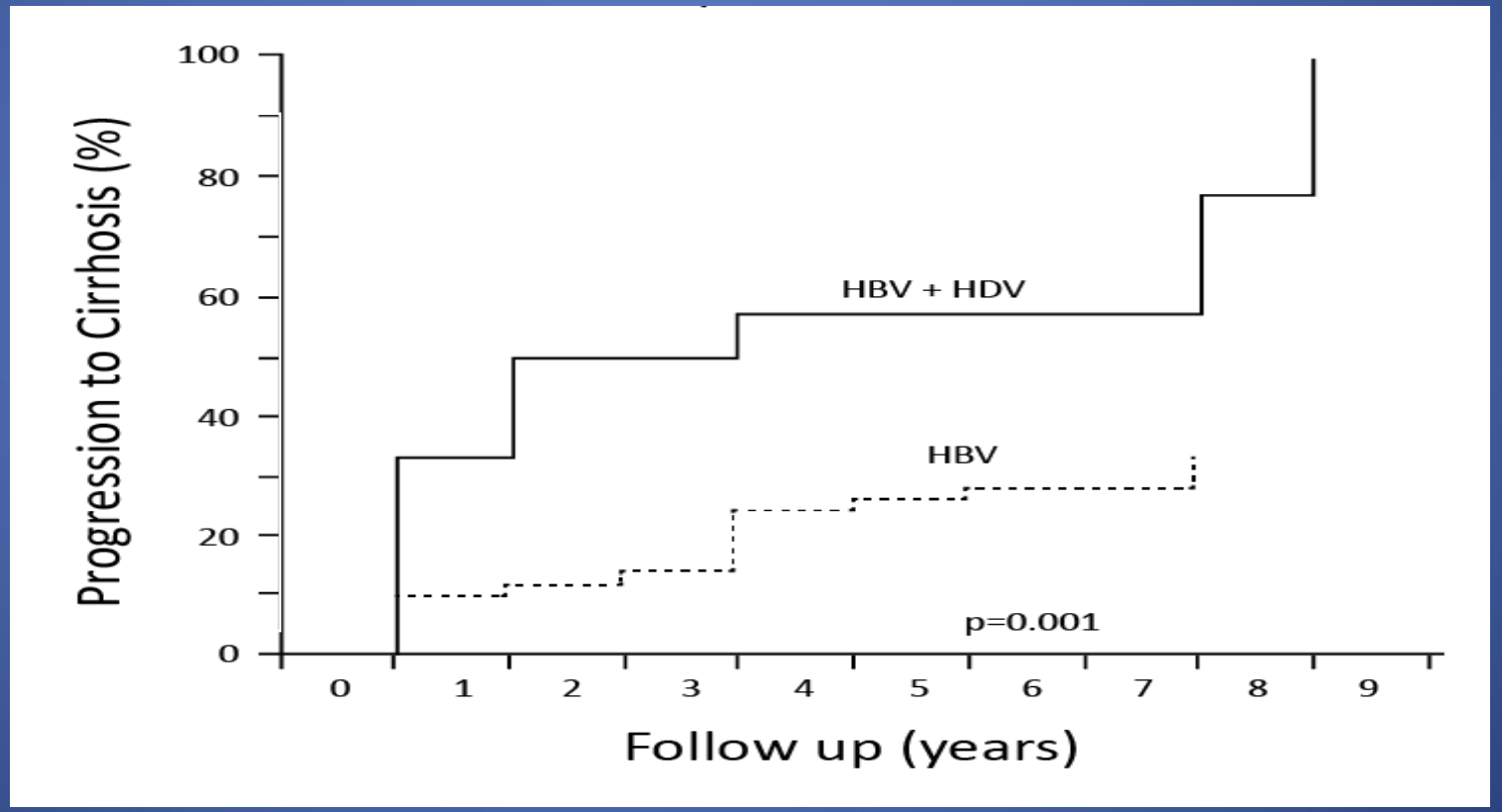


1-2 decades later: Hepatitis Delta still takes a more severe long-term course than HBV mono-infection



Manesis et al., J Hepatol 2013

HDV has a much faster progression to Cirrhosis compared to HBV mono-infection !



Fattovich et al, *J Infect Dis*, 1987; Fattovich et al, *Gut*, 2000.

Chronic HDV
Treatment

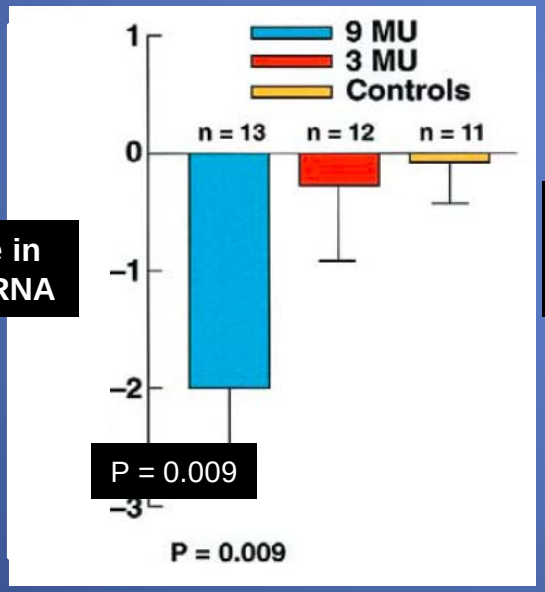
- Interferon high dose (9 MU TIW) for 48 months or at least 12 months after normalization of ALT.
- Liver Transplant with HBIG post-op; graft re-infection in 9-12 %

Reducing HDV-RNA with IFNa Improves Survival

Improved Clinical Benefit without Clearance of HDV-RNA

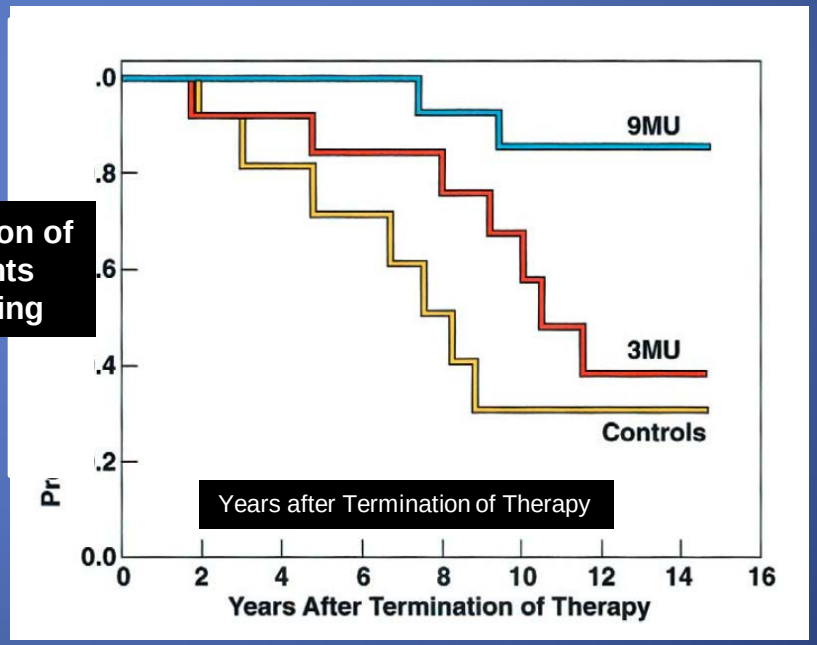
Interferon-α for 48 weeks with 15 year Follow Up

Change in HDV-RNA



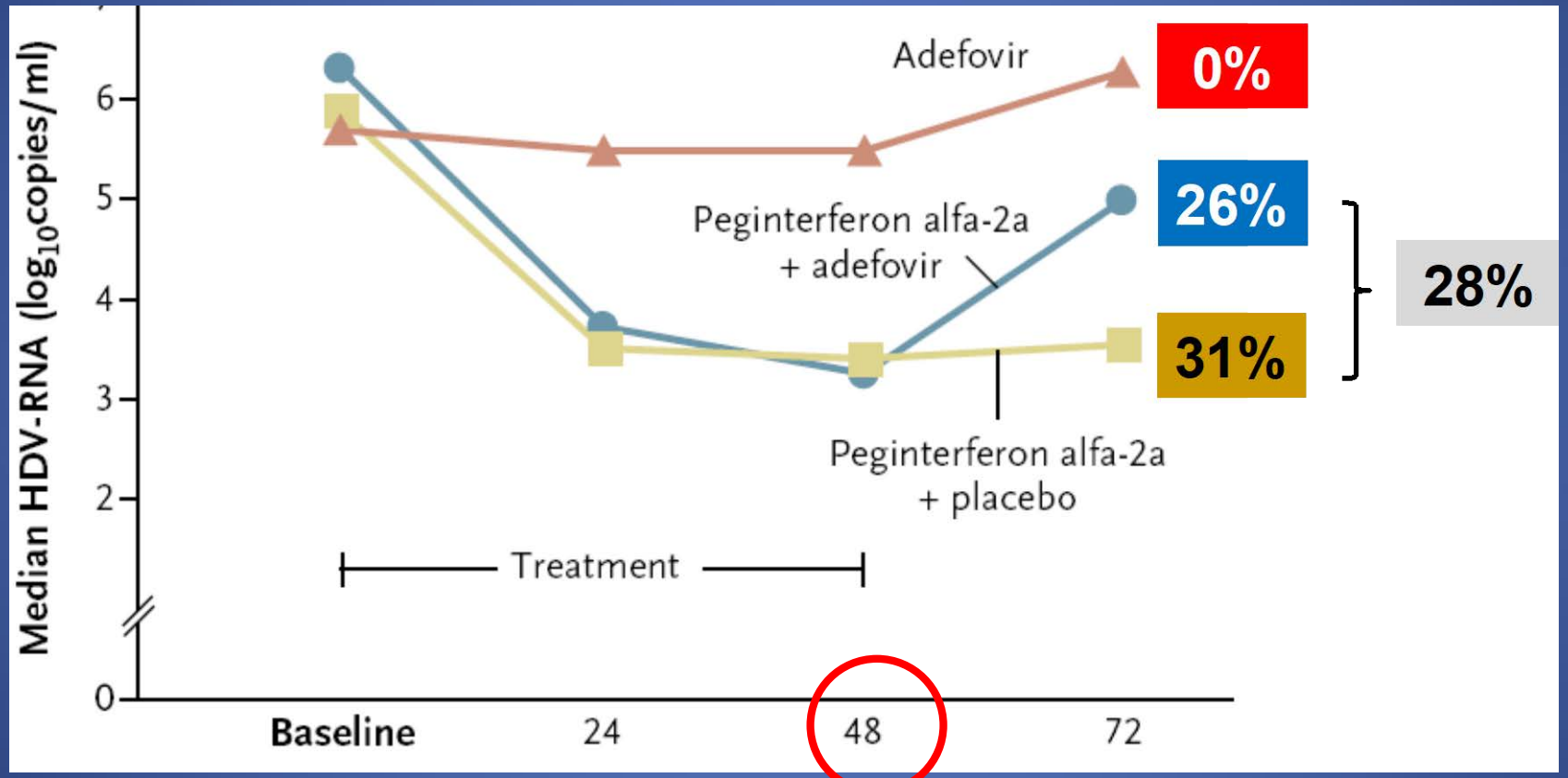
Log Change in Serum HDV-RNA

Survival



Farci et al, *Gastroenterology* 2004: Long-Term Benefit of Interferon-α Therapy of Chronic HDV: Regression of Advanced Hepatic Fibrosis

Treatment of Chronic Hepatitis Delta: Only PEG-IFN leads to decline of HDV RNA

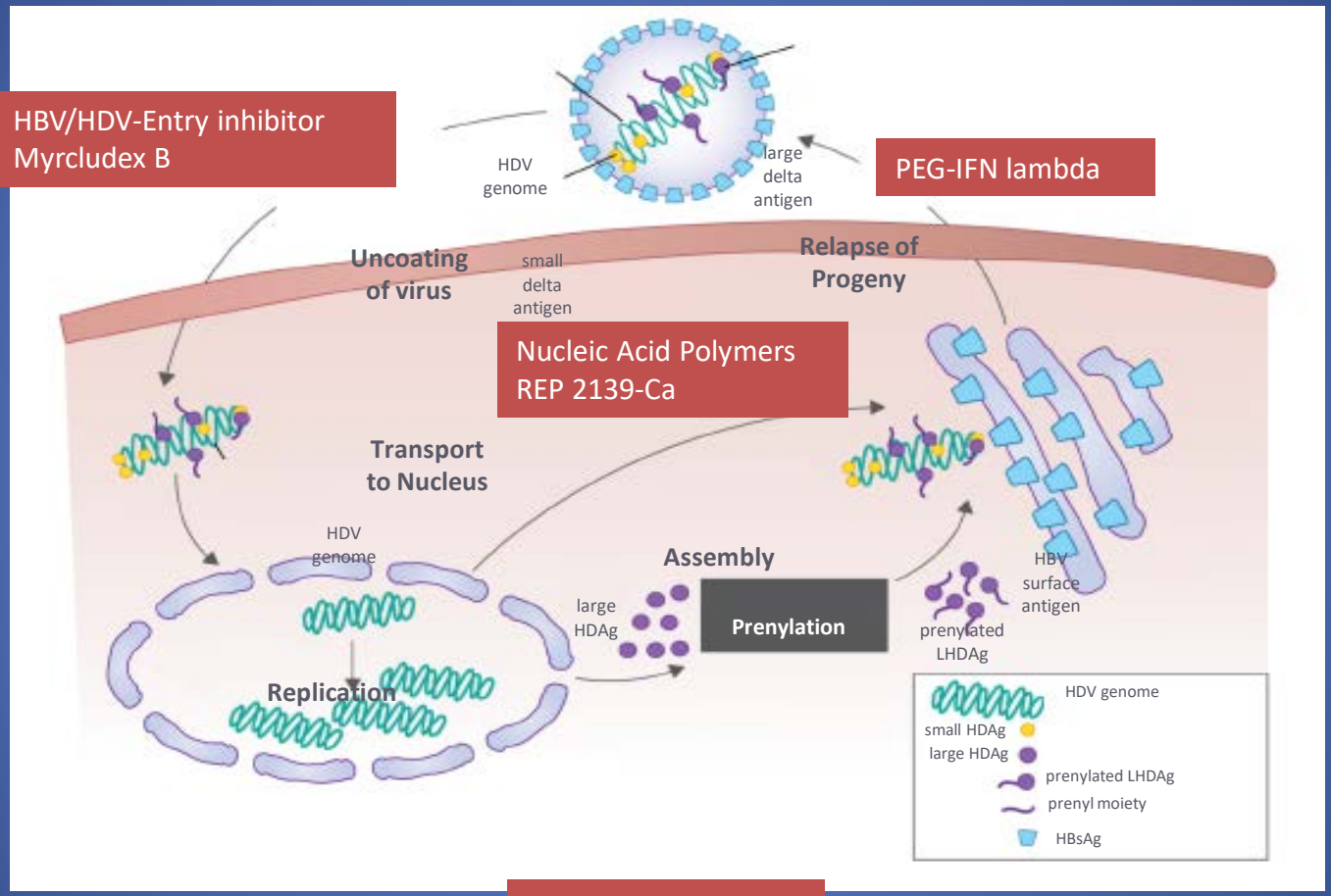


Wedemeyer, Yurdaydin….Manns New Engl J Med 2011, 364(4); 322-31

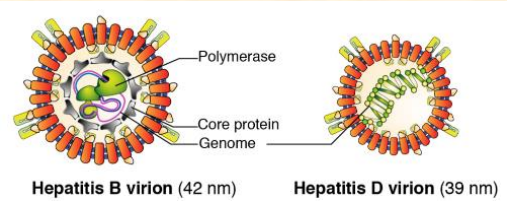
HDV RNA negative at week 24 post-treatment is not SVR

Heidrich et al. Hepatology. 2014 Jul;60(1):87-97.

