
OFFICERS WARD
WELLCOME

Efficacy & safety of drug treatment of Chronic Hepatitis ‘B’ infection

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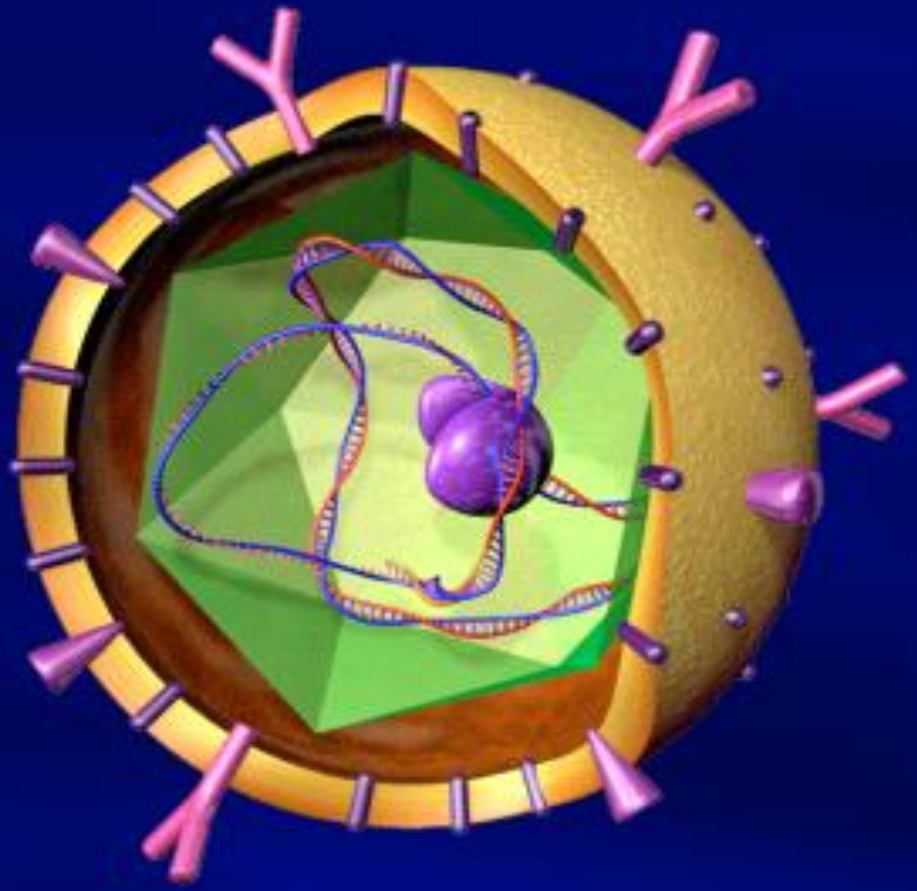
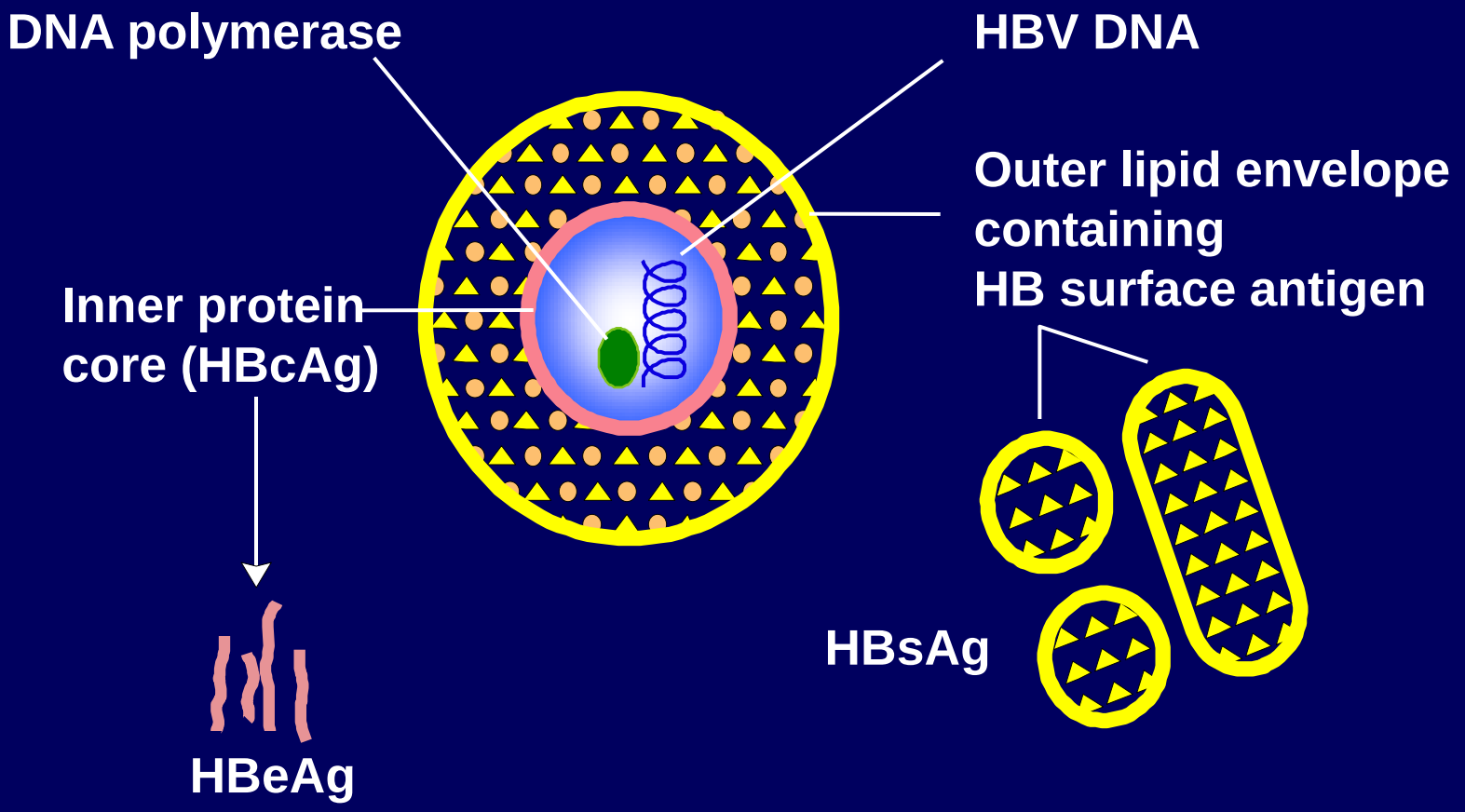
- Australia antigen was discovered by Prof. Blumberg – 1967
- He was awarded nobel prize – 1977

HEPATITIS B VIRUS



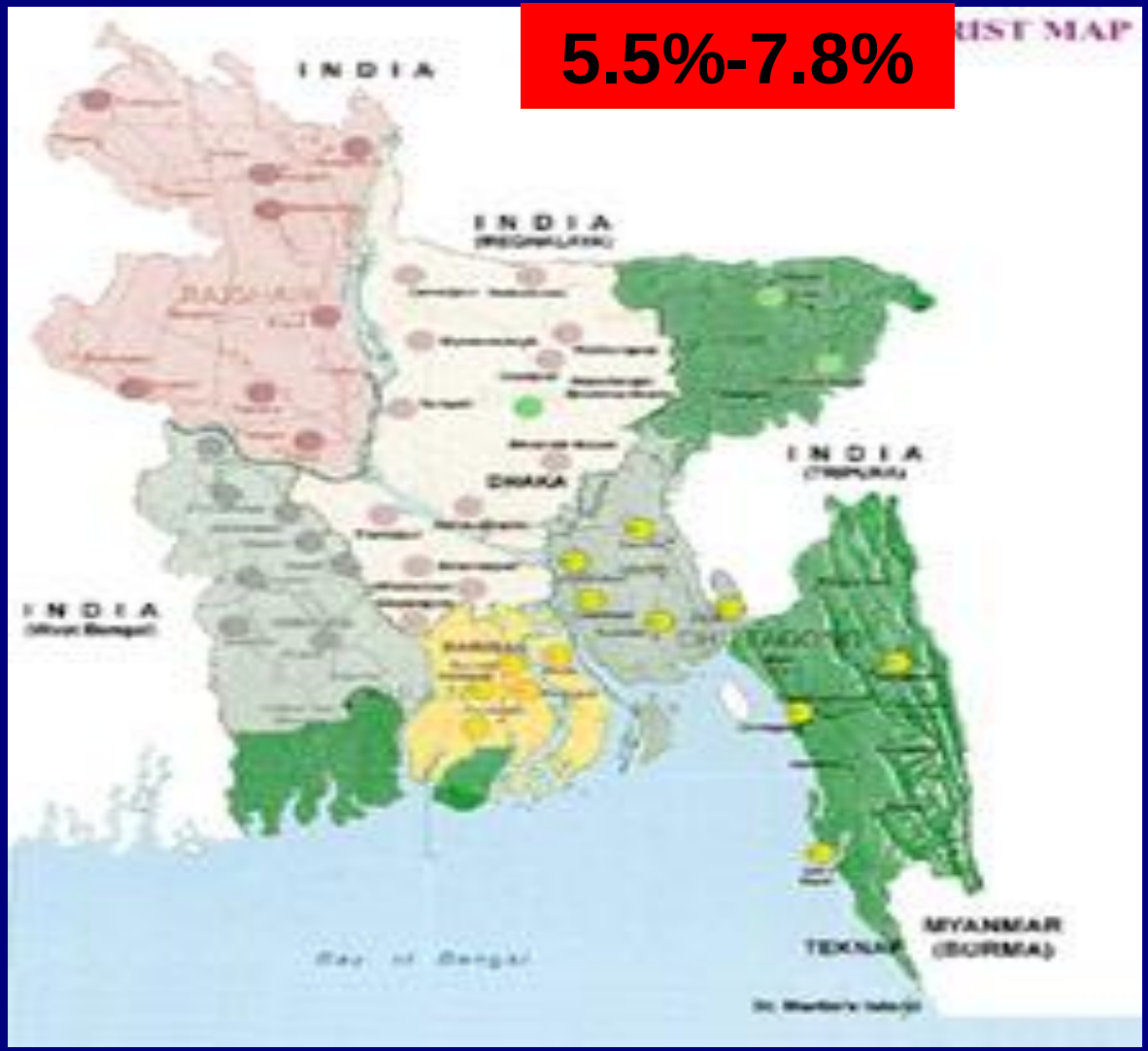
Schematic Representation of HBV



Significance of Markers of HBV

- HBsAg – Infection
- HBeAg – Replication
- HBV DNA – Replication
- Anti HBs – Immunity
- Anti HBe – Seroconversion of HBeAg
- Anti HBc (IgM) – Acute infection/reactivation
- Anti HBc (IgG) – Remote past infection

Prevalence of HBV in Bangladesh



Khan M et al. *J Gastro Hepato* 2004;19:S419–S430

HBV infection

- Acute - < 6 months
- Chronic - > 6 months

HBV infection

- Childhood infection - > 95% chronic
- Adult infection - > 95% acute

Pathogenesis

HBV infection is an immune – based disorder

Clinical manifestation

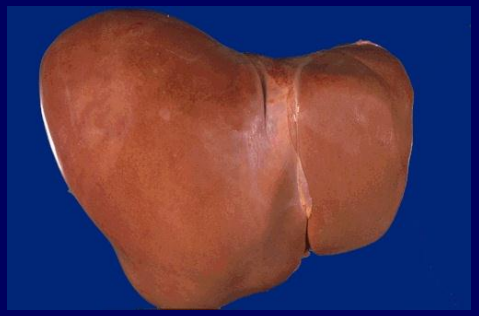
- Acute hepatitis – Jaundice
- Chronic hepatitis – Asymptomatic