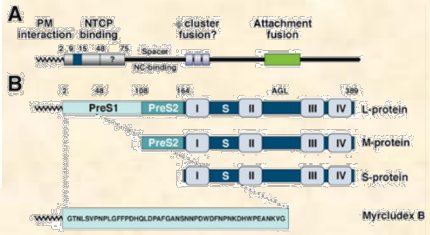
Hepatitis Delta: New Therapies



Myrcludex B (Bulevirtide) an entry inhibitor for HBV and HDV



Lempp et al., Nature Reviews Gastro. & Hepatol., 2016

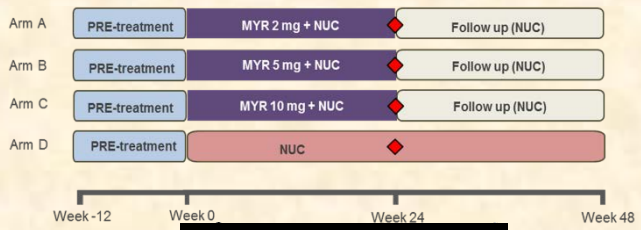


Specifically binds to sodium taurocholate co-transporting polypeptide (NTCP) at the basolateral membrane of differentiated hepatocytes
(Ni et al., *Gastroenterology 2014; Urban et al., Gastroenterology 2014)*

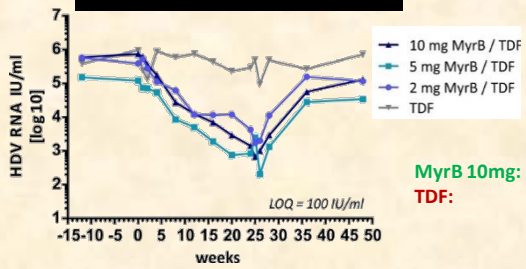
Shows strong inhibitory potential for HBV/HDV infection (IC_{50} ca 80 pM in PHH) *(Schulze et al., J. Virology 2010)*

Exclusively targets parenchymal liver cells *(Meier et al., Hepatology 2013)*

Myr-202 Trial (combination with NUC)

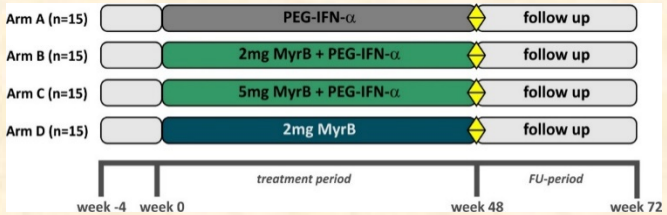


HDV serum RNA levels

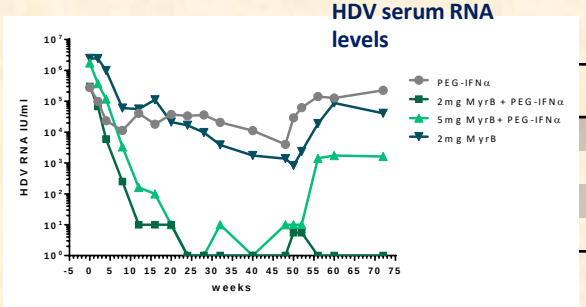


MyrB 10mg: -2.70 log
TDF: -0.18 log

Myr-203 Trial (combination with IFNα)



HDV serum RNA levels

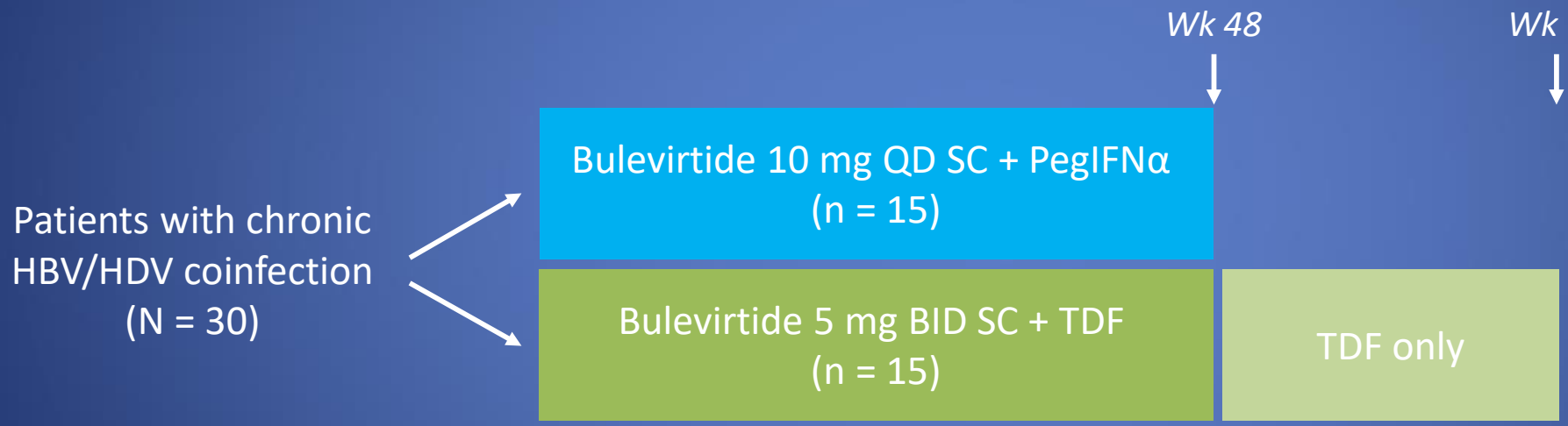


Median serum HDV RNA log reduction	week 48	week 72
PEG-IFNα	-1.30	-0.26
2mg MyrB + PEG-IFNα	-4.81	-4.04
5mg MyrB + PEG-IFNα	-5.59	-1.48
2mg MyrB	-2.84	-1.08

Courtesy S. Urban , Heidelberg

High-Dose Bulevirtide for Chronic HBV/HDV Coinfection

- **Bulevirtide**: investigational entry inhibitor targeting NTCP on hepatocytes with strong inhibitory potential against HBV/HDV coinfection[1]



- Primary endpoint: undetectable HDV RNA (LOD < 10 IU/mL) at Wk 72[2]
- Secondary endpoints: ALT normalization, combined treatment response (ie, ≥ 2 log serum HDV RNA decline + normal ALT levels), HBsAg response[2]

1. Koh. Clin Liver Dis. 2019;23:557. 2. Wedemeyer. EASL 2020. Abstr AS072.

High-Dose Bulevirtide: Efficacy and Safety

- Treatment-related AEs: n = 143 overall (none considered serious)
  - No treatment discontinuations for Bulevirtide AEs

Wk 48 Outcome	Bulevirtide 10 mg QD SC + PegIFNα (n = 15)	Bulevirtide 5 mg BID SC + TDF (n = 15)
Median HDV RNA reduction, log_{10} IU/mL	-6.09	-4.58
HDV RNA undetectable, %	86.7	40
ALT normalization, %	26.7	40
HBsAg undetectable, n	1	0

Wk 72 Outcome	Bulevirtide 10 mg QD SC + PegIFNα (n = 15)	Bulevirtide 5 mg BID SC + TDF (n = 15)
HDV RNA undetectable, %	7	33
ALT normalization, %	33	33
HBsAg undetectable, n	2	0

Wedemeyer. EASL 2020. Abstr AS072.

Conclusions & Outlook for MYR

- Monotherapy with Myrcludex B is a safe and promising strategy for maintenance therapy of chronic hepatitis D
- Combination therapy of Myrcludex B with PEG-IFNα induces cure of HBV/HDV co-infection in a subset of patients
- Multicenter Phase 3 in HDV infection is running (MYR301)

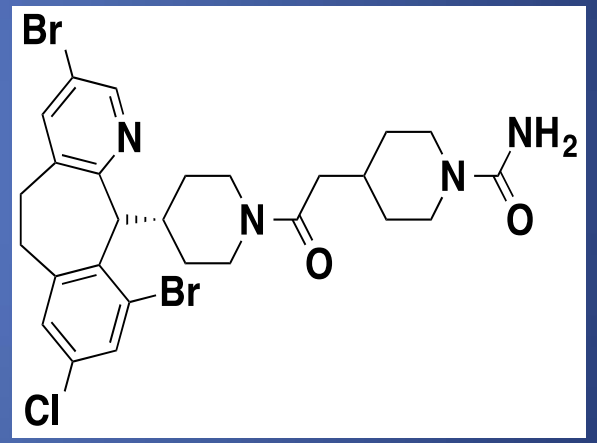
- **Myrcludex B received "orphan drug status" by the FDA and EMA for HDV**
- **Myrcludex B received prime eligibility status from EMA**
- **Myrcludex B received "breakthrough therapy designation" by the FDA**

Application for approval of Myrcludex B in Russia has been submitted (Approval expected soon)

Procedures for conditional marketing authorization in France successful: ATU program running for F3, F4

Oral Lonafarnib for HDV

- Small molecule, oral, prenylation inhibitor
- Well-characterized through Phase 3
  - >2,000 patients dosed in oncology program by Merck (Schering)
  - Dose limiting toxicity is GI (class effect)
- Over 120 HDV patients dosed across international sites
- HDV Orphan Designation in US & EU, Fast Track in US
- Prenylation is a host target; potential barrier to resistance

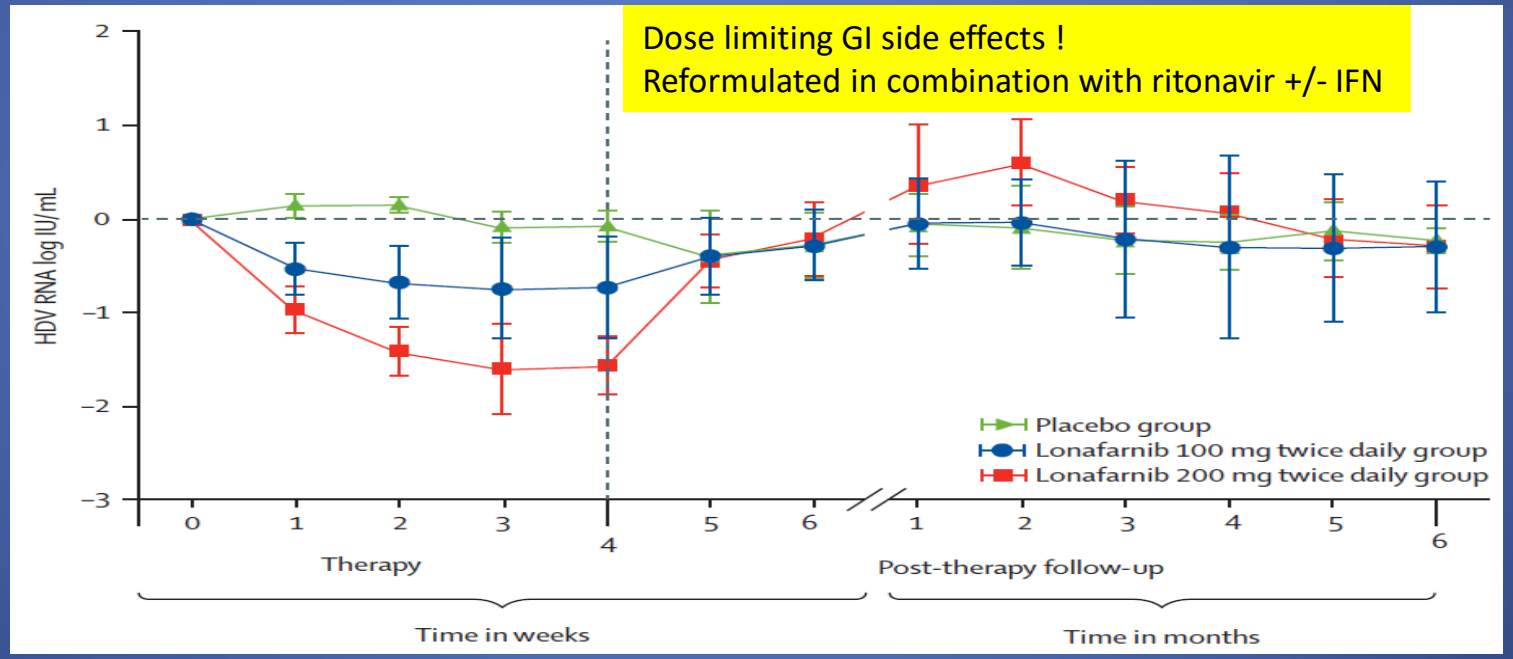


Phase 2 proof of concept study conducted at NIH; NIH Phase 2 study results published: Koh et al, Lancet Infect Dis, 2015.

Oral prenylation inhibition with lonafarnib in chronic hepatitis D infection: a proof-of-concept randomised, double-blind, placebo-controlled phase 2A trial

Christopher Koh, Laetitia Canini, Harel Dahari, Xiongce Zhao, Susan L Uprichard, Vanessa Haynes-Williams, Mark A Winters, Gitanjali Subramanya, Stewart L Cooper, Peter Pinto, Erin F Wolff, Rachel Bishop, Ma Ai Thanda Han, Scott J Cotler, David E Kleiner, Onur Keskin, Ramazan Idilman, Cihan Yurdaydin, Jeffrey S Glenn*, Theo Heller**

Dose limiting GI side effects !
Reformulated in combination with ritonavir +/- IFN



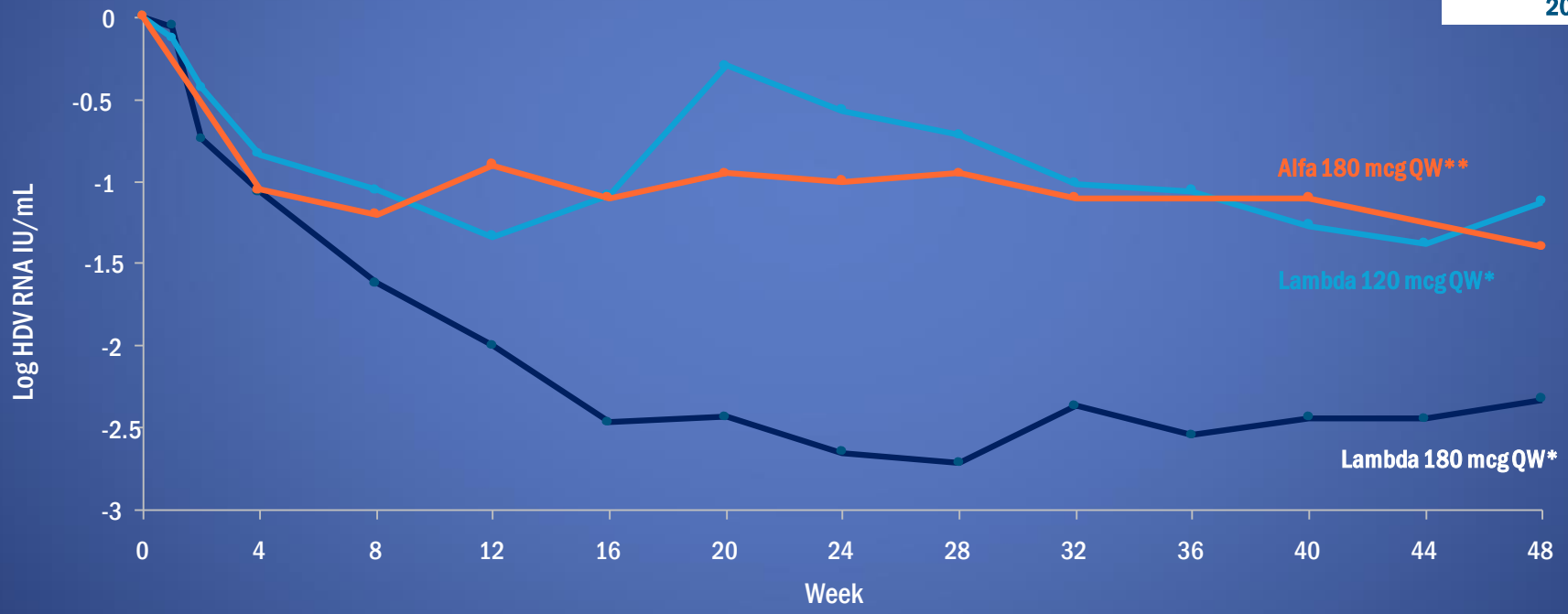
Koh et al. Lancet ID 2015

Pegylated Interferon Lambda

- A (novel) first in class Type III interferon
- Never approved for HCV HBV or delta
- Binds to a unique receptor versus Type I interferons
  - Highly expressed on hepatocytes
  - Limited expression on hematopoietic cells and CNS cells
- Uses similar downstream signaling pathway as Type I interferons
- Greater than 3,000 patients in 17 clinical trials (HCV / HBV) have been dosed with IFN lambda
- Antiviral activity with less of the typical IFN alfa related side effects*

HDV-RNA Reduction with LAMBDA thru Week 48

Lambda 180 mcg Better than Alfa 180 mcg with Improved Tolerability



* Randomization dose, dose reductions allowed; Etzion et al, EASL 2019, PS-052: J. Hepatology, 2019, Vol. 70, e32.