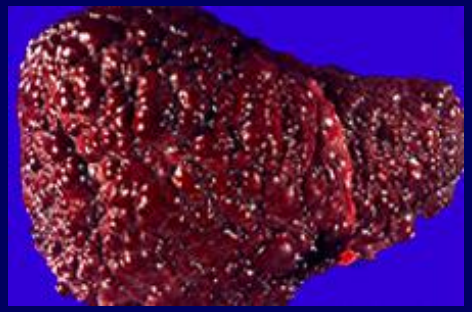
Chronic Hepatitis B - Consequences

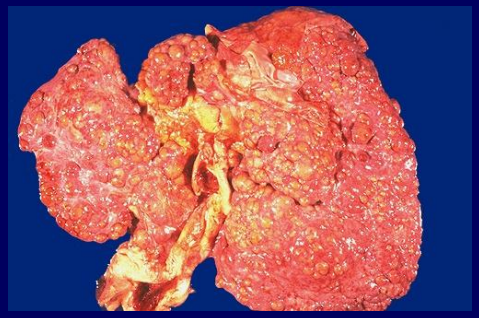
Liver disease progression over time

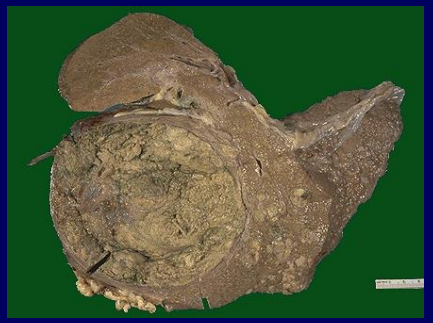
20–30 years

Normal | Cirrhosis | Cirrhosis | HCC



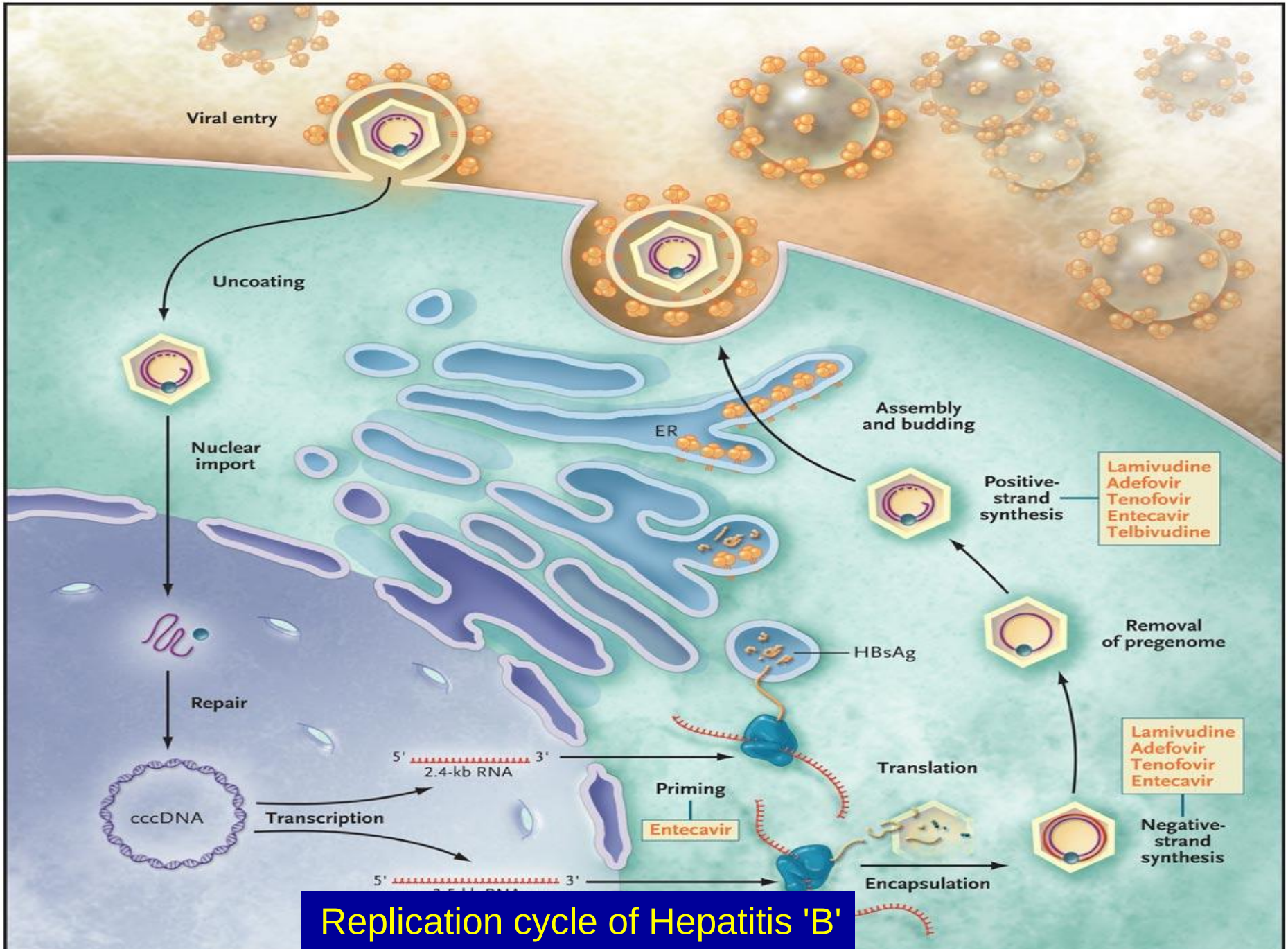






HBV → **ACUTE /CHRONIC HEPATITIS B** → **CIRRHOSIS ESLD** → **HEPATOCELLULAR CARCINOMA**

Liver damage = the result of attempts, usually unsuccessful, to clear infected hepatocytes as part of the immunoclearance stage of disease



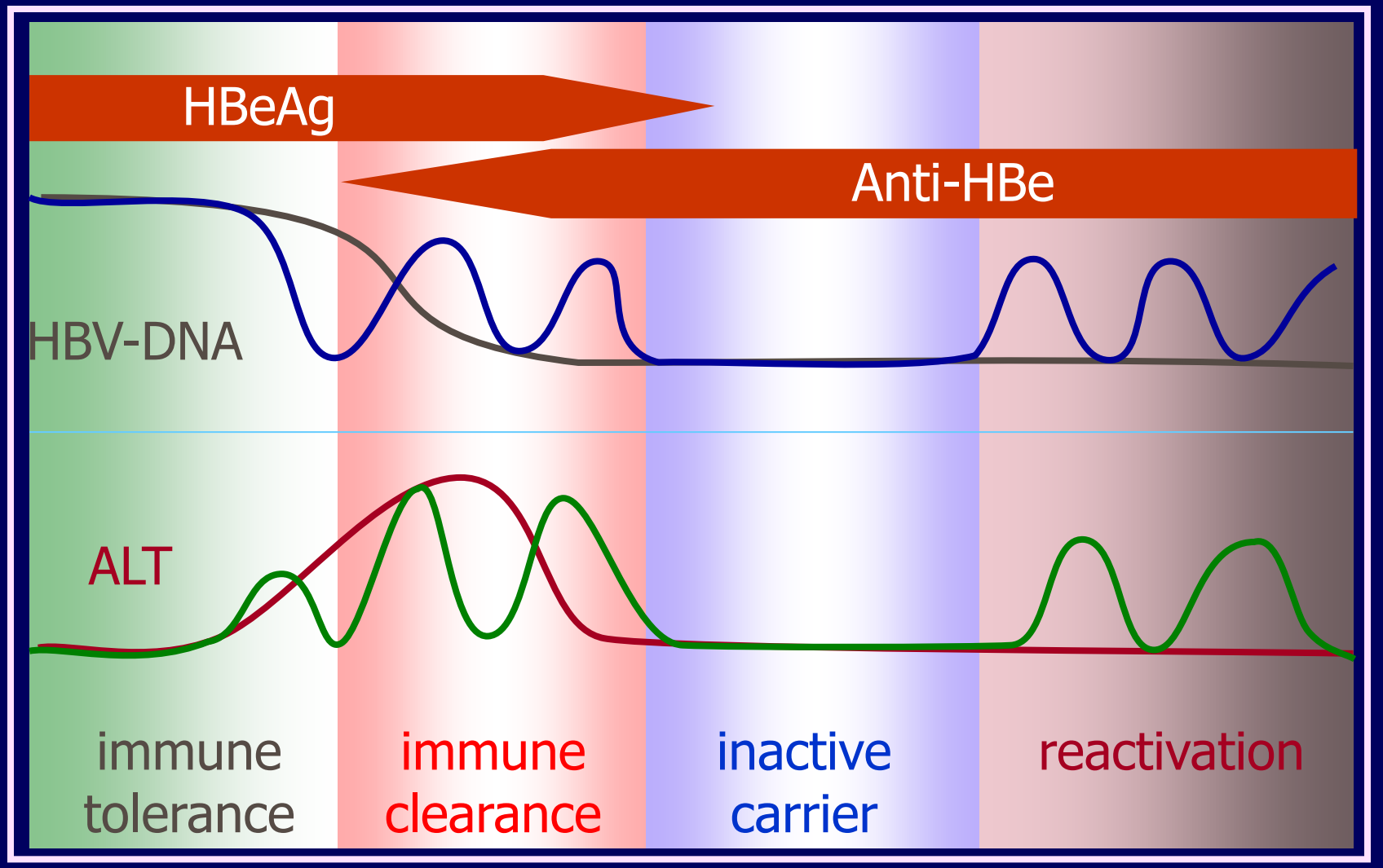
Replication cycle of Hepatitis 'B'

Stages of hepatitis ‘B’ viral infection

- Stage 1: Immune tolerance stage
- Stage 2: Immune clearance stage
- Stage 3: Inactive carrier stage
- Stage 4: Reactivation stage

Contd..

Stages of HBV infection



Contd..

Stages of chronic hepatitis ‘B'

Immune tolerance:

- HBsAg +ve > 6 months
- HBeAg +ve, Anti HBe -ve
- Serum HBV DNA > 20,000 i.u./ml
- Persistent normal ALT
- Liver biopsy - normal or minor change.

Stages of chronic hepatitis ‘B'

Immune clearance (HBeAg +ve CHB):

- HBsAg +ve > 6 months
- HBeAg +ve, Anti HBe -ve
- Serum HBV DNA > 20,000 i.u./ml
- Persistent or intermittent elevation of ALT
- Liver biopsy - Chronic hepatitis (HAI≥ 4)

Stages of chronic hepatitis ‘B'

Inactive HBV carrier:

- HBsAg +ve > 6 months
- **HBeAg -ve, Anti HBe +ve**
- Serum HBV DNA < 2000 i.u./ml
- **Persistent normal ALT**
- Liver biopsy - Absence of significant hepatitis (HAI < 4)

Contd..

Stages of chronic hepatitis 'B'

Reactivation (HBeAg -ve CHB):

- HBsAg +ve > 6 months
- **HBeAg -ve, Anti HBe +ve**
- Serum HBV DNA > 2000 i.u./ml
- **Persistent or intermittent elevation of ALT**
- Liver biopsy - Chronic hepatitis (HAI $\geq$ 4)

Risk factors for development of Cirrhosis

- Older age
- Male sex
- High viral load
- HBV genotype C
- Coinfection with HCV,HIV, HDV
- Heavy alcohol consumption
- Aflatoxin
- Smoking

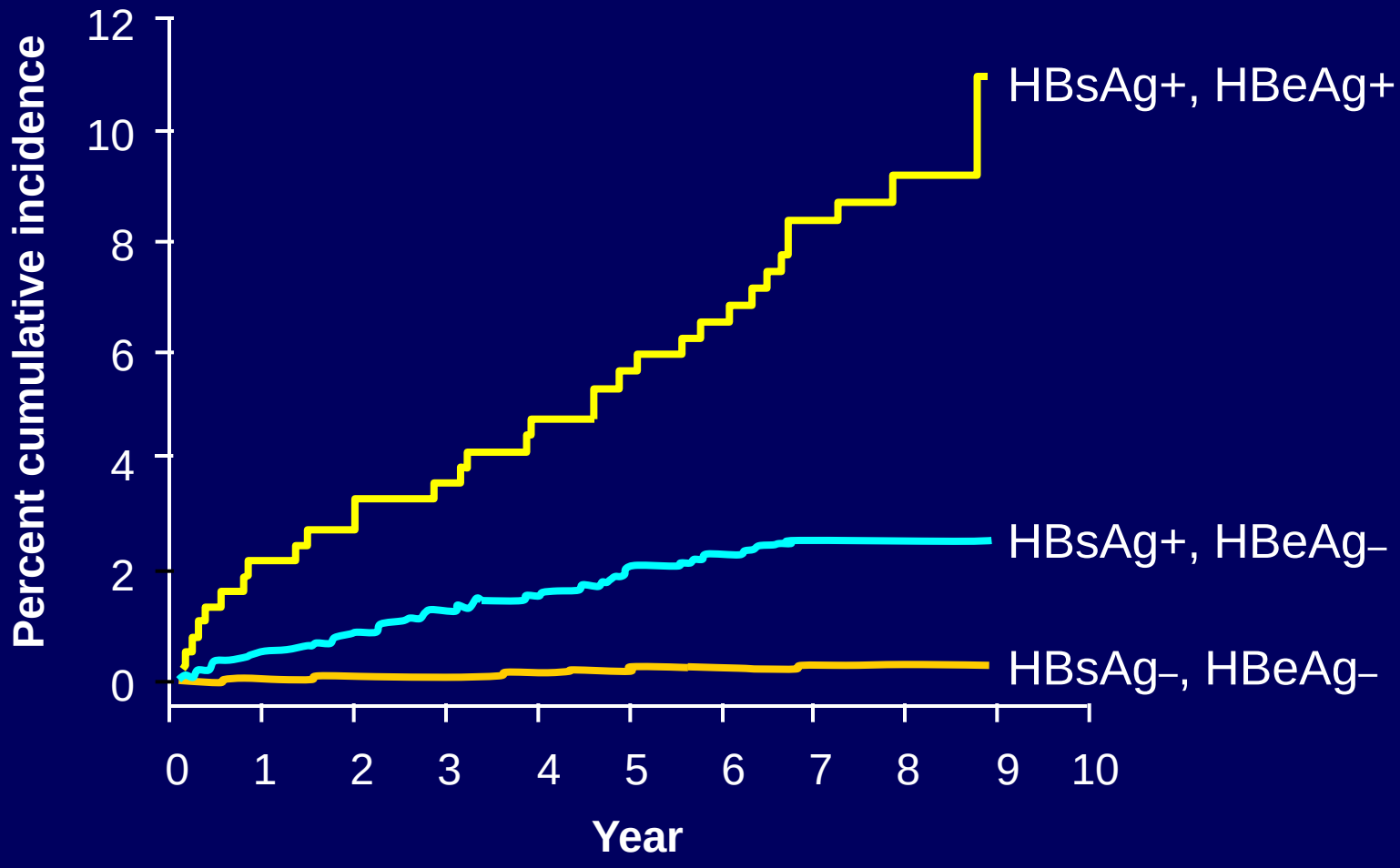
Risk factors for HCC

- Older age
- Male sex
- Family history of HCC
- Cirrhosis of liver
- Core promotor mutation
- Coinfection with HCV,HIV,HDV
- History of reversion from anti-HBe to HBeAg
- Presence of HBeAg & high viral load is an independent risk factor for HCC

- Persistent seropositivity for HBeAg & HBV DNA > 2000 i.u./ml are significant risk factors for Cirrhosis and HCC

  - Ref: Yang H I et al N Eng J Med 2002;347:168-174
  - Ileoje UH et al. Gastroenterol 2006;130:678-686

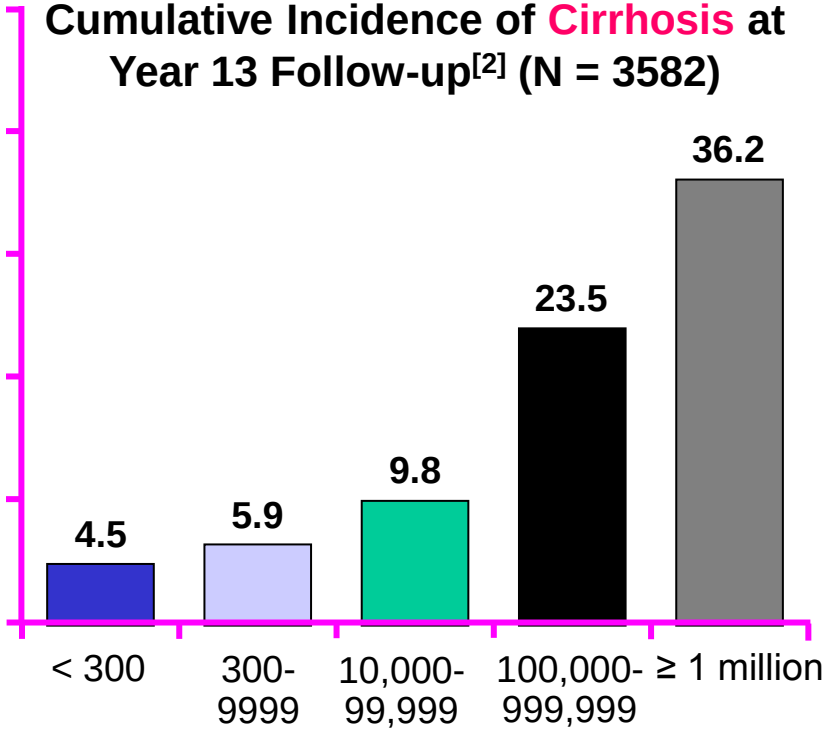
Positivity for HBeAg is Associated with an Increased Risk of HCC – Taiwanese Data