** Wedemeyer EASL 2019, G-13: J. Hepatology, 2019, Vol 70, e81
Robogene® 2.0 HDV RNA PCR assay used for Lambda and Alfa data sets, LLOQ = 14 IU/mL

Combination therapy with Lonafarnib/r and Peg-IFN Lambda

Phase 2a, open-label, prospective treatment trial x 24 weeks

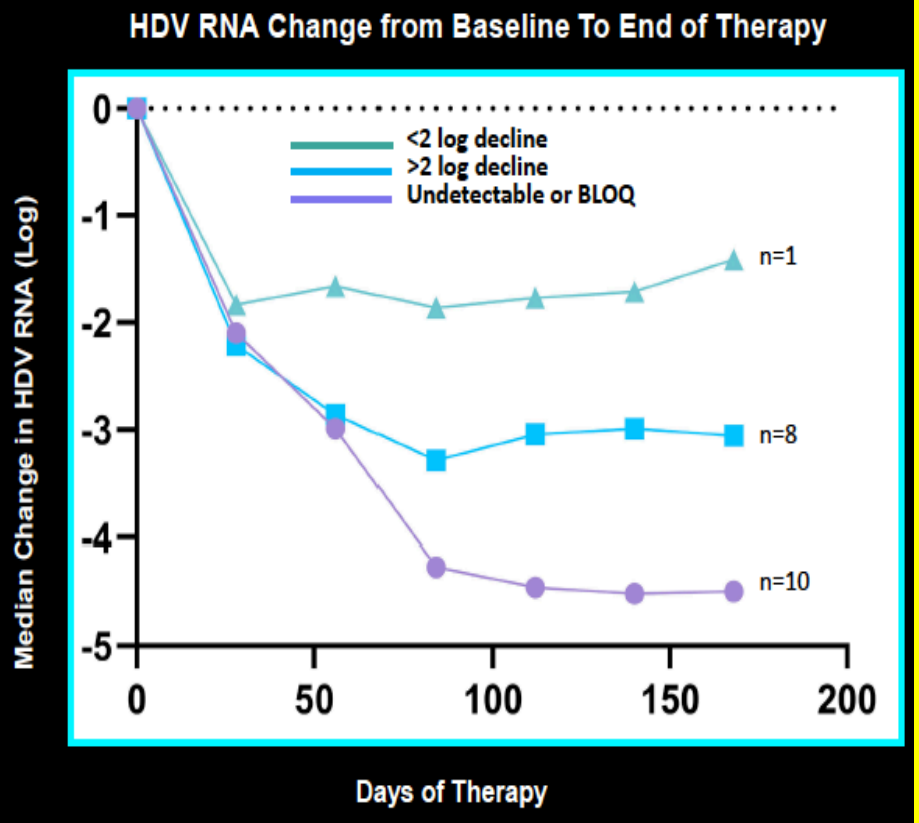
Efficacy

- At the end of therapy (n=19), median HDV RNA decline was 3.4 log IU/mL ($p<0.0001$)
  10/19 (53%) patients achieved HDV RNA undetectable or below LLOQ in serum

Safety

- GI symptoms most common AEs
- Hyperbilirubinemia
- Dose reduction occurred in 3 patients
- Discontinuation of therapy occurred in 4 patients

Promising results, await longer follow-up



Koh et al. AASLD 2019; Abstract L08

Summary of New Treatment Concepts for Hepatitis Delta

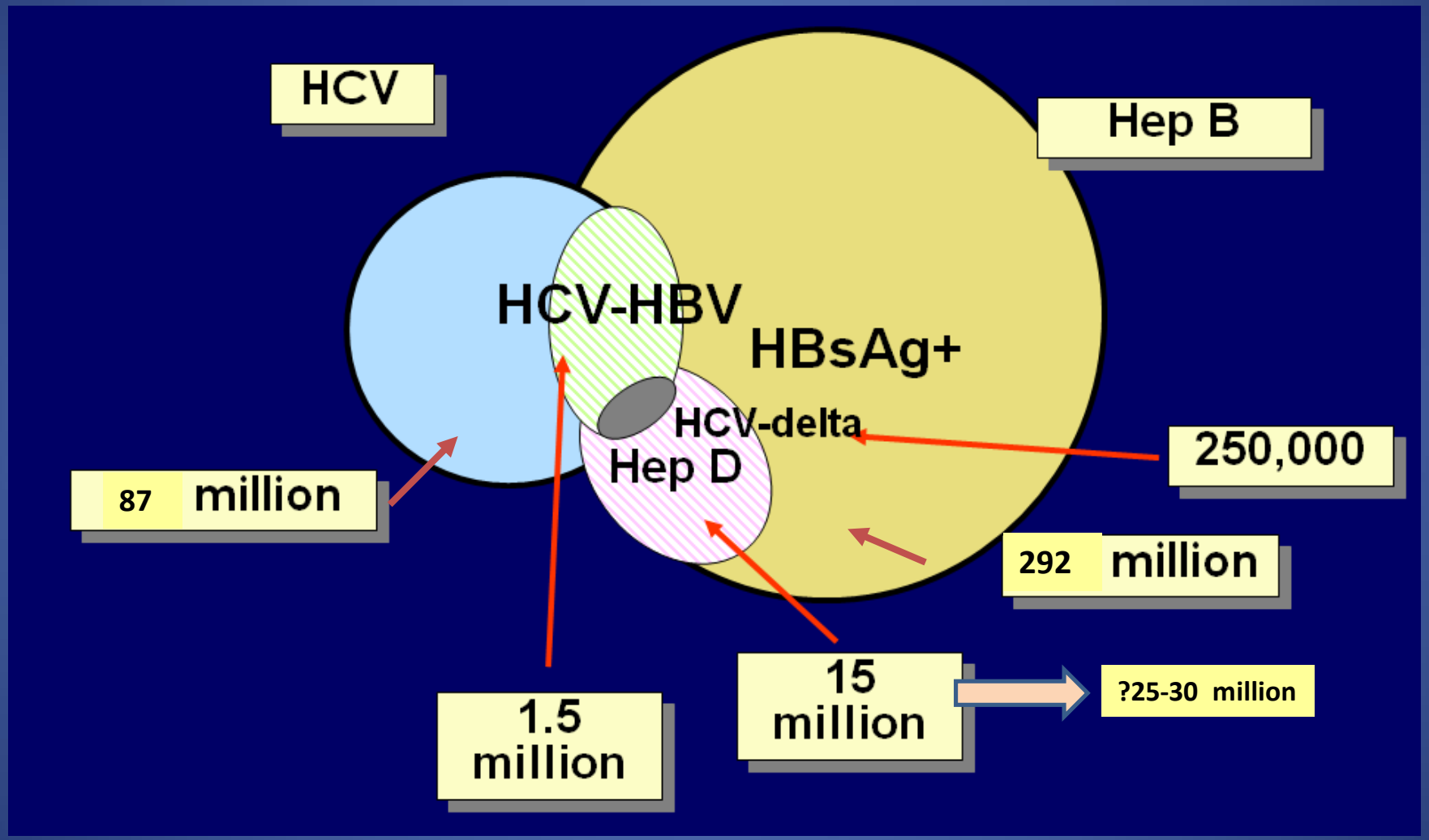
		HDV patients treated or in trials	HDV RNA decline	HBsAg decline	ALT decline
Entry inhibitor *Myrcludex*	s.c.	>100 Phase 3	☑	Only with PEG-IFN	☑ flares post Tx
Nucleic Acid Polymers *REP2139*	i.v. s.c. planned	12	☑	☑	☑ flares
Prenylation inhibitor *Lonafarnib*	p.o.	>100 Phase 3	☑	(post Tx)	☑ flares post Tx
Peg-Interferon lambda	s.c.	33 19 with LNF	☑	Interim data (no EOT data)	☑ flares

very subjective and simplified grading of the data

Do we need HDV cure in the era of HBV cure ?

- HDV is the most severe form of hepatitis
- 15 – 20 Million chronically infected, presumably more
- Lack of global epidemiology data
- HDV requires only small amounts of HBsAg to complete viral packaging
- Only sterilizing HBV cure will obviate a need for an HDV cure
- Functional HBV cure: Maybe, but when ? Sufficient for HDV cure/control ?
- Sterilizing HBV cure: Not in sight, seems necessary for HDV cure
- **Do we need HDV cure: YES !**

Overlapping HBV, HDV & HCV Epidemics



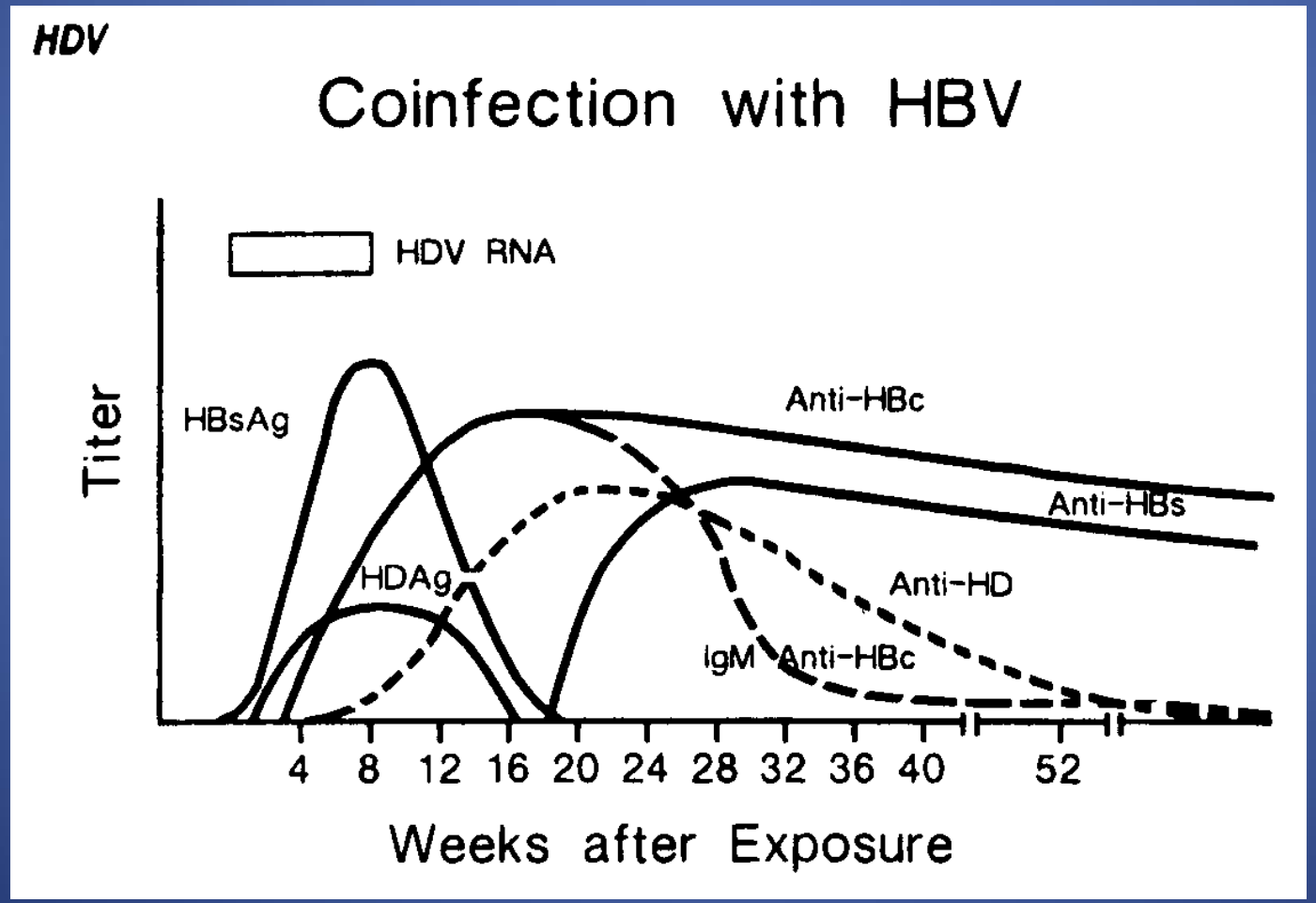
Modified from: Soriano

Conclusions for 2020 and Beyond

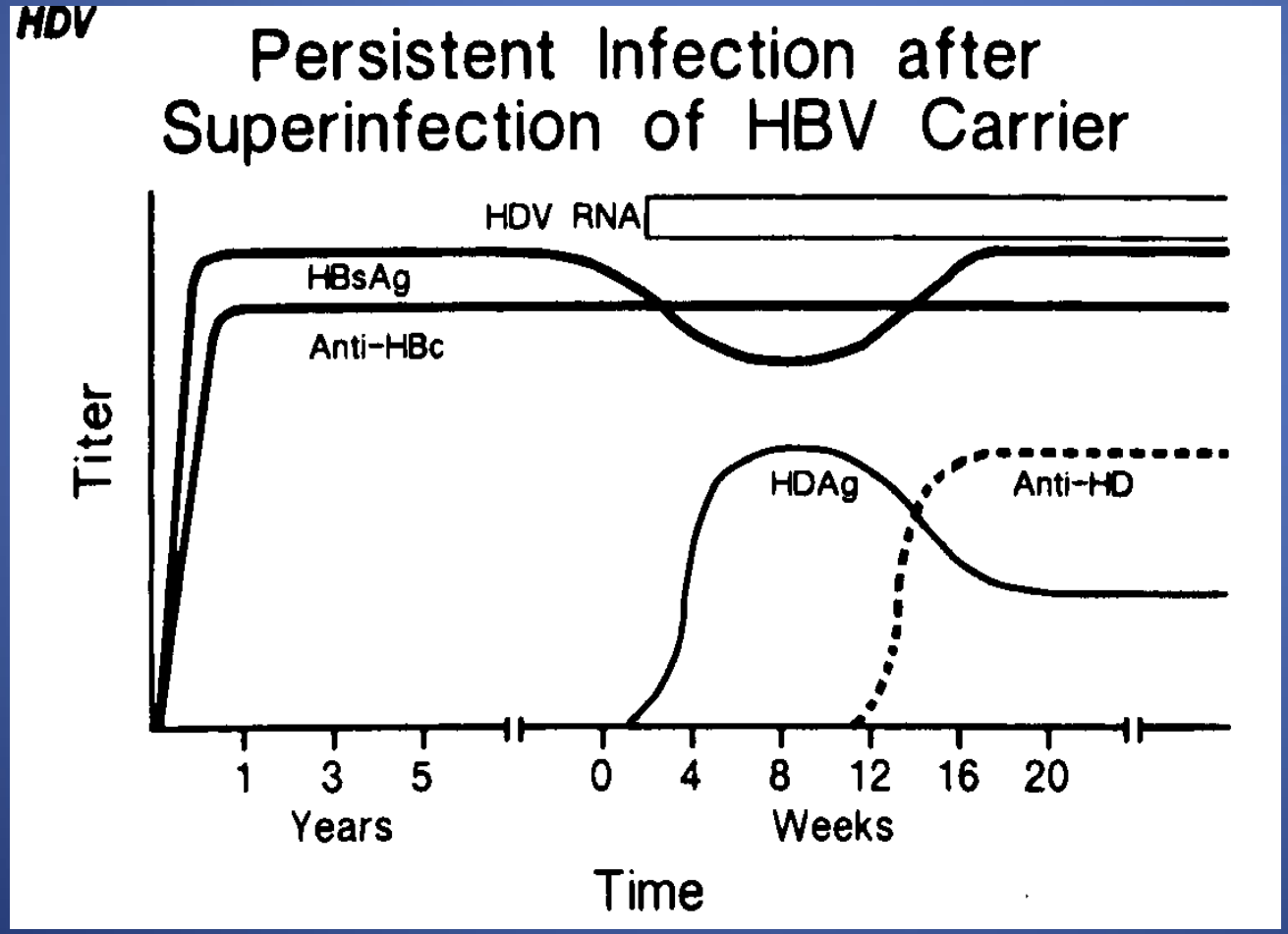
- HDV in underdiagnosed
- All HBsAg+ patients should be tested for HDV by antibody testing
- Need rapid test on the global market
- No difference in Genotype in terms of response to interferon but some genotypes not studied
- HDV has poor testing frequency and very low linkage to care
- Best treatment is INF with MVR rate of 20%, this does not define cure of HDV
- Major need for new therapies to result in MVR/SVR/DVR, or 2 log reduction = reset of disease activity
- New therapies with INF/Combination
- Lambda, Lonafarnib, vs Myr, Vs STOP/NAPs vs HBsAg clearance
- Next HBV therapies will have 40% HBsAg loss, new HDV therapies will have a MVR/SVR of 40% with an additional 20% set of patients who will have a “reset” of virus levels by 2 logs
- HDV may survive with other viruses: we must keep looking with HDV PCR testing