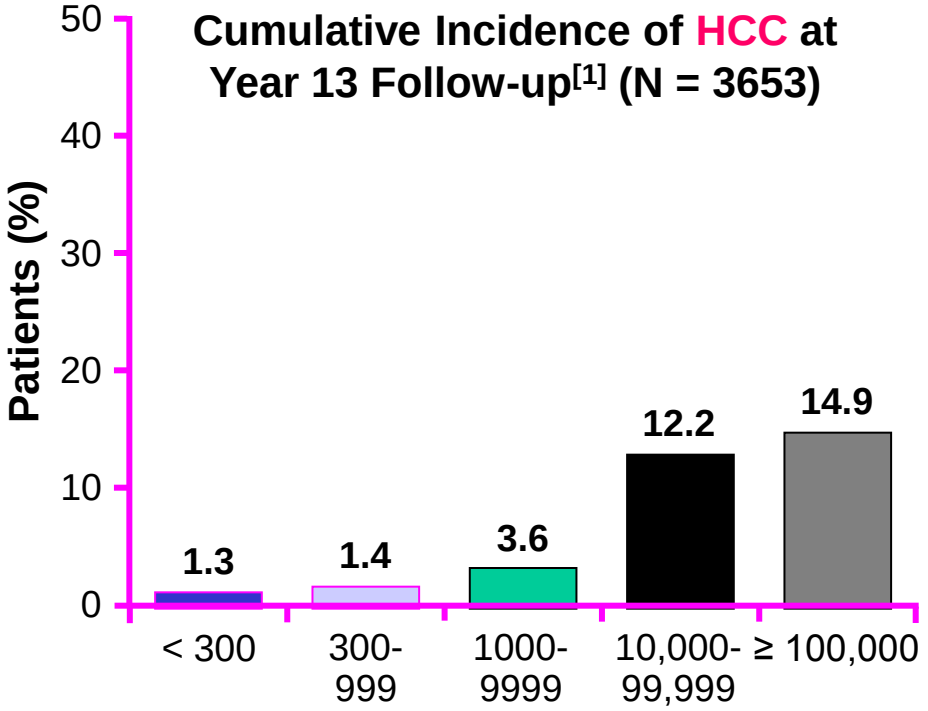


Yang et al. *NEJM* 2002

Persistence HBV DNA Associated With Increased Risk of HCC and Cirrhosis

Long-term follow-up of untreated HBsAg positive individuals in Taiwan



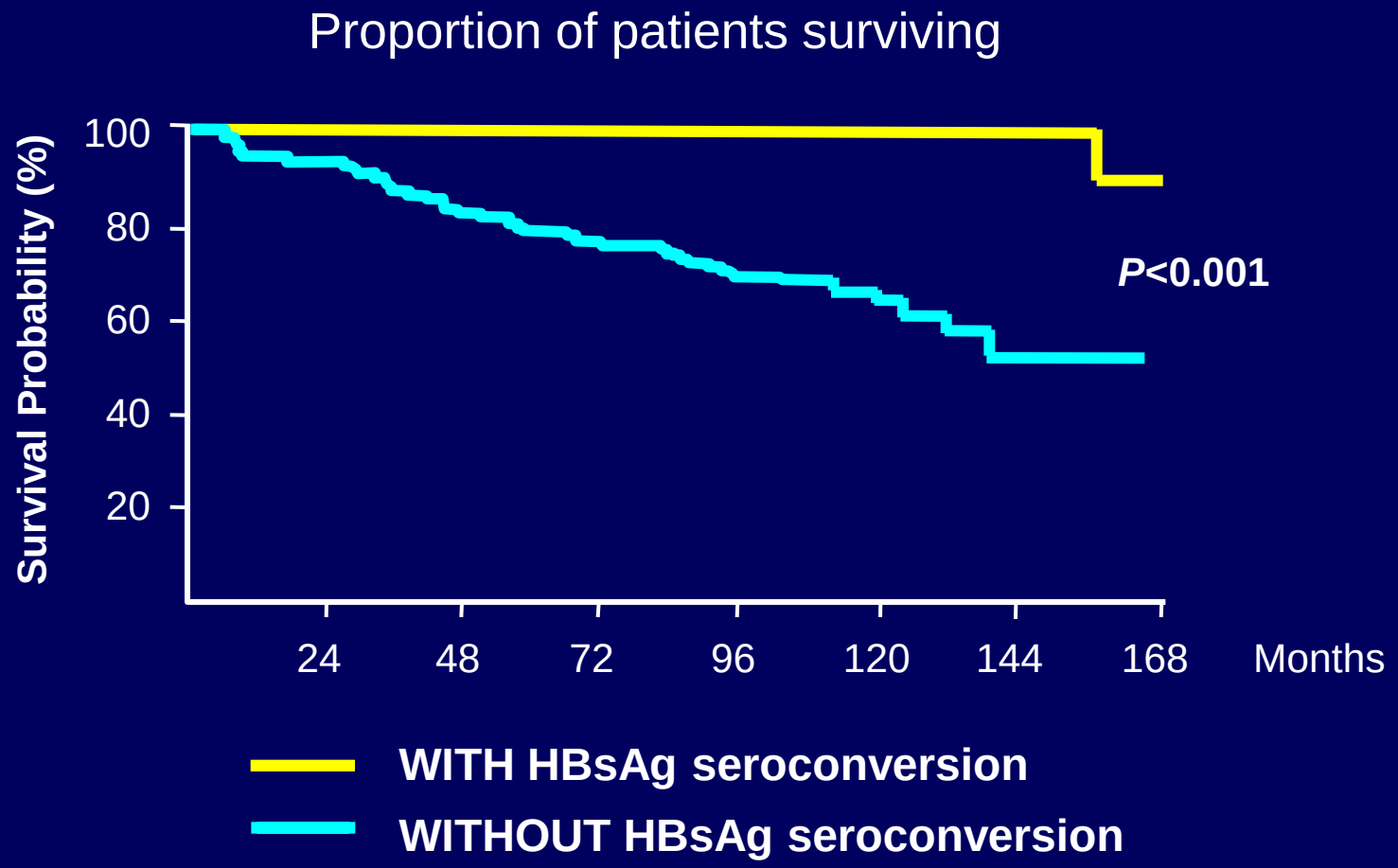


Baseline HBV DNA (copies/mL)

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

HBsAg Seroconversion Improves Survival Rates

Retrospective study of 309 patients over mean follow-up of 5.7 years



Fattovich G et al. *Am J Gastroenterol* 1998

Treatment of CHB

Ref:

AASLD guideline -2009

APASL guideline -2008

EASL guideline -2008

BGS Guideline - 2011

Goals of HBV therapy

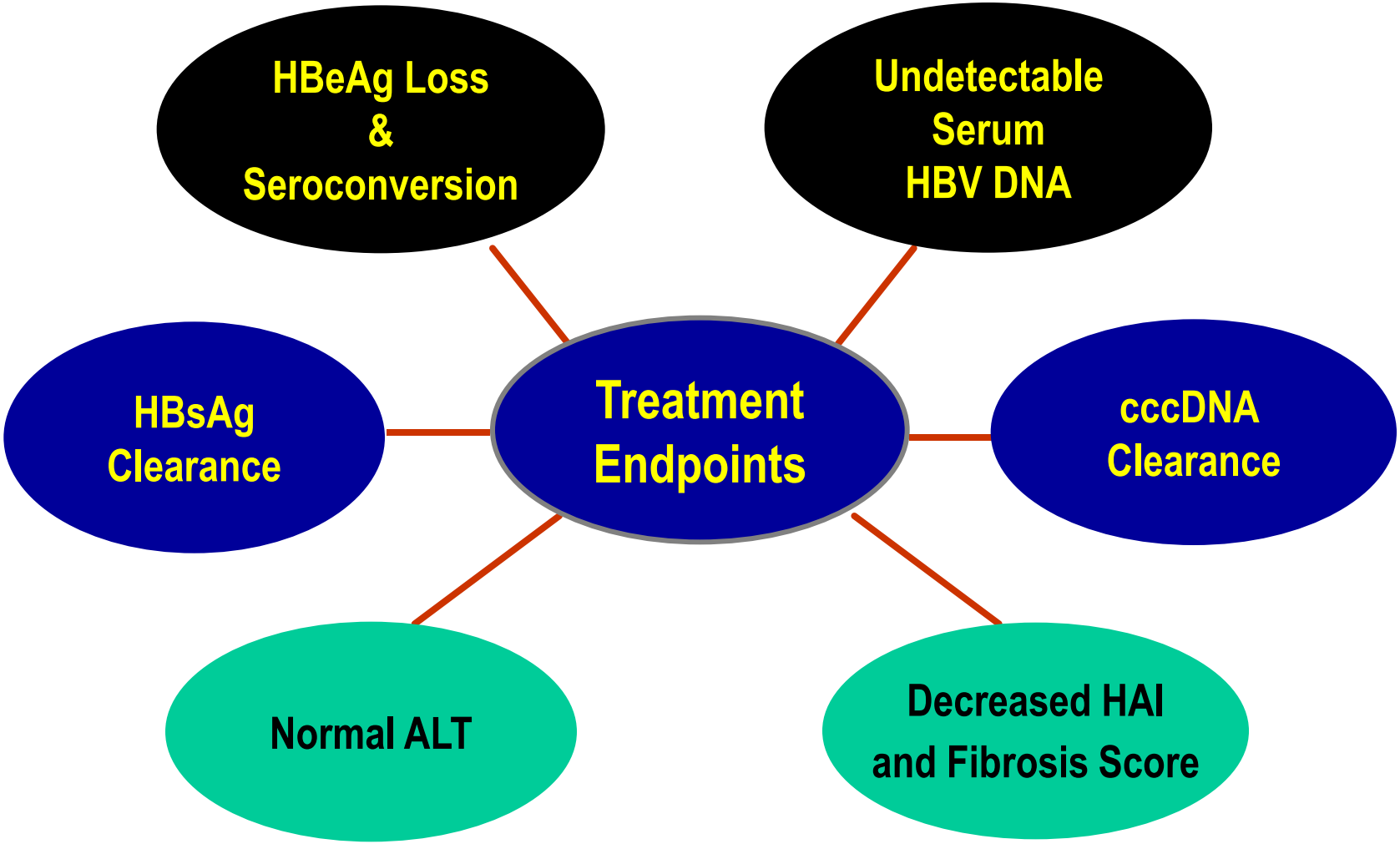
- Long term goals:
  - Improve survival
  - Prevention of cirrhosis and HCC
  - Prevention of complication

Goals of HBV therapy

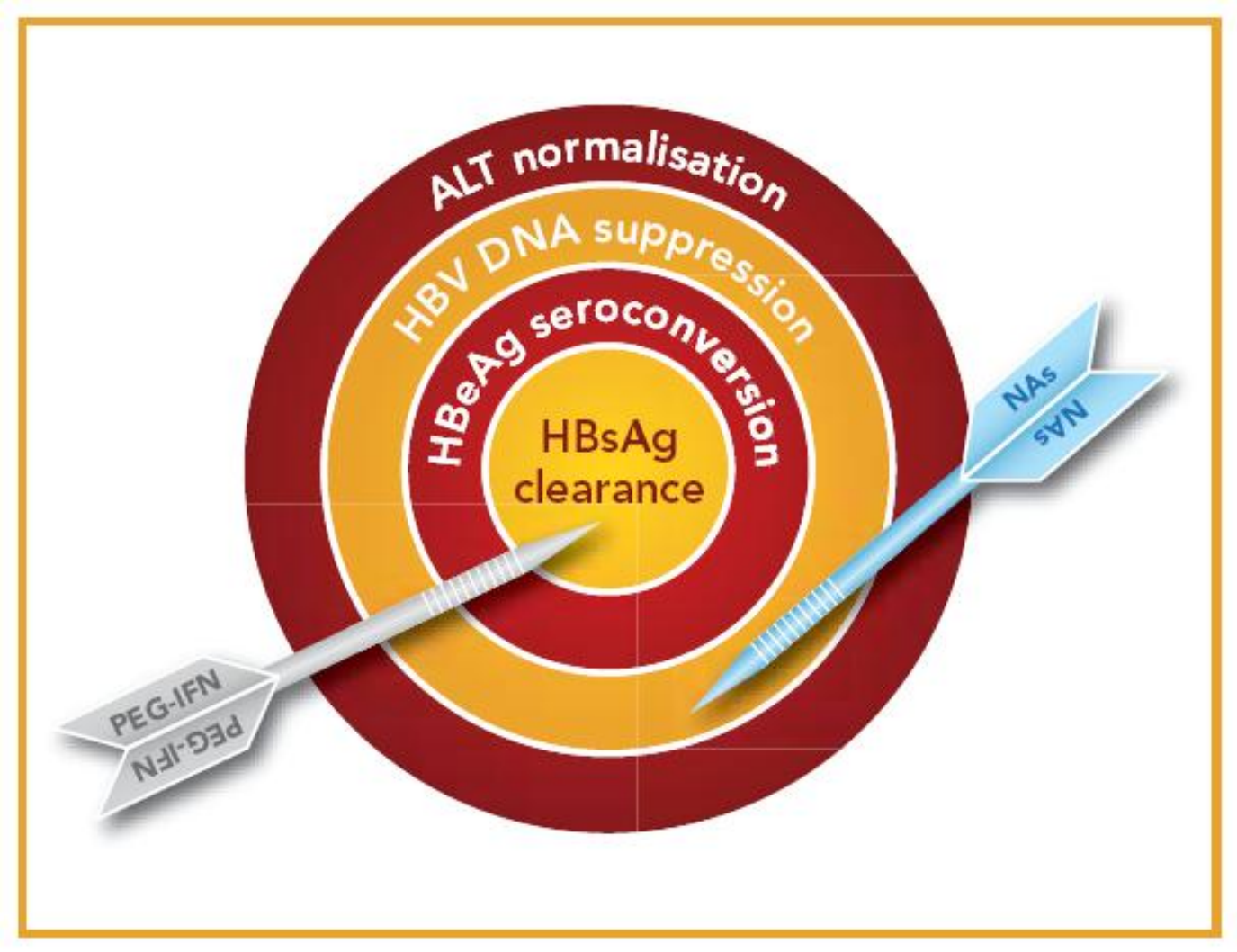
- Short term goals:
  - Biochemical: Normalisation of ALT
  - Serological : HBeAg seroconversion
  - Virological : Undetectable serum HBV DNA
  - Histological : Reduction of necro-inflammatory score

HBsAg seroconversion – Close to cure

TREATMENT ENDPOINTS IN CHB



TARGETED THERAPY CHRONIC HEPATITIS 'B'



Indications of treatment

HBeAg positive CHB

- ALT ≥2 X ULN
- HBV DNA > 20,000 IU/ml
- Active necroinflammation or fibrosis

Indication of treatment

- HBV DNA > 2000 IU/ml in HBeAg –ve
- Compensated cirrhosis with detectable DNA may be considered for treatment even if ALT is normal & DNA is < 2000 IU/ml.
- Treatment should be started as early as possible if there is hepatic decompensation.

Indication of treatment

- Immunotolerent patient < 30 yrs of age with persistently normal ALT & high HBV DNA level without any suspicion of liver disease & without a family history of HCC or cirrhosis donot not require immediate liver biopsy or treatment.
- Follow up is mandatory

Definition of response

- Biochemical response:

  - Decrease in serum ALT to normal range

- Virological response:

  - Decrease in serum HBV DNA to undetectable level by PCR assays within 48 weeks of NUCs therapy.

  In Interferon therapy virological response is defined as HBV DNA conc < 2000 IU/ml at 24 weeks of therapy.

- Serological response:

  - Loss of HBeAg & development of antiHBe

Definition of response

- Primary non-response:

  < 1 log10 IU/ml decrease in HBV DNA from baseline at 12 weeks of therapy
- Partial virological response:

  Decrease in HBV DNA > 1 log10 IU/ml but detectable by RT-PCR assay at 24 weeks of therapy.
- Virological breakthrough:

  Increase in HBV DNA level of > 1 log10 IU/ml compared to nadir DNA level on therapy after achieving virologic response during continued therapy
- Viral rebound: Increase in viral DNA to > 20,000 IU/ml or above pretreatment level after achieving virologic response during continued treatment

- Histological response:

  - Decrease in histological activity index by at least 2 points & no worsening of fibrosis score compared to pre-treatment liver biopsy.