Thank You

HDV Coinfection with HBV



Chronic Hepatitis D



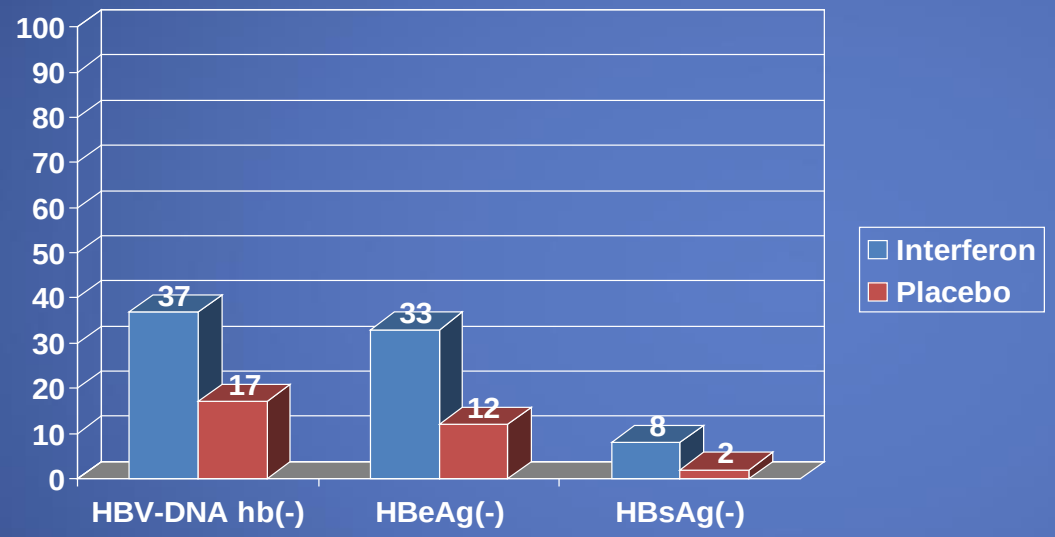
Regular Interferon

Interferon in HBV

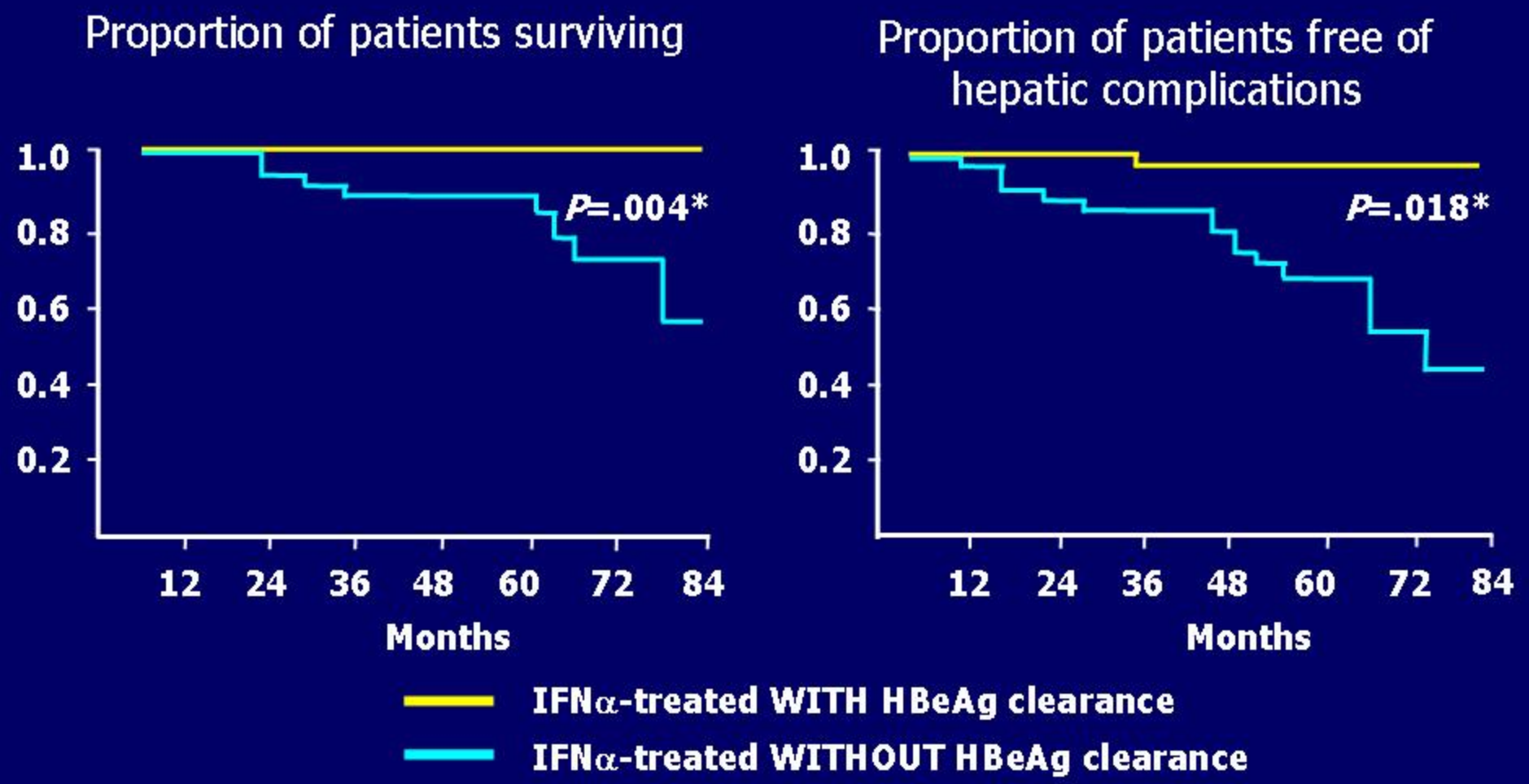
- Usual dose: 5M QD or 10M TIW x 16-32 wks in HBe(+), or 48-96 wks in HBe(-)
- Best in: HBV-DNA < 12 x 10^6 IU/mL (57 x 10^6 copies/mL), ALT > 5xULN, females, adult acquisition.
- Flare up in 30-50%; can cause decompensation
- Sero-conversion maintained in most
- Genotype A responds better than g-D in both, HBe(+) (46 vs. 24%) & HBe(-) (59 vs. 29%)
- Good response slows progression and decreases HCC risk.

Meta-Analysis of IFN in HBe(+)

Wong D et al. Ann Intern Med 1993; 119:312-323



Survival After HBeAg Clearance in HBeAg-positive CHB



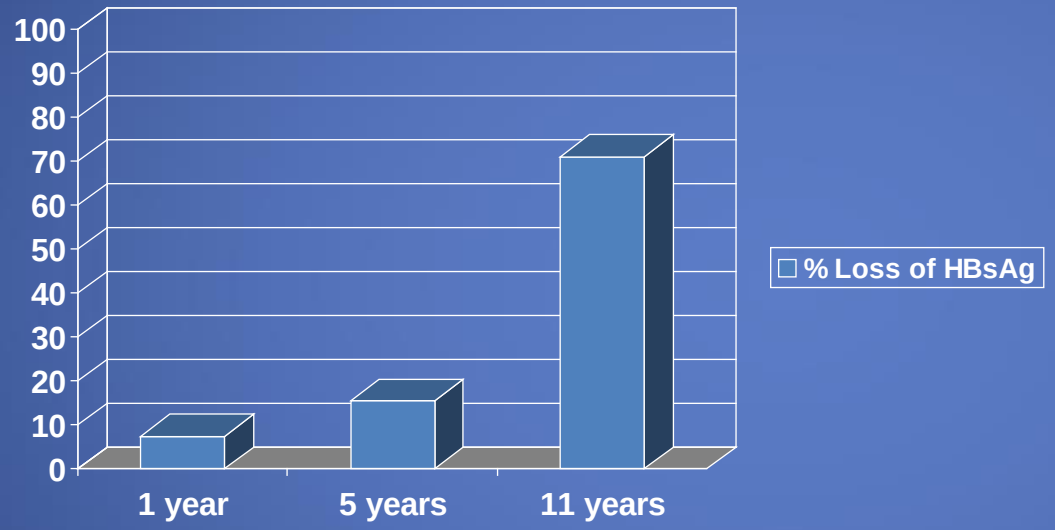
*According to the proportional hazards model

Niederau C et al. *N Eng J Med.* 1996.

Long term F/U of Interferon Responders

Loss of HBsAg (Europeans & Americans)

Gut 2000;46:715-718, Am J Gastroenterol 1998;93:896-900, Gastroenterology 1997;113:1660-1667



Pegylated Interferons

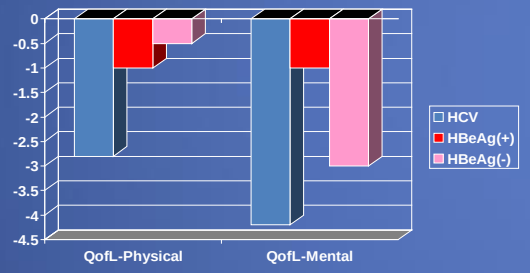
Tolerability of Pegasys in Chronic HBV vs. HCV

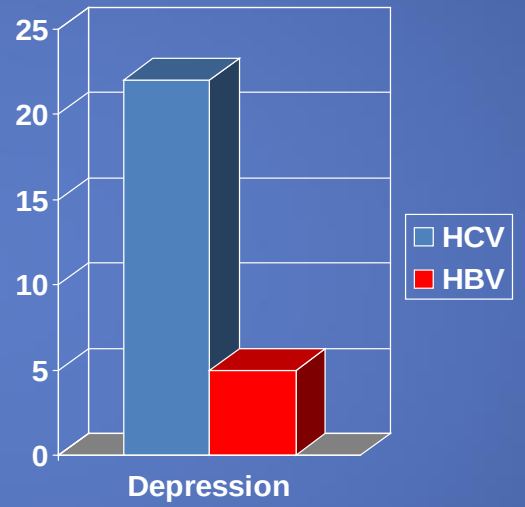
Marcellin et al. AASLD Abstr.# 1158, 2004

- Comparison of Safety, Depression and QofL during Pegasys 180 monotherapy in Chronic HCV and HBV (HBeAg(+) and(-))
- Pooled data of 448 HBV and 827 HCV pts.
- Safety at: 1,2,4,6,8,&12 weeks and then q 6 weeks until 24 weeks post-EOT
- QofL at: 12, 24, 48, and 72 weeks.

Tolerability of Pegasys in Chronic HBV vs. HCV

Marcellin et al. AASLD Abstr.# 1158, 2004





Conclusions

Abstr # 1158

- Treatment with Pegasys 180 mcg/week is associated with lower rates of side effects and depression, and with less impact in Quality of Life, in patients with chronic HBV compared with those with chronic HCV.

Adverse Events with PEGASYS® Monotherapy in CHB

Side Effects	PEGASYS in CHB (n=448)
Pyrexia	54%
Fatigue	36%
Headache	27%
Myalgia	26%
Decreased appetite	16%
Arthralgia	11%
Alopecia	18%
Diarrhea	10%
Injection site reaction	8%
Pruritus	8%
Depression	4%

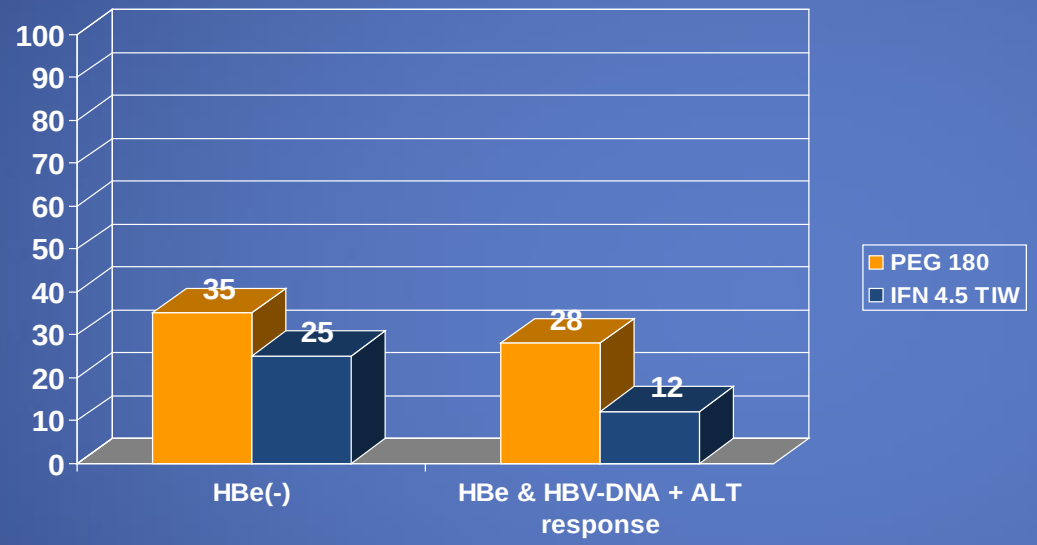
PEGASYS® (Peginterferon alfa-2a) [package insert]. Nutley, NJ: Hoffmann-La Roche Inc.; 2005.

Peg-Interferon in HBeAg(+)

Pegasys 180 x 24 wks in HBe(+)

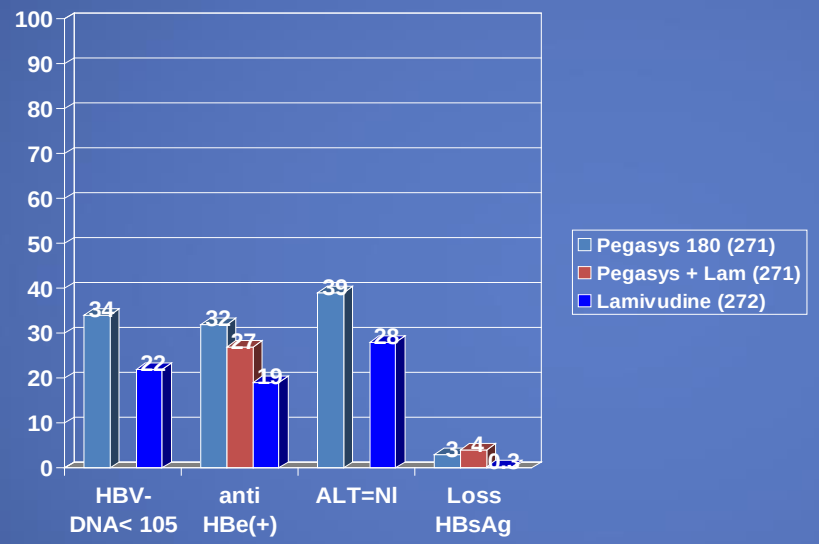
Week 48 (SVR ?) Data

Cooksley W et al. J Viral Hepat 2003, 10:298-305

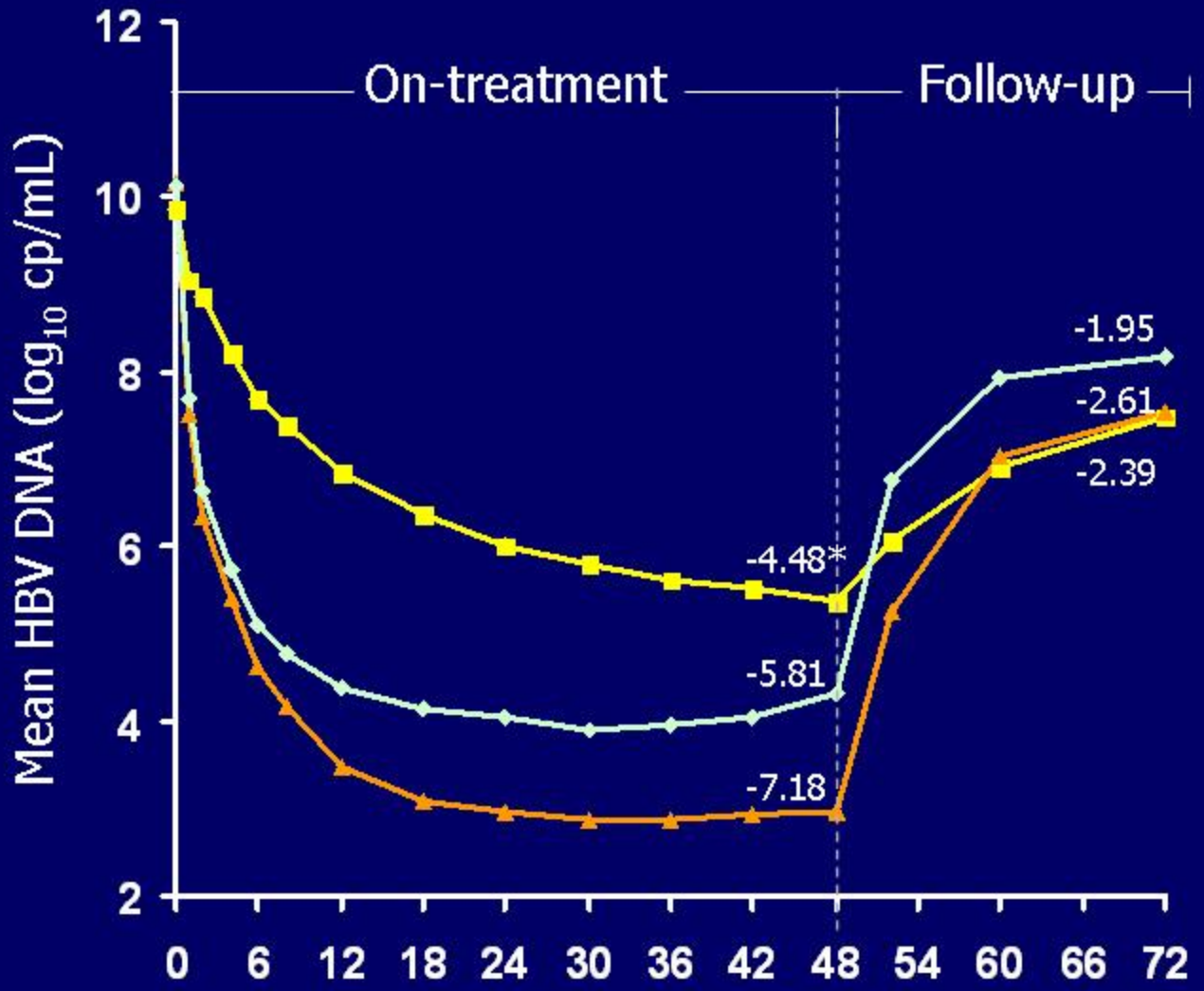


Pegasys 180 x 48 wks in HBe(+)
Week 72 (SVR ?) Data

Lau G et al. Hepatology 2004; 40:171A



HBV DNA Levels Over Time



PEGASYS® + placebo
HBeAg seroconversion
EOT=27%; EOF=32%

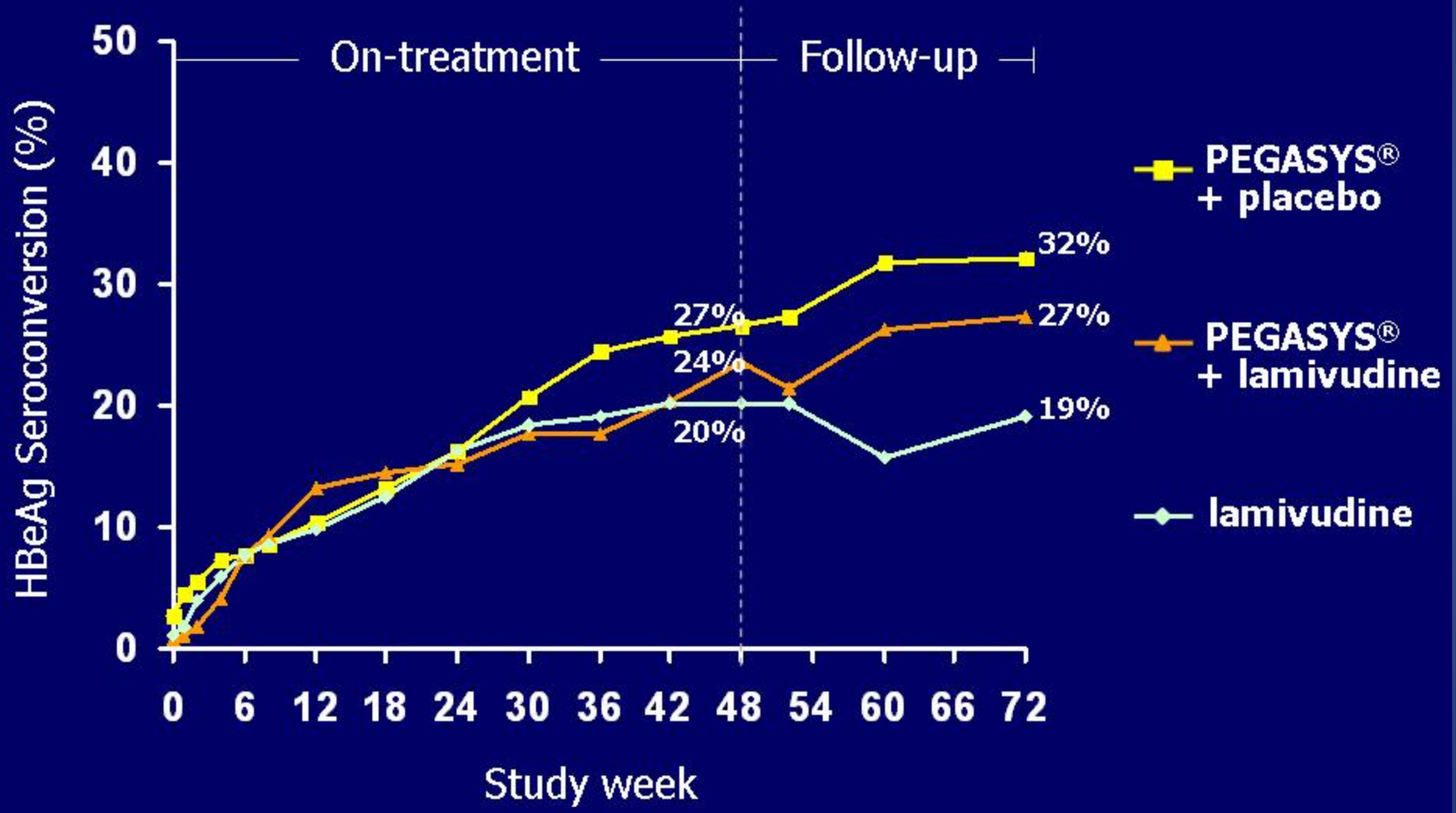
PEGASYS® + lamivudine
HBeAg seroconversion
EOT=24%; EOF=27%

lamivudine
HBeAg seroconversion
EOT=20%; EOF=19%

* all numbers shown are log_{10} reduction from baseline

Lau et al. AASLD. 2004.