- Complete response:

  - Biochemical response, virological response & loss of HBsAg

- Virological relapse:

  - Increase in serum HBV DNA of 1 log10 IU/ml after discontinuation of treament in at least 2 determinations > 4 weeks apart

Resistance

- Genotypic resistance:

  - Detection of mutation that confer resistance to NUC

- Phenotypic resistance:

  - Mutation detected decreases susceptibility to NUC (increase MIC)

Drugs available for treatment of CHB

- Interferon : Standard, Pegylated
- Nucleotide analogue : Adefovir, Tenofovir
- Nucleoside analogue : Lamivudine,
  Entecavir,
  Telbivudine,
  Emtricitabine

History of antiviral drug development

- Interferon – 1989
- Lamivudine – 1998
- Adefovir – 2002
- Entecavir – 2005
- Pegylated Interferon – 2005
- Telbivudine – 2006
- Tenofovir – 2008

Adult dose of the drugs

- Interferon alfa 2a – 5 MU/d or 10 MU tiw
- Pegylated Interferon alfa 2a – 180 mcg / wk
- Entecavir – 0.5 mg / d
- Tenofovir – 300 mg/d
- Telbivudine – 600 mg/d
- Lamivudine – 100 mg/d
- Adefovir – 10 mg/d

Mechanism of action of Interferon

- Antiviral
- Anti proliferative
- Immunomodulatory

Mechanism of action of Nucleoside/ tide Analogue (NUC)

- Inhibit priming of reverse transcriptase
- Inhibit viral minus strand DNA synthesis (RNA dependent DNA polymerase activity)
- Inhibit viral plus stand DNA synthesis (DNA dependent DNA polymerase activity)

Preferred 1st line drugs

- Pegylated Interferon alfa 2a/2b
- Tenofovir
- Entecavir

Interferon Therapy

- Advantages
  - No resistance so far
  - Durable off-treatment response
  - Higher rate of HBsAg clearance
    (11-12% in 4 yrs) → Closest to cure
  - Finite duration of course (6-12 months)

Interferon Therapy

Disadvantages:

- High initial cost
- Parenteral administration
- Increased side effects
- Contraindicated in the decompensated disease
- Response varies according to genotype

  (genotype A & B > C & D)

Response to Interferon alfa 2a therapy

- 33% HBeAg seroconversion (control – 12%)
- 20-40% response in relapsed cases
- Seroconversion is sustained in 80%-90% cases after 4-8 yrs follow up
- Delayed clearance of HBsAg – 12% - 65% within 5 yrs of HBeAg loss

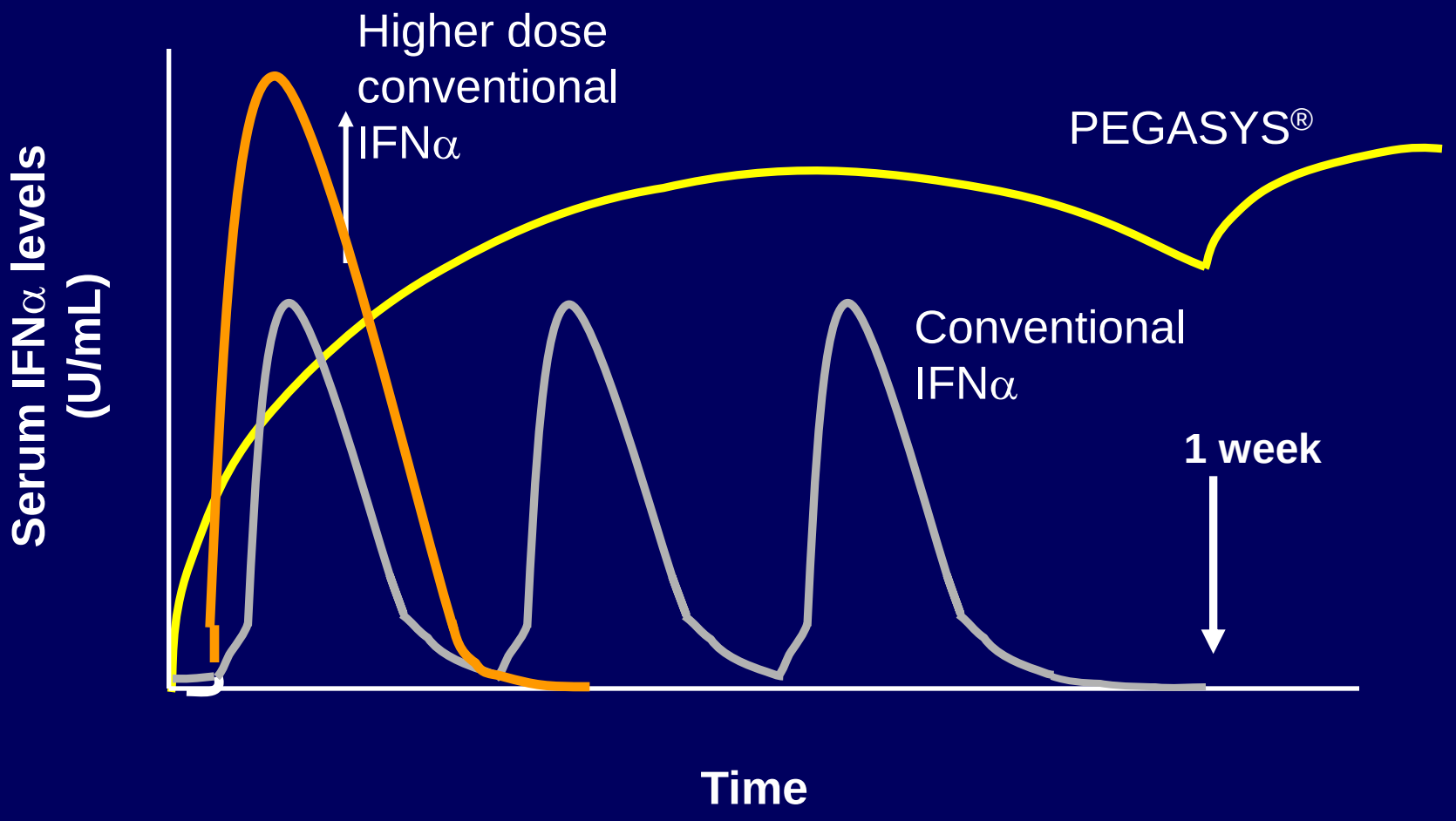
Ref: Piravisuth T.Hepatol Int ,2008:doi10.1007/s12072-008-9046-5

Peginterferon (alfa 2a/2b)

- Higher seroconversion than standard interferon (33% vs 25% ; $p > 0.05$)
- Higher combination response(HBeAg loss,HBV DNA reduction & normal ALT) 24% VS 12%; P=0.036

Ref: CooksleyWG et al. J Viral Hepatol 2003;10:298-305

Optimizing IFNα Pharmacokinetics



Kozlowski et al *BioDrugs* 2001; Perry and Jarvis *Drugs.* 2001; Glue et al *Clin Pharmacol Ther* 2000

Side effects of interferon

- Flu-like symptoms
- Fatigue
- Bone marrow suppression
- Major depression, suicidal tendency
- Hypothyroidism
- Hyperthyroidism
- Mild ALT flare

Nucleoside/Nucleotide Analogue (NUCs)

- Advantages:
  - Oral administration
  - Low initial cost
  - Potent antiviral effect
  - Good tolerance

Nucleoside/Nucleotide Analogue (NUCs)

- Disadvantages:
  - Duration of therapy indefinite - ? life long
  - Resistance rate is high except newer drugs like Entecavir & Tenofovir
  - Relapse rate is high after stopping
  - Lower rate of HBeAg & HBsAg seroconversion