HBeAg Seroconversion Rates Over Time

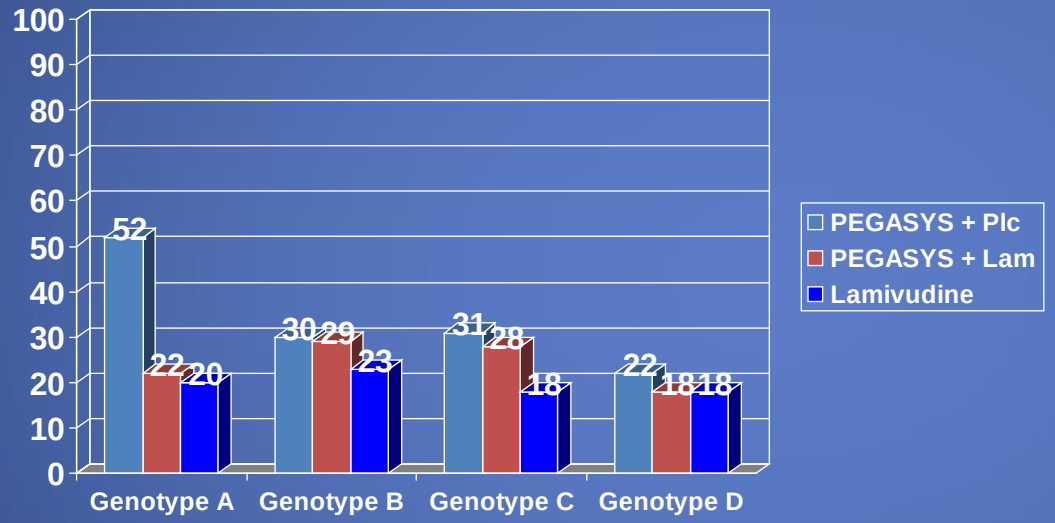


Lau et al. AASLD. 2004.

Effect of HBV Genotype

HBe Seroconversion 24 wks after EOT

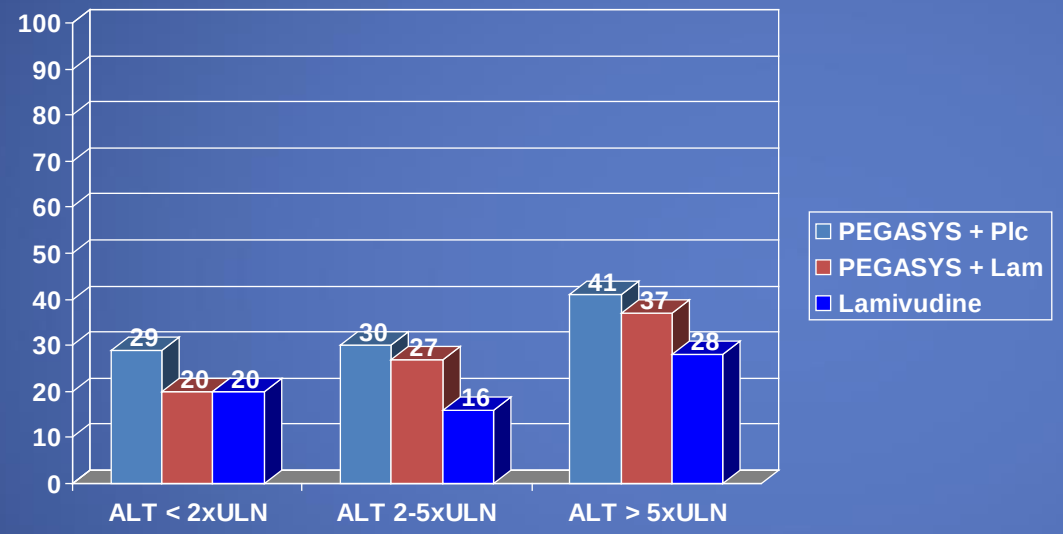
Cooksley W et al. EASL 2005



Effect of Pre-Treatment ALT

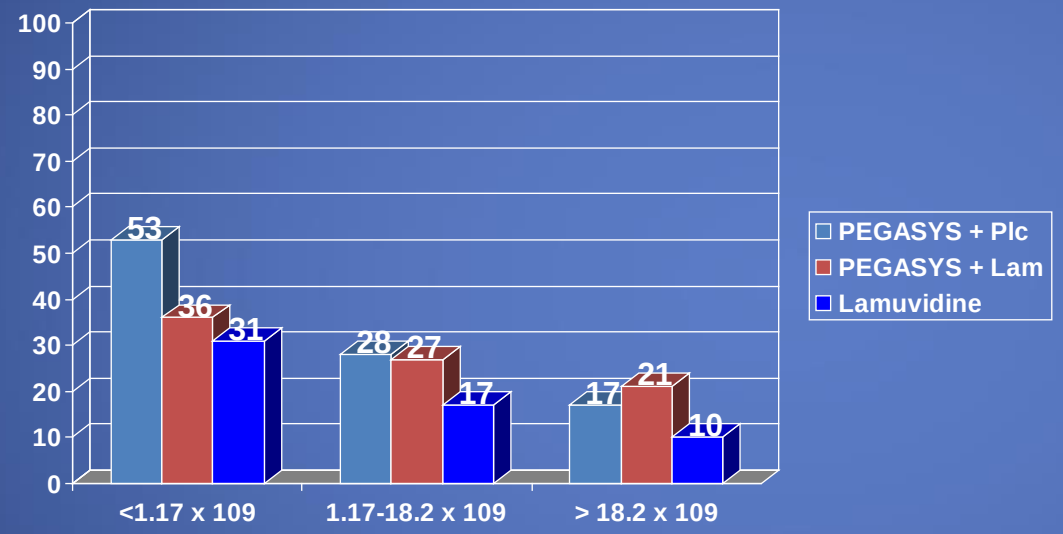
HBe Seroconversion 24 wks after EOT

Cooksley W et al. EASL 2005



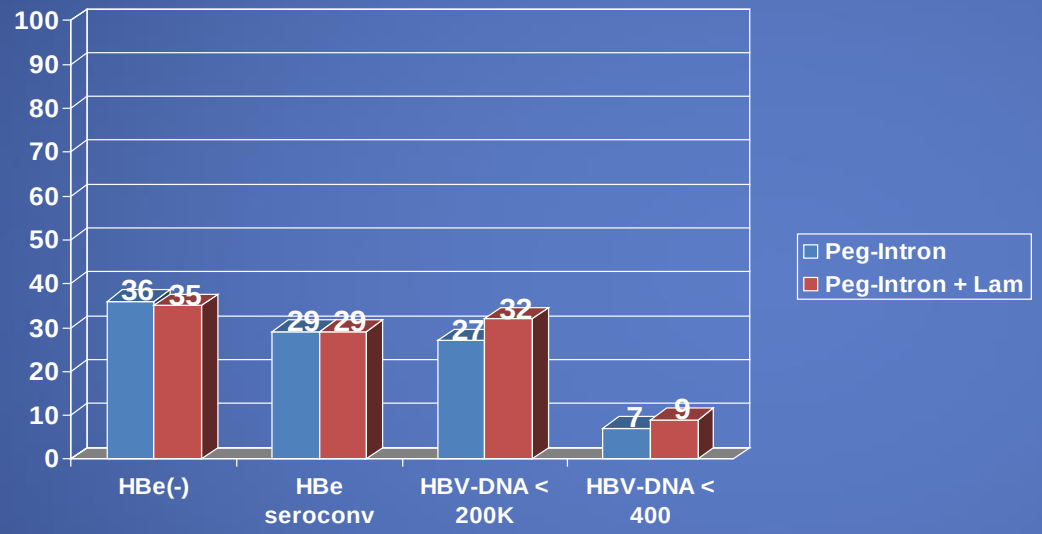
Effect of Baseline HBV-DNA

HBe Seroconversion 24 wks after EOT Cooksley W et al. EASL 2005



Peg-Intron 100x 32w + 50x20w in HBe(+)
Week 78 Data

Janssen et al. Lancet 2005;365:123-129



CONCLUSIONS

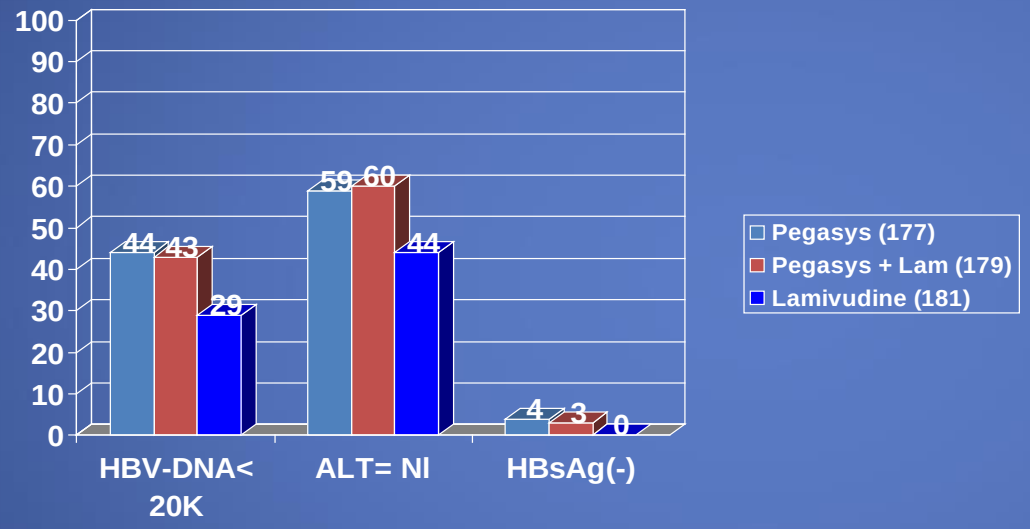
Peg-IFN in HBeAg(+) Chronic HBV

- One third of chronic HBeAg(+) infected patients achieve sustained seroconversion
- Loss of HBsAg occurs in 3 to 4% in the first year. Additional HBsAg loss is expected in long-term follow up.
- Genotypes A, B, and C respond better than genotype D
- Test genotype with: INNO-LiPA HBV Genotyping
- Viral loads of up to 2 x 10^8 IU/mL (1.17 x 10^9 copies/mL) respond best.
- Patients with ALT > 5xULN respond best

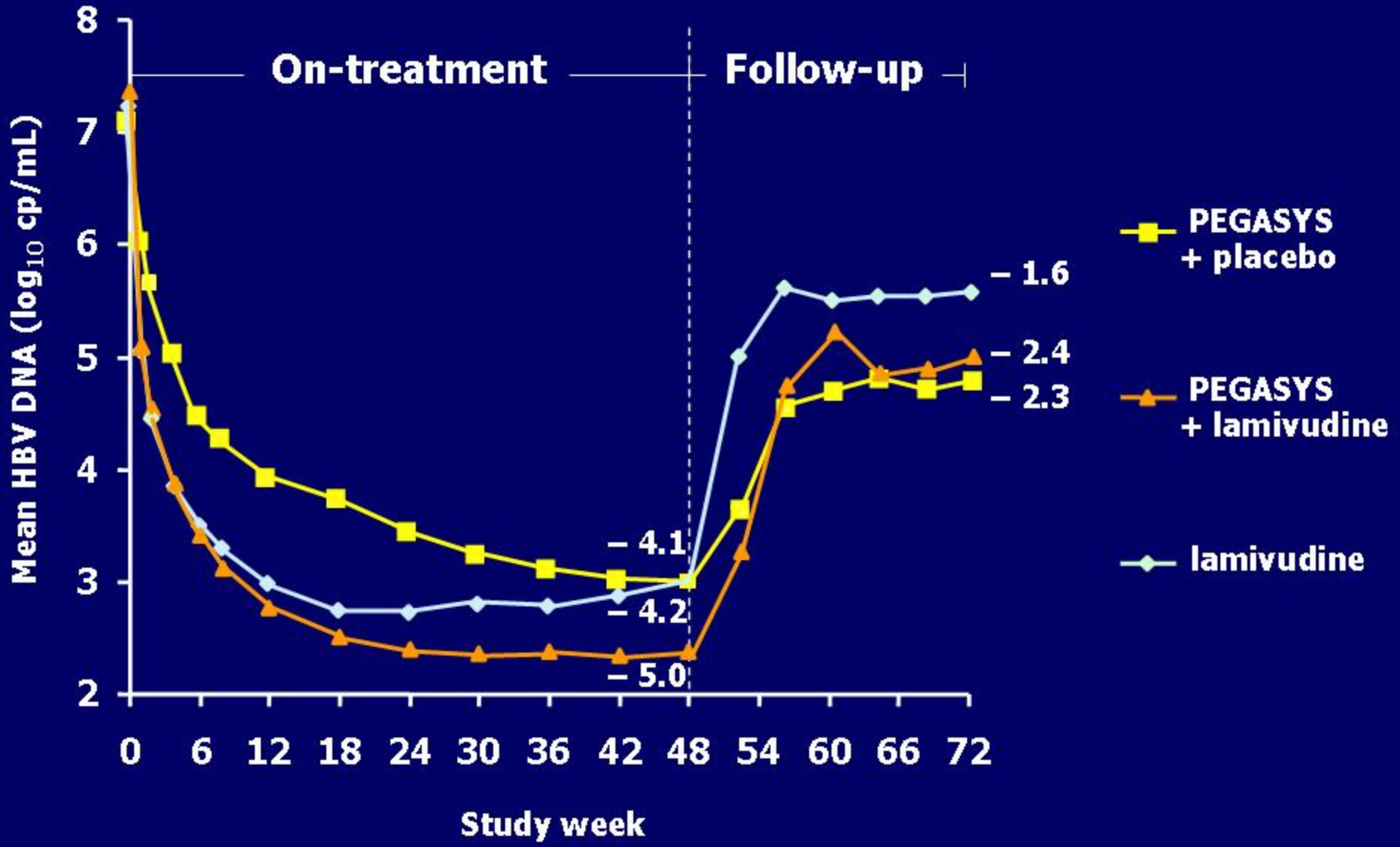
Peg-Interferon in HBeAg(-)

Pegasys 180 x 48 wks in HBe(-)
Week 72 Data

Marcellin P et al. N Engl J Med 2004;351:1206-17

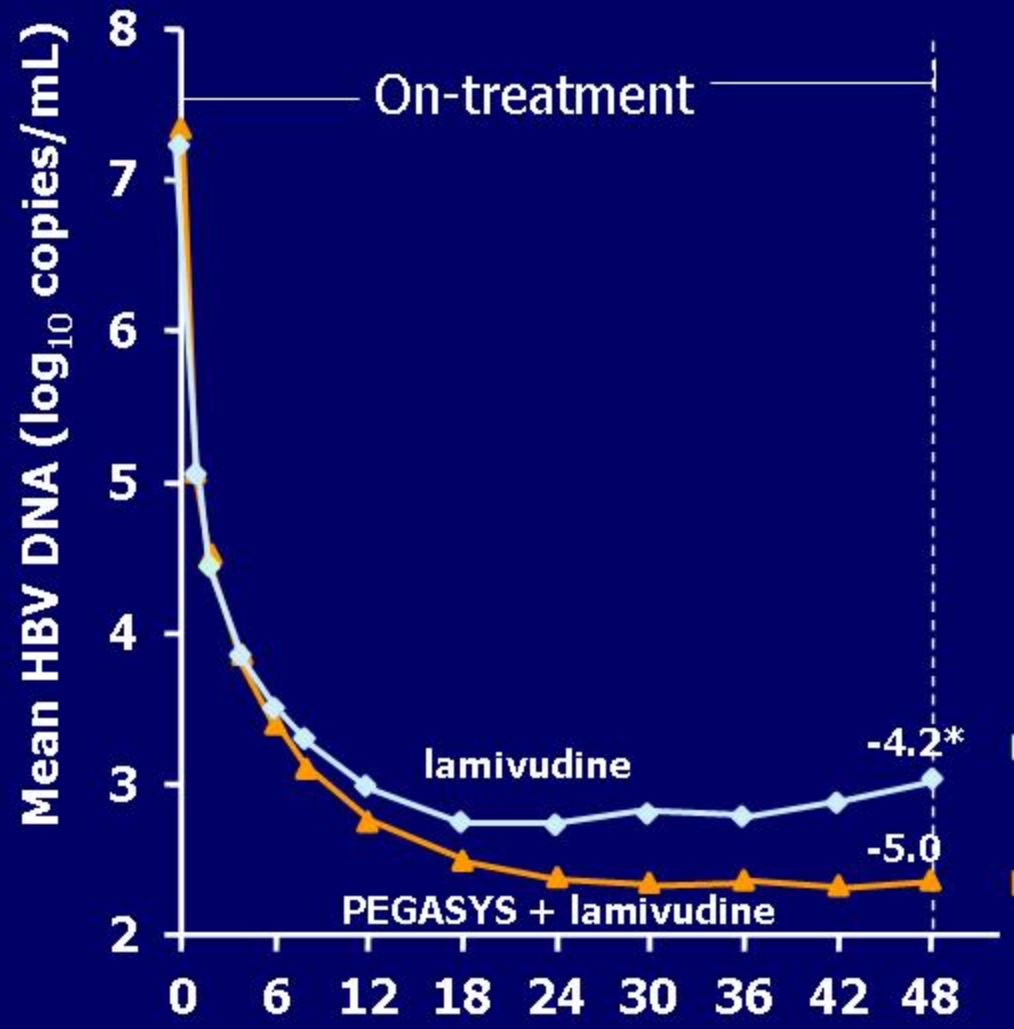


HBV DNA Levels Over Time



Marcellin et al. *N Engl J Med*. 2004;351:32-43.

On-therapy HBV DNA Suppression and LAM Resistance



YMDD mutation development at end of treatment

32/179 = 18%

1/173 = <1%

P<.001

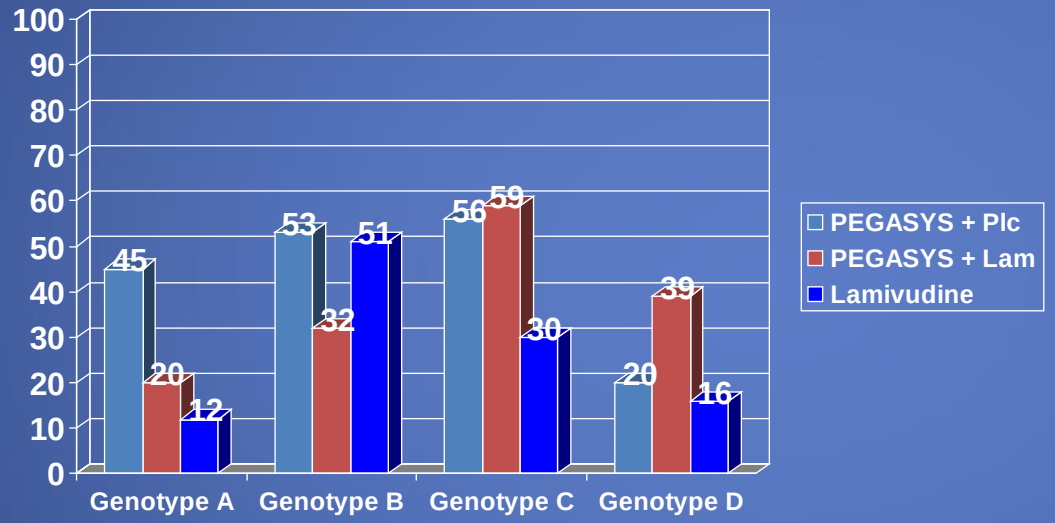
* All numbers shown are log_{10} reduction from baseline.

Marcellin et al. *NEJM.* 2004;351:1206–17.

Effect of Genotype

HBV-DNA < 20,000 @ 24 wks after EOT

Marcellin P et al. EASL 2004



CONCLUSIONS

Peg-IFN in HBeAg(-) chronic HBV

- More than 40% of patients achieve conversion to low replicative state
- Genotypes A, B, and C respond better than genotype D
- Test genotype with: INNO-LiPA HBV Genotyping
- Loss of HBsAg occurs in 3-4% after first year of therapy and in 11% by year 4 (Marcellin P, EASL 2008). Additional HBsAg losses may occur with further follow-up
- Resistance to Lamivudine is very rare during combination therapy with Peg-interferon

Prediction of Sustained Response to Peg-Ifn a2a in HBeAg(-) Patients

Rijckborst V et al. Hepatology 2010;52:454-461

- HBeAg(-) patients treated with Pegasys 180 +/- RBV x 48 wks.
- Measurement of decline in HBsAg (Abbott Architect) & HBV-DNA (TaqMan) @ wks 4, 8, 12, 24, 48, 60, 72.
- Sustained response defined as HBV-DNA < 2000 IU/mL and Normal ALT @ wk 72.
- Best predictors for sustained response (SR) were 12 wk parameters.

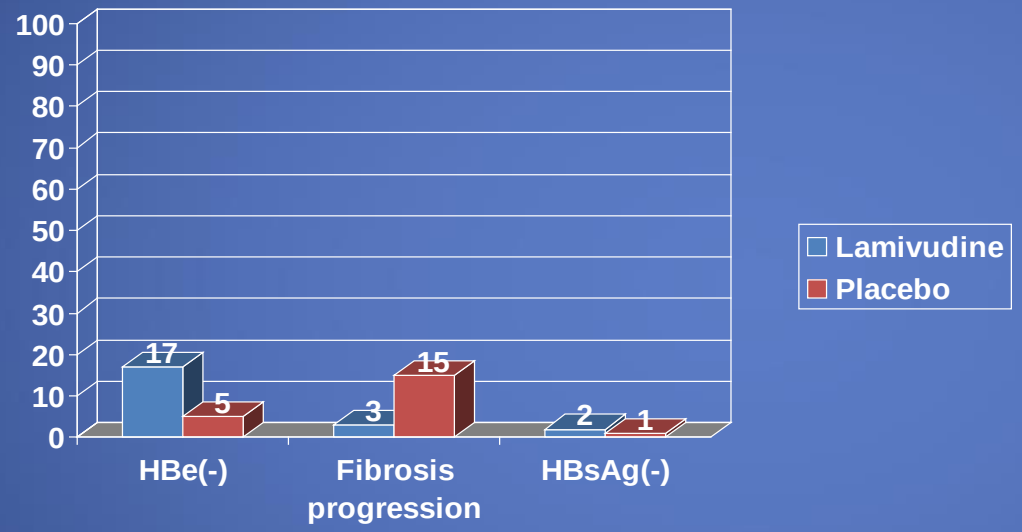
Change from Baseline to Wk 12

HBsAg decline	HBV-DNA drop >/= 2 log	Recommendation	SR Rate
No	No	STOP	0%
No	Yes	Continue	24%
Yes	No	Continue	25%
Yes	Yes	Continue	39%

Lamivudine

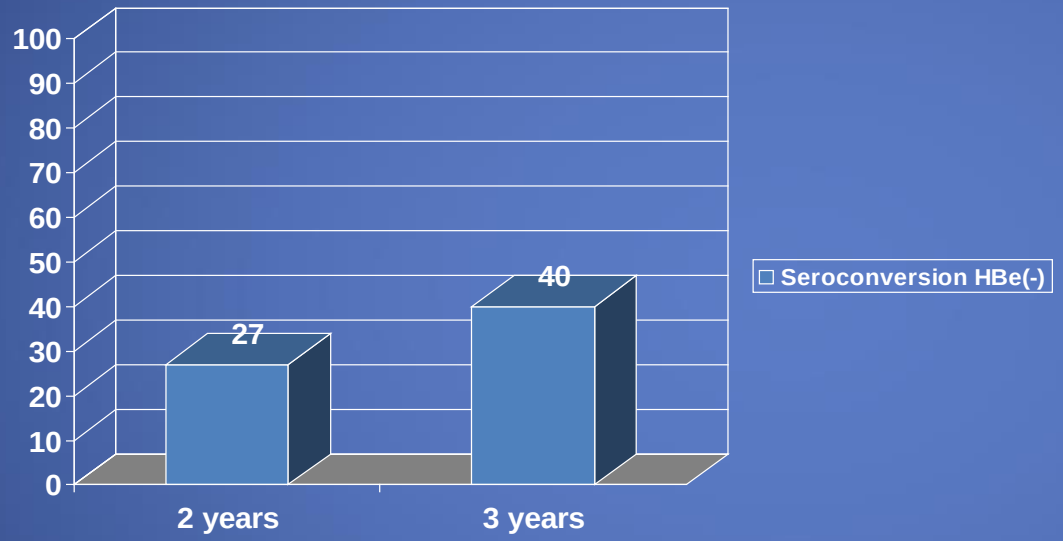
Lamivudine x 48 wks in HBe(+)

Diengstag J et al. N Engl J Med 1999;341:1256-63
Lai G et al. N Engl J Med 1998;339:61-68

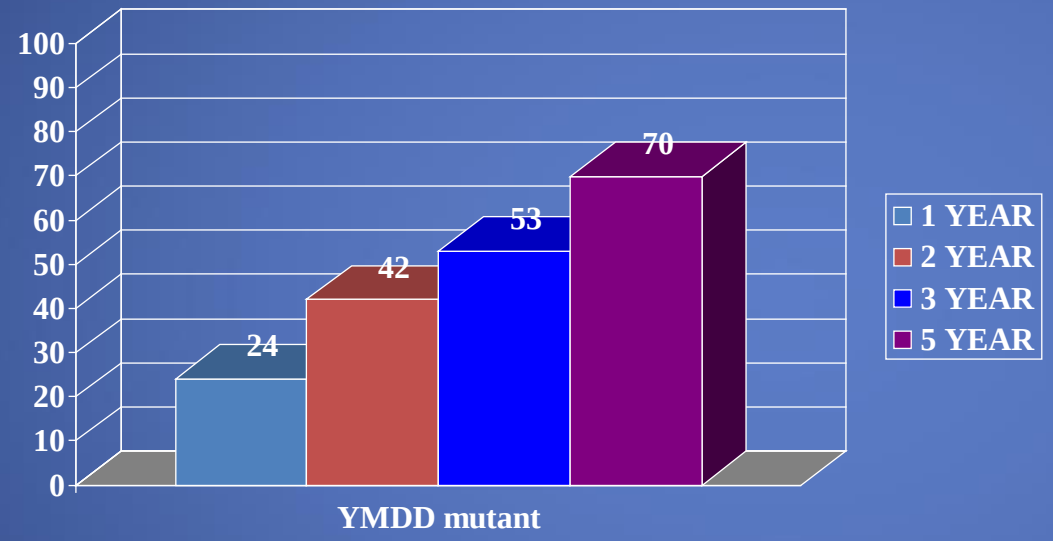


Lamivudine in HBe(+) x 3 y

Leung N et al. Hepatology 2001;33:1527-32



Lamivudine Resistance
YMDD mutants



CONCLUSIONS

Lamivudine in Chronic HBV

- Lamivudine induces loss of HBeAg in 17, 27, and 40% after 1, 2, and 3 years of therapy, respectively
- Therapy with Lamivudine decreases progression of fibrosis and can reverse hepatic decompensation
- Decompensated cirrhotics have a 1 y survival of 79%; most deaths occur within initial 6 months.
- Loss of HBsAg is extremely rare
- Resistance to Lamivudine occurs rapidly, and reaches 70% after 5 years of therapy
- Resistance to Lamivudine increases risk of resistance to Entecavir, Telbivudine, and Emtricitabine; do not give them together.

Adjustment of Adult Lamivudine dose by Creatinine Clearance

- >/= 50 mL/min 100 mg/day
- 30-49 mL/min 100 mg x1, then 50 mg/day
- 15-29 mL/min 35 mg x1, then 25 mg/day
- 5-14 mL/min 35 mg x1, then 15 mg/day
- < 5 mL/min 35 mg x1, then 10 mg/day

Adefovir

Adefovir Dipivoxil

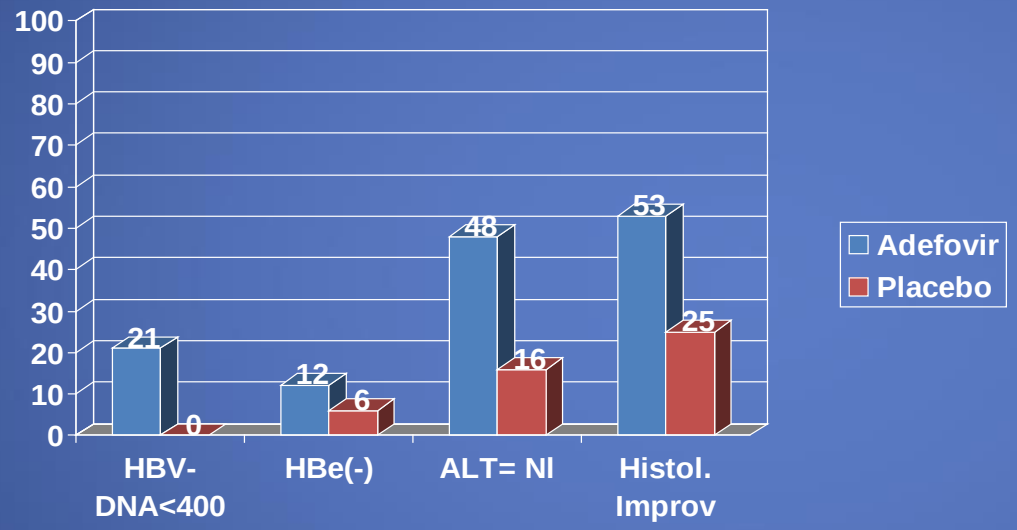
- Oral adenosine nucleotide analog.
- Moderately active in wild, HBe(-), and YMDD mutant.
- Good choice for HBe(-) mutant, and as second drug for YMDD mutant, and as monotherapy in HIV co-infection.
- Decreases levels of intrahepatic cccDNA.
- Used together with Peg-IFN, increases rate of HBe seroconversion and of HBsAg loss.
- Dose 10 mg/day; correct by renal fx.
- Escape mutants are sensitive to Lamivudine.
- Nephrotoxic in 1%; creatinine raise and waste of phosphate & glucose (Fanconi)
- When changing from Lamivudine to Adefovir, continue both long term to decrease resistance to adefovir.

Adjustment of Adult Adefovir dose by Creatinine Clearance

- >/= 50 mL/min 10 mg/day
- 20-49 mL/min 10 mg every other day
- 10-19 mL/min 10 mg every third day
- Hemodialysis 10 mg a week after dialysis

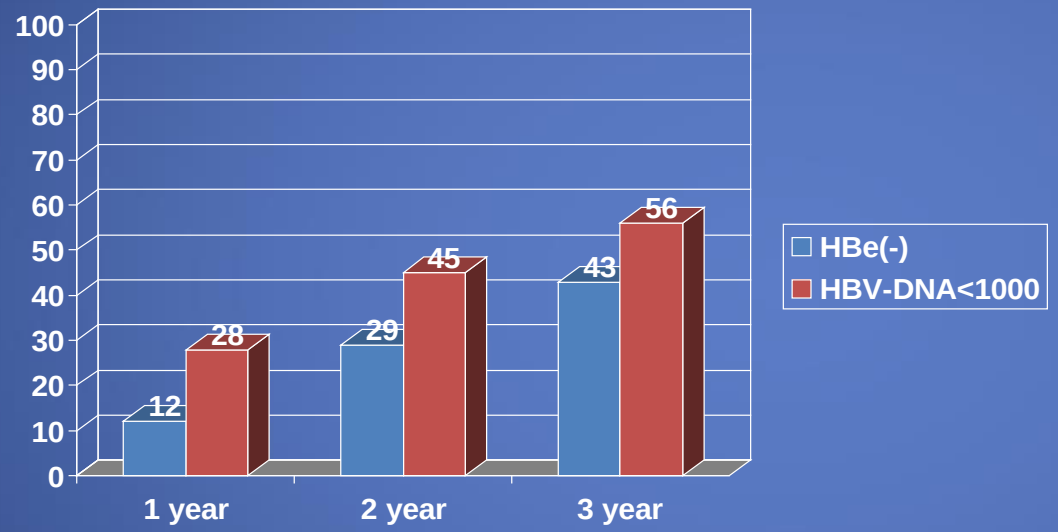
Adefovir x 48 wks in HBe(+)

Marcellin P et al. N Engl J Med 2003;348:808-816



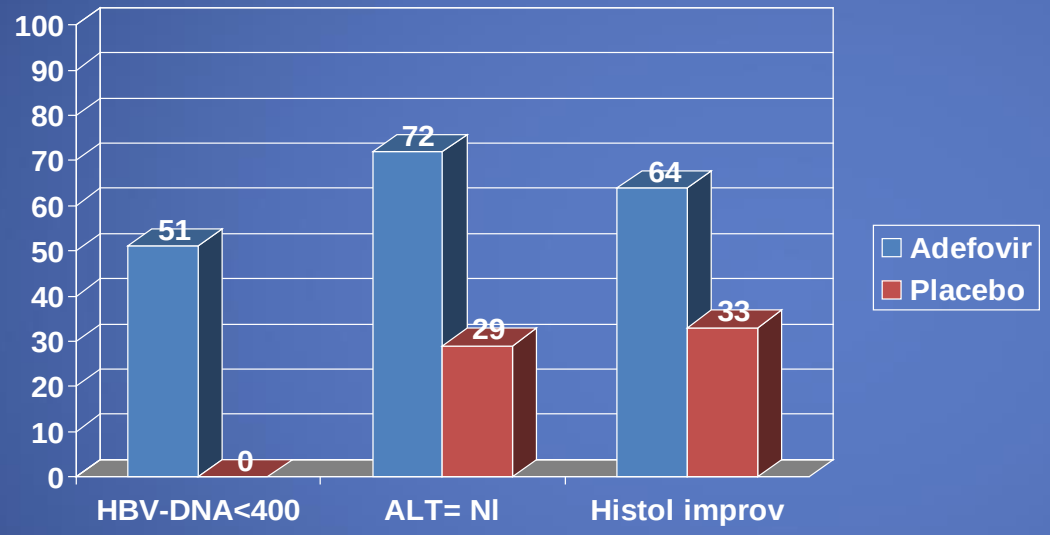
Adefovir x 3 y in HBe(+)

Marcellin P et al. AASLD Abst 1135, 2004

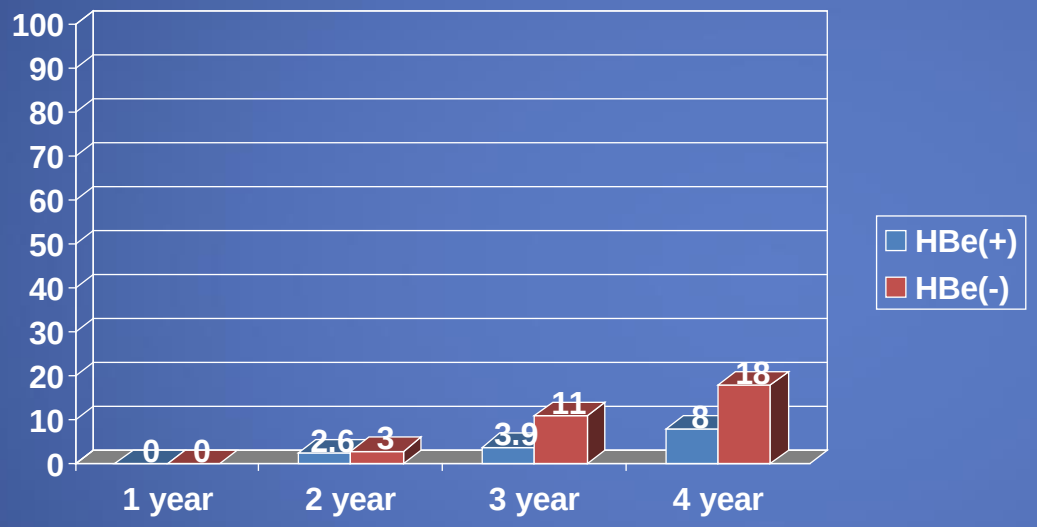


Adefovir x 48 wks in HBe(-)

Hadziyannis S et al. N Engl J Med 2003; 348:800-807

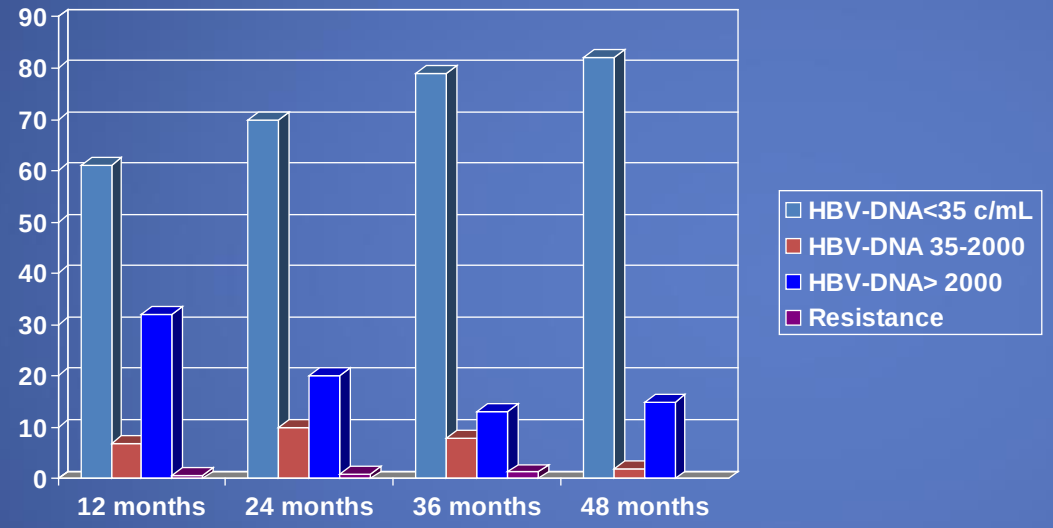


Adefovir
Resistant Mutants (%)



Adefovir + Lamivudine in Lam-Resistant HBV

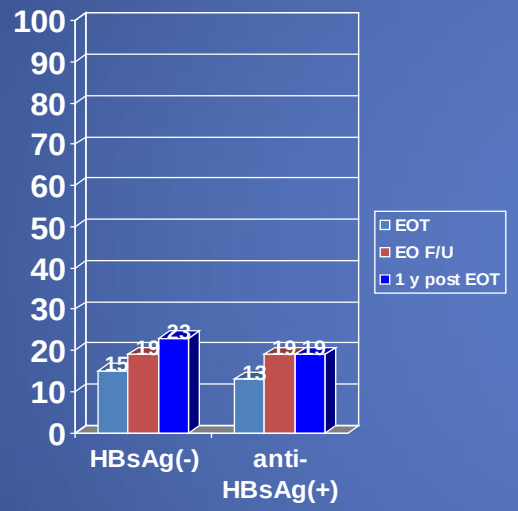
Gastroenterology 2007;133:1445-1451



High rate of HBsAg loss and HBsAg seroconversion in chronic hepatitis B patients on combination therapy with Peginterferon alfa-2a (Pegasys®) and Adefovir (Hepsera®): HBsAg titer predicts HBsAg loss or seroconversion. (Abstr LB 14)

- **Population:** 73 patients with chronic HBV; 34 HBe(+), 38 HBe(-).
- **Treatment:** 48 weeks of Peg-IFNa2a 180 mcg/w + Adefovir 10 mg/d; then 24 weeks without therapy.
- **Results:**
  - a) No difference in baseline HBV-DNA in seroconvertors & non-seroconvertors.
  - b) Baseline HBsAg titer (IU/mL) was lower in patients who loss HBsAg and seroconverted.

High rate of HBsAg loss and HBsAg seroconversion in chronic hepatitis B patients on combination therapy with Peginterferon alfa-2a (Pegasys®) and Adefovir (Hepsera®): HBsAg titer predicts HBsAg loss or seroconversion. (Abstr LB 14)



- **CONCLUSION:**
  - Combination of Peg-IFN + ADV causes higher rates of seroconversion than current monotherapies.
  - Baseline HBV-DNA does not predict HBsAg loss nor seroconversion
  - Baseline HBsAg levels predict HBsAg loss and seroconversion.
  - Larger studies are needed to confirm these findings.

CONCLUSIONS
Adefovir in Chronic HBV

- Adefovir is effective in controlling replication of HBe(+), HBe(-), and YMDD mutant HBV.
- Response increases with length of therapy but is slower than that to Lamuvidine
- Resistance to Adefovir is relatively low, but is higher in HBeAg(-) mutant.
- When Adefovir id added to Lamivudine in YMDD mutant HBV, resistance is low.
- Decompensated cirrhotics have a 1 y survival of 84% with adefovir; clinical benefits seen after 6 months of therapy.

Entecavir

Entecavir

- Oral deoxyguanidine nucleoside analog
- Active in wild, HBe(-), and YMDD
- **Dose**: - 0.5 mg/d in HBe(+) or (-); - 1 mg/day in YMDD mutant; - modify in renal impairment.
- No interaction with Lamivudine, Adefovir, nor Tenofovir.
- Should be taken in empty stomach.
- In HIV co-infection, may induce HIV drug resistance.
- In Lamivudine- or Telbivudine- resistant HBV, these drugs must be discontinue when Entecavir is initiated.

Entecavir

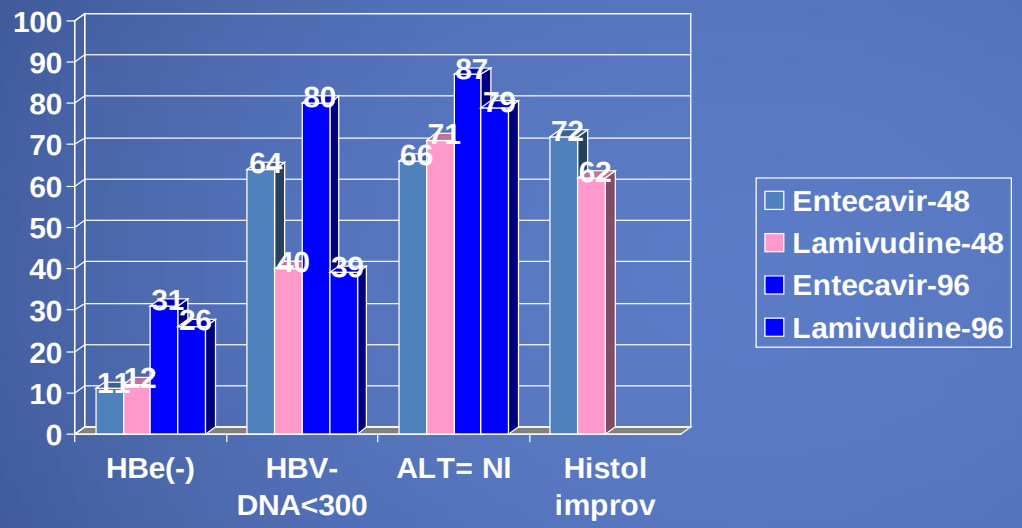
- **Side effects**: headache, fatigue, nausea
- **Viral Response after 1 y therapy**:
  - HBe(+)=82%,
  - HBe(-)=48%
- **Resistance:**
  - YMDD mutant (Lamivudine resistant): 7% @ 1 y, 26% @ 3y, & > 50% @ 5y.
  - In Naïve: 1.2% @ 5 y.
  - Resistance to Lamivudine increases risk of resistance to Entecavir, Telbivudine, and Emtricitabine; do not give them together.

Adjustment of Adult Entecavir dose by Creatinine Clearance

	Naive	**Lam Resistant**
>/= 50 mL/min	0.5 mg/day	1 mg/day
30-39 mL/min	0.25 mg/day	0.5 mg/day
10-29 mL/min	0.15 mg/day	0.3 mg/day
< 10mL/min, Hemodialysis, Peritoneodialysis	0.05 mg/day	0.1 mg/day

Entecavir x 48 & 96 wks in HBe(+)

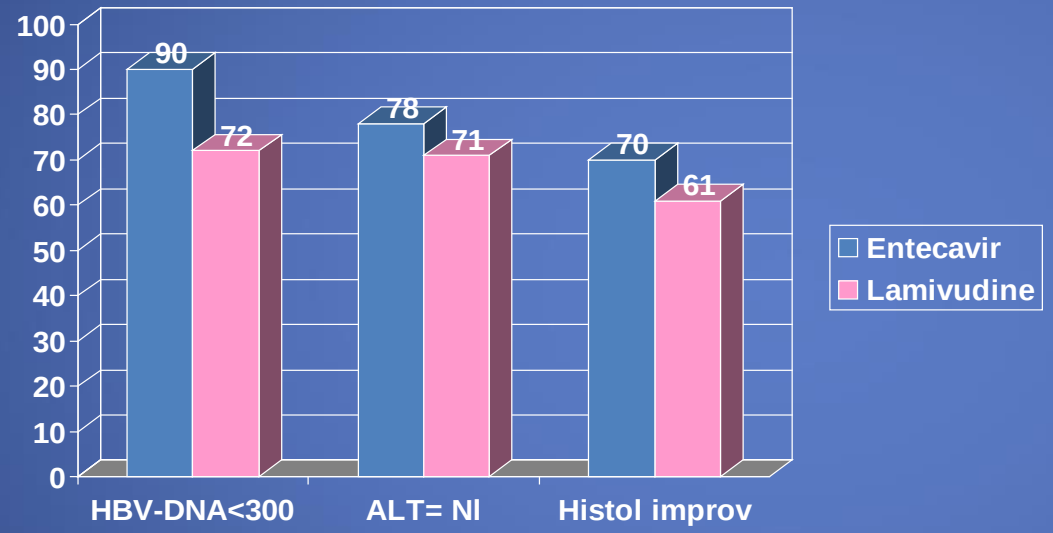
Gastroenterology 2007;133:1437-1444



1 of 354 patients developed Entecavir resistance & 13 had virologic breakthrough

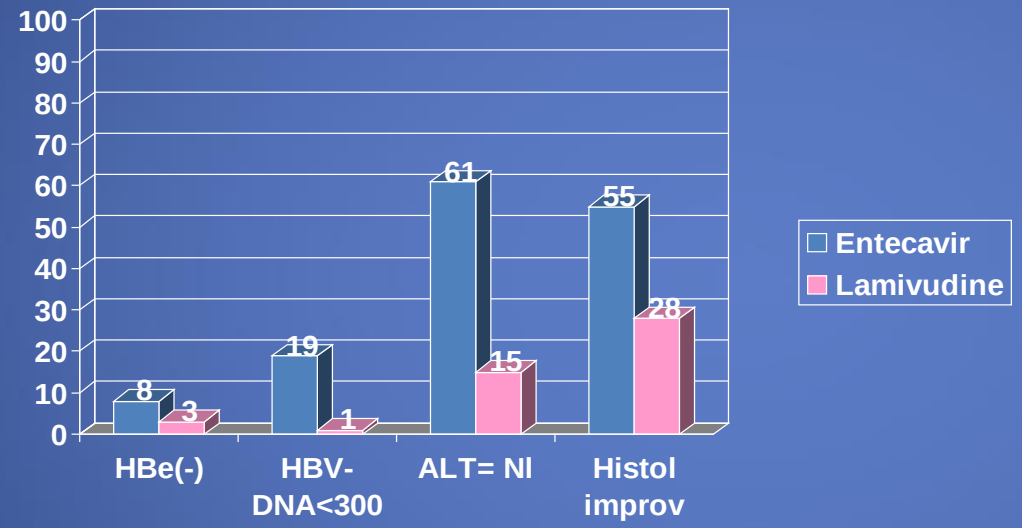
Entecavir x 48 wks in HBe(-)

Bristol-Myers Squibb package insert



Entecavir x 48 wks in YMDD mutant

Bristol-Myers Squibb package insert



CONCLUSIONS

Entecavir in Chronic HBV

- Entecavir is effective in controlling viral replication in HBe(+), HBe(-), and YMDD mutant chronic HBV
- Entecavir controls viral replication, normalizes ALT, and improves histology faster than Lamivudine
- Resistance has been reported more in YMDD mutant (Lamuvidine resistance) and is very high after 5 years (is not a good choice); is very uncommon in Lam-naïve.
- When changing from Lamuvidine to Entecavir, DO NOT OVERLAP therapies (D/C Lam).
- When changing from Adefovir to Entecavir, overlap for at least 3 months.

Telbivudine (LdT)

- Telbivudine: specific inhibitor HBV polymerase.
- Oral beta-L-deoxynucleoside of thymidine
- Causes 2-3 log HBV-DNA drop by wk 4; not effective in YMDD mutant.
- Dose: 400-600 mg/d
- May cause CPK elevation
- Resistance to Lamivudine increases risk of resistance to Entecavir, Telbivudine, and Emtricitabine; do not give them together.

Adjustment of Adult Telbivudine dose by Creatinine Clearance

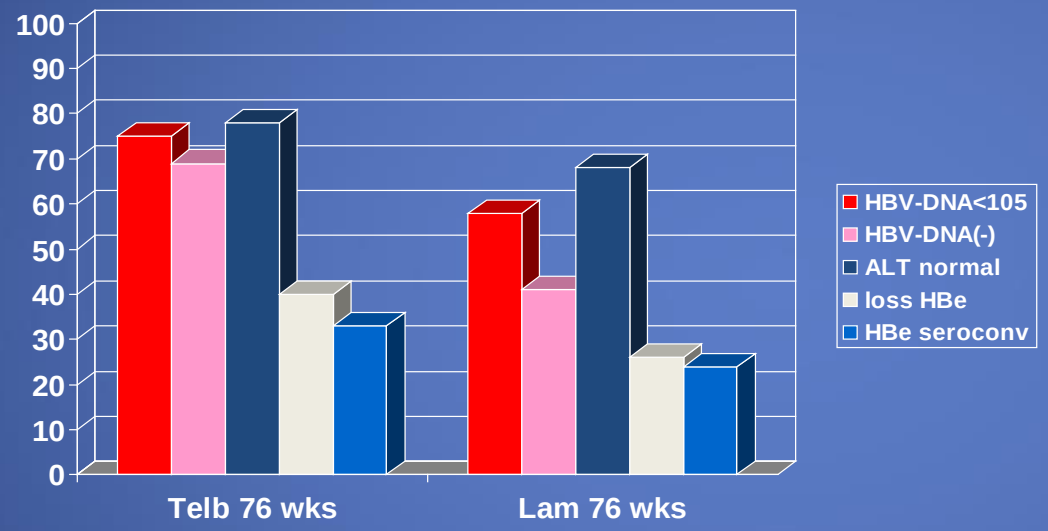
- >/50 mL/min 600 mg/day
- 30-49 mL/min 400 mg/day
- 10-29 mL/min 200 mg/day
- Hemodialysis 200 mg after each dialysis

Telbivudine (LdT) vs Lamivudine in Chronic HBV – Phase III GLOBE Study

- Double blind, prospective, randomized 1:1
- 2 years of Telbivudine vs Lamivudine
- **Patients**:
  - 1367 [921 HBeAg(+) & 446 HBeAg(-)] with
  - Liver Bx c/w Ch. HBV, HBV-DNA > 10^5 copies/mL, ALT > 1.3 ULN
- **1st end-point**: HBV-DNA < 10^5 + [normal ALT or loss HBeAg]
- **2nd end-point**:
  - a) Histologic response: Drop histol. Activ > 2 pts,
  - b) Viral response: Drop of HBV-DNA or HBV-DNA(-) by PCR
  - c) Normalization of ALT
  - d) Loss of HBeAg, or HBe seroconversion

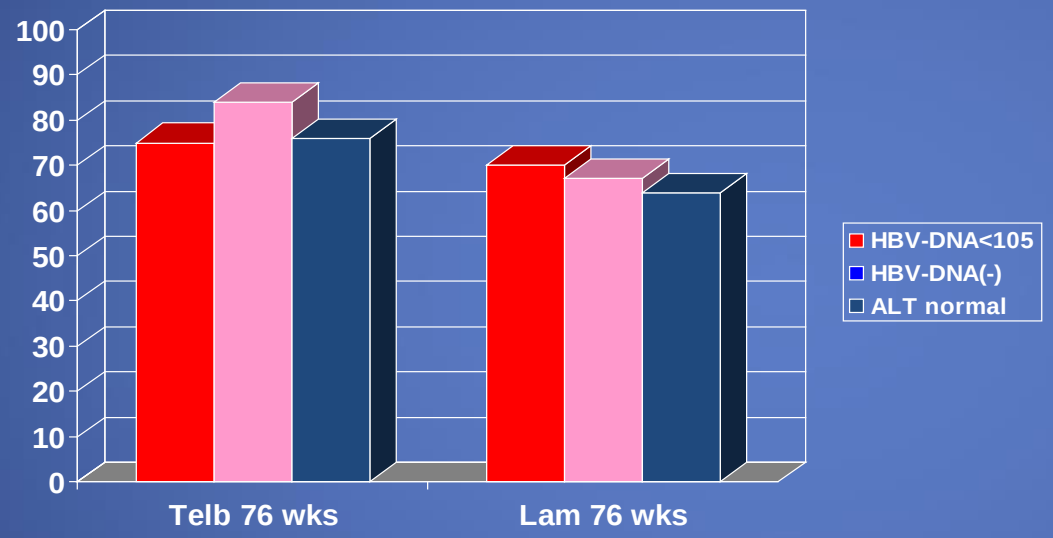
Telbivudine (LdT) vs Lamivudine in Chronic HBV – Phase III GLOBE Study

HBeAg(+)



Telbivudine (LdT) vs Lamivudine in Chronic HBV – Phase III GLOBE Study

HBeAg(-)



Telbivudine (LdT) vs Lamivudine in Chronic HBV – Phase III GLOBE Study

CONCLUSION

- Telbivudine is faster and more effective than Lamivudine in HBeAg(+) and HBeAg(-) chronic HB
- There is incremental effect from 1 year to 18 months of therapy.

Telbivudine vs. Adefovir
HBeAg(+) patients

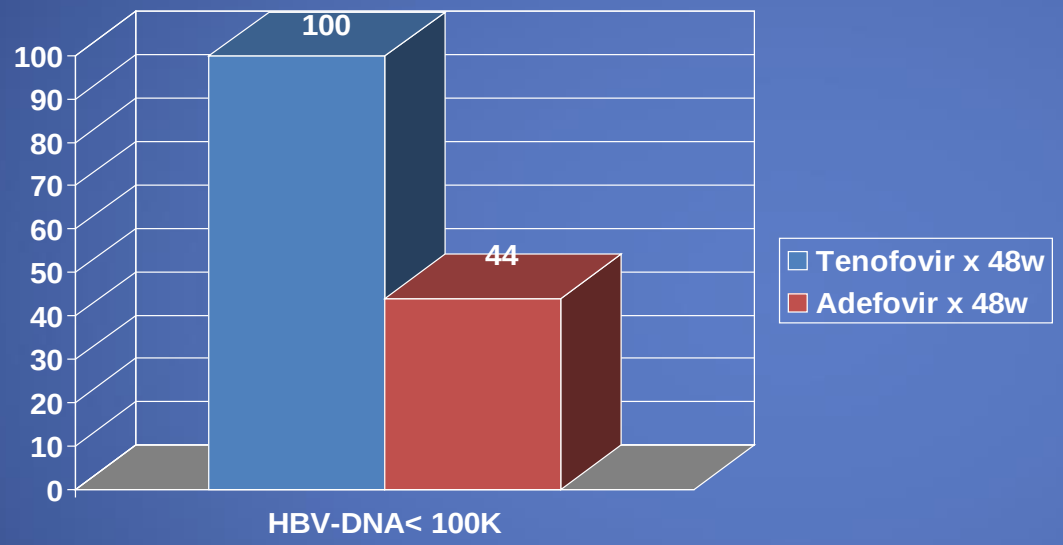
- **log drop HBV-DNA at week 24:**
  - Telbivudine = 6.3, Adefovir = 4.97
- **HBV-DNA < 300 copies/mL @ wk 24:**
  - Telbivudine = 38.6%, Adefovir = 12.4%
- **Loss of HBeAg:**
  - Telbivudine = 16%, Adefovir = 10%
- **Normalization of ALT:**
  - No difference.

Tenofovir Disoproxil

- Oral adenosine nucleotide analog
- Dose: 300 mg/day; adjusted by renal function
- Effective in wild and YMDD mutant
- Causes 4-5 log drop HBV-DNA @ 48 weeks
- No resistance in up to 130 wks

Tenofovir x 72-130 wks in YMDD mutant

von Bommel et al. Hepatology 2004; 40:1421-1425



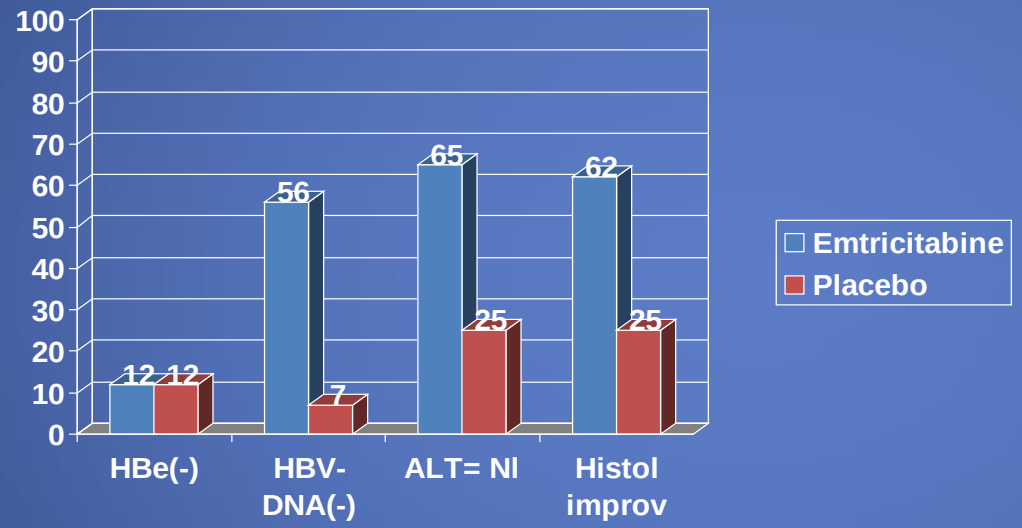
Other Oral Agents

Emtricitabine (FTC)

- Oral cytosine nucleoside analog
- **Dose**: 200 to 300 mg/d; adjust by renal function.
- Resistance by YMDD mutation in 12% at 48 weeks.
- **Side effects**: lactic acidosis, fatty liver, fat redistribution, neutropenia.
- Resistance to Lamivudine increases risk of resistance to Entecavir, Telbivudine, and Emtricitabine; do not give them together.

Emtricitabine x 48 wks in HBe(+) or (-)

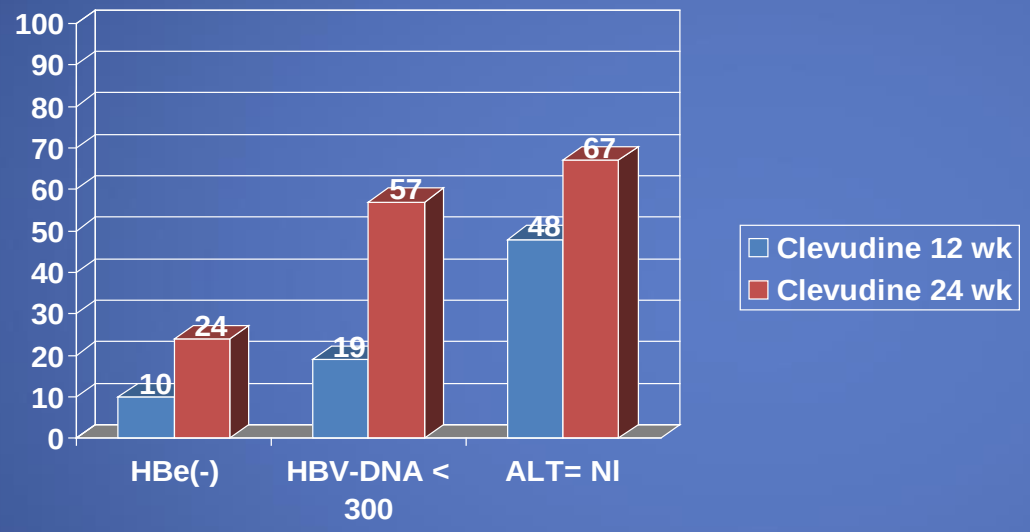
Schiffman et al. AASLD 2004, Abstr# 22



Clevudine

- Oral pyrimidine analog (L-FMAU = 2-fluoro-5-methyl-beta-L-arabino furanosyl uridine)
- Is phosphorylated inside the cell and is slowly removed: sustained viral inhibition.
- Causes 3-4 log drop in HBV-DNA by wk 4.
- Dose: 30-50 mg/day

Clevudine x 12-24 wks in HBe(+)



Percutaneous Injuries in Healthcare Workers (HCWs)

- Frequency has decreased over the last decade
  - in 1998 were 590164 reported percutaneous hospital-based exposures in the US. Is estimated that 39% were not reported.
- Currently estimated at 384000 - 600000 percutaneous injuries per year at US Hospitals (> 1000/day)
- Only 43% are reported.
- In 2004, the U.S. work-productivity cost was 188.5 million dollars.
- Highest rate is in OR Nurses (39.7 exposures/FTE/year).
- By the end of their training, 99% of surgical residents will have at least 1 needle stick injury; more than 50% will not be reported.
- Frequency with hollow-needles has decreased (due to safer devices) but with solid-needles has increased.

Percutaneous Injuries in Healthcare Workers (HCWs)

- Worldwide, in the year 2000, needle injuries caused 66000 cases of HBV, 16000 cases of HCV, and 1000 cases of HIV in HCWs.
- Factors that increase risk:
  - Poor organization climate or administrative support
  - High workload
  - Poor training in use of safer device
  - Believe that following precautions with place patient at risk
  - HCW's state of mental anguish or social dysfunction

Frequency of sharp injuries by surgeons in Teaching Hospitals - England 1992

Ann R Coll Surg 1996;78:447-449

Frequency	CT Surgery	OB/GYN Surgery	General Surgery	Other Surgery
> 1/month	60%	63%	54%	19%
< 1/month, > 1/year	40%	31%	23%	35%
< 1/year	0	6%	23%	47%
Always Reports	0	6%	14%	28%

Frequency of sharp-injuries and re-contact* exposure in Teaching Hospital – US 1992

JAMA 1992;267:2899-2904

	CT Surgery	GYN Surgery	General Surgery	Orthopedic Surgery	Trauma Surgery
Procedures with Injury	9%	10%	8%	4%	5%
Re-contact	3%	4%	1%	0.3%	3%

Re-contact: instrument contacted patient after HCW injury, or bone fragment or wire fixed to patient injured the HCW

Worldwide Cases of HCW-to-Patient HIV, HBV, or HCV Transmission 1991-2005

Am J Infect Control 2006;34:313-319

	# HCW	# Infected Patients	# Patients tested in look-back	% Infected Patients
HIV	3	3	3527	0.09%
HBV	12	91	3079	2.96%
HCV	11	38	9678	0.36%

Factors Affecting Viral Bloodborne Pathogens Transmission to HCWs

- Prevalence of the pathogen in the population served by the healthcare facility.
- Frequency of exposure
- Type of exposure (percutaneous, mucosal, nonintact skin)
- Infectivity of the virus (HBV > HCV > HIV)
- Titer of the virus in the body fluid or inanimate object.
- Availability of pre-exposure prophylaxis (HBV), and post-exposure prophylaxis (HBV, HIV)

Risk of HBV Infection in HCWs

- HBV is much more infectious than HCV and HIV.
- HBV can be transmitted by percutaneous, mucosal, or nonintact skin exposure.
- Inanimate objects (fomites) can transmit HBV: finger-stick devices, jet gun injectors, multi-dose vials, endoscopes.
- Infectious HBV can survive up to for 7 days in contaminated surfaces.
- OSHA-required HBV vaccination of HCWs since 1991, has decreased HBV infections by 95% between 1983 to 1995.
- Only 75% of HCWs have received HBV vaccination.

Risk Minimization

- All HCWs with reasonably anticipated exposure to blood or contaminated body fluids must receive from the healthcare facility:
  - yearly education about bloodborne pathogen transmission and risk minimization.
  - HBV vaccination (and post vaccination testing) at no cost. Quantitative anti-HBs titers should be tested 1-2 months after final (3rd) vaccine dose.
  - If anti-HBs titer is < 10 mIU/mL, the 3-dose vaccination should be repeated, and anti-HBs titers repeated. Failure to obtain titers > 10 mIU/mL after the second 3-dose vaccine series classifies the patient as “non-responder”.
  - If HCW refuses HBV vaccination, he/she must sign mandated declination form.

Risk Minimization

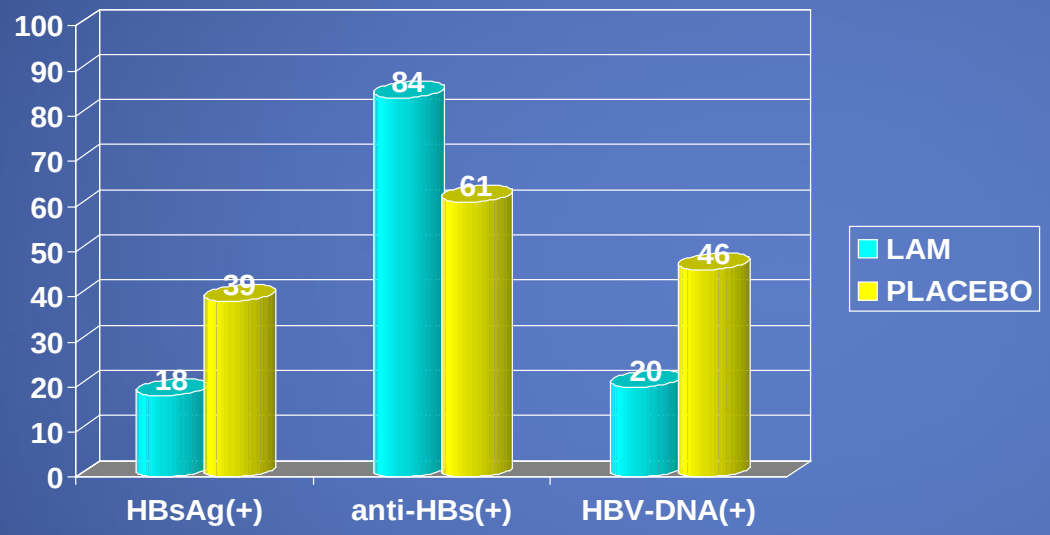
- engineering controls proven to reduce exposure risk
  - leak-proof containers to transport blood,
  - impervious needle-disposal containers,
  - needles IV medication systems,
  - blunted suture needles
- “Personal Protective Equipment” , that HCWs must use it when performing procedures with blood exposure risk
  - impervious gowns,
  - gloves,
  - face/eye shields

Effect of Lamivudine on HBV Vertical Transmission from Highly Infectious Mothers

Xu WM et al. AASLD Abstr # 246, 2004
Xu WM et al. J. Viral Hepat 2009:16, 94-103

- Multicenter, double blind, randomized, placebo controlled.
- **Population**: 114 pregnant women with HBsAg(+) & HBV-DNA > 200 million IU/mL (Chiron bDNA).
- **Treatment**: Lamivudine 100 mg/d vs. placebo starting @ wk 32 until 4 wks post-partum
- All neonates received: HBIG 200 IU + HBV vaccine @ birth, 4 & 24 weeks.
- **End-point**: HBsAg(+) & HBV-DNA(+) @ age 53 wks

RESULTS # 246


100
90
80
70
60
50
40
30
20
10
0
84
61
39
46
18
20
HBsAg(+)
anti-HBs(+)
HBV-DNA(+)
LAM
PLACEBO

CONCLUSION

Abstr # 246

- In mothers with HBV-DNA > 200 million IU/ml, the addition of Lamivudine 100 mg/d in the 8 weeks prior to delivery plus 4 weeks post-partum, to the regimen of HBIG & Vaccination, decreased the rate of vertical transmission of HBV.
- No safety concerns were observed on mothers nor infants.
- Lamivudine was well tolerated.

Testing for HB Pre-core & Core-Promoter Mutant

- 70% of anti-HBe(+)/HBeAg(-) have HBV-DNA ≤ 20000 IU/mL; may have "wild" or "mutant" HBV. **Testing for Pre-core/Core-promoter mutation should be done.**
- Commercial Test: Inno-LiPA HBV PreCore
- If HBV-DNA is < 2000 IU/mL and patient is HBeAg(-). Patient may have:
  - Wild HBV "inactive carrier state": no need to treat, or
  - Precore or core-promoter HBV "inactive carrier state": no need to treat.