Response to treatment at 1 yr in HBeAg positive patient

Drugs	HBeAg seroconverson (%)
• PEG-IFN	30
• Lamivudine	22
• Adefovir	12
• Entecavir	21
• Telbivudine	23
• Tenofovir	21

Response to treatment at 1 yr in HBeAg positive patient

Drugs	Undetectable HBV DNA (%)
• PEG-IFN	25
• Lamivudine	39
• Adefovir	21
• Entecavir	67
• Telbivudine	60
• Tenofovir	74

Response to treatment at 1 yr in HBeAg positive patient

Drugs	Normalisation of ALT (%)
• PEG-IFN	39
• Lamivudine	66
• Adefovir	48
• Entecavir	68
• Telbivudine	77
• Tenofovir	69

Response to treatment at 1 yr in HBeAg negative patient

Drugs	Normalisation of ALT (%)
• PEG-IFN	38
• Lamivudine	74
• Adefovir	72
• Entecavir	78
• Telbivudine	74
• Tenofovir	77

Response to treatment at 1 yr in HBeAg negative patient

Drugs	Undetectable HBV DNA (%)
• PEG-IFN	63
• Lamivudine	72
• Adefovir	51
• Entecavir	90
• Telbivudine	88
• Tenofovir	91

Lamivudine

- L-Nucleoside analogue
- Potent inhibitor of reverse transcriptase
- HBeAg seroconversion:
  - 1 year - 18%
  - 2 year - 26%
  - 3 year - 40%
  - 5 year - 35%-65%

Leung N. Hepatol Int 2008

Lamivudine (contd..)

- Combination therapy using lamivudine with adefovir, telbivudine and IFN has no significant efficacy advantage

Leung N. Hepatol Int 2008

Lamivudine (contd..)

- Undetectable HBV DNA :

Years	HBeAg +ve	HBeAg -ve
1	36%	72%
2	39%	57%
3	20%	40%

Leung N. Hepatol Int 2008

Lamivudine Resistance

Year	%
1	23
2	46
3	55
4	71
5	65

Leung N. Hepatol Int 2008

Side effects of Lamivudine

- Very safe & well tolerated
- Mild rise of ALT may occur

Adefovir Dipivoxil

- Acyclic adenine nucleotide analogue
- Potent inhibitor of HBV reverse transcriptase

Adefovir Dipivoxil

- HBeAg Seroconversion :

Years	HBeAg +ve
1	12%
2	29%
3	40%

Leung N. Hepatol Int 2008

Adefovir Dipivoxil (HBeAg -ve CHB)

- ALT Normalisation - 69%
- Undetectable HBV DNA (<200 IU/ml) - 67%
- Improvement in necroinflammation - 83%
- Regression of Fibrosis - 73%

Hadziyannis SJ et al. Gastroenterology 2006

Adefovir Dipivoxil

- There was reversible increase in serum creatinine of > 0.5 mg/dl (Maximum 1.5 mg/dl) reported in 3% of patients when therapy was extended to 5 years.

Hadziyannis SJ et al. Gastroenterology 2006

Adefovir Dipivoxil

- Adefovir resistance:

Year	%
1	0
2	3
3	11
4	18
5	29

Lampertico P et al. Gastroenterology 2006

Side effects of Adefovir

- Nephrotoxicity – 3% after 4 - 5 yrs

Serum creatinine should be tested every 3 months

Entecavir

- Cyclopentyl gunaosine analogue
- Potent selective inhibition of priming, DNA dependent DNA synthesis and RNA dependent DNA synthesis (reverse transcription) function of the HBV polymerase
- It is superior to Lamivudine in reducing in HBV DNA & lack of resistance

Entecavir

- HBeAg seroconversion

Year	%
1	21
2	31

Chang TT et al. NEJM 2006

Entecavir

- Undetectable DNA:

Year	HBeAg +ve	HBeAg -ve
1	67%	90%
2	80%	NA
3	89%	NA

Chang TT et al. NEJM 2006

Entecavir Resistance

Year	Resistance (%)
1	0.2
2	0.5
3	1.2
4	1.2
5	1.2

Side effects of Entecavir

- Safety profile is similar to Lamivudine

Telbivudine

- L-nucleoside analogue
- Potent & specific anti HBV activity
- It is more potent than Lamivudine & Adefovir

Telbivudine

HBeAg Seroconversion:

Year	%
1	23
2	30

Lai CL et al. N Engl J Med 2007

Telbivudine

Undetectable DNA:

Year	HBeAg +ve	HBeAg -ve
1	60%	88%
2	56%	82%

Lai CL et al. N Engl J Med 2007

Telbivudine Resistance

Year	%
1	4
2	17

Side effects of Telbuvudine

- Myopathy
- Peripheral neuropathy

Peripheral neuropathy is more common when combined with pegIFN

Tenofovir

- Acyclic adenine nucleotide analogue
- It has strong and early suppression of HBV including Lamivudine resistant mutants
- It is more potent than Adefovir

Response to Tenofovir at 1 yr (%)

Characteristics	Tenofovir	vs Adefovir
HBV DNA loss	76	13
ALT normalisation	68	54
HBe seroconversion	21	12
HBsAg	3	0

Tenofovir Resistance

- No resistance detected so far in 5 yrs

Side effects of Tenofovir

- Renal impairment
- Osteomalacia
- Deceased bone density
- Fanconi syndrome

Treatment of Chronic Hepatitis B in special groups

Pregnancy:

- Telbivudine & Tenofovir are category B drugs
- Lamivudine, Adefovir & Entecavir are category C drugs
- IFN based therapy is contraindicated
- Who are already on therapy can continue treatment with cat B drugs
- Cat B – no risk in animal studies but unknown in human
- Cat C – Teratogenic in animal but unknown in human
- No firm recommendation can be made on the use of nucleoside (tide) analogue in prevention of transmission from viraemic mother

Pediatric Patient

- IFN – 6 MU/m^2 thrice weekly
- Lamivudine – 3 mg/kg/d
- Adefovir – 0.3 mg/kg/d in age 2 – 10 yrs .
  - 10 mg/d in age >11 yrs.
- PegiIFN and newer Nucleoside /tide analogue are not recommended till now.
- Long term safety and drug resistance are more important.

Patients with Renal failure

- All antivirals can be used with dose modification
- All NUCs can be used with in renal transplant cases
- Entecavir is preferred

Co-infection with HCV

- Higher incidence of cirrhosis, HCC and mortality in co-infection with HCV,HDV & HIV virus.
- Dominant virus should be identified and treated.
- If HBV dominant, treatment of HBV should be aimed.
- If HCV is dominant, IFN + Ribavirin can achieve SVR similar to monoinfection with HCV.

Co-infection with HDV

- Inj. IFN 9 MU TIW for 12 months
- PegIFN 180 microgram/ wk for 12 months
- Lamivudine is ineffective

Co-infection with HIV

- If CD4 count > 500 cells/µl & HIV infection does not require treatment , IFN, Adefovir, Telbivudine montherapy is the treatment of choice
- If HIV infection requires treatment , Tenofovir or Lamivudine/ Tenofovir combination should be included in HAART
- IFN is preferred because of absence of resistance .
- Both Lamivudine and Tenofovir are active against HBV & HIV
- If CD4 count is < 500 cells/cmm and liver disease is active, HBV should be treated first.

Decompensated Liver Disease

- IFN – contraindicated
- Treatment should be started as early as possible
- Lamivudine, Entecavir, Telbivudine and Tenofovir are effective.

Patient on immunosuppressive drugs or chemotherapy

- Reactivation and / decompensation occur in 20 – 50% cases.
- **Lamivudine & Entecavir are effective.**
- Prophylactic use of lamivudine should be started 1 wk before start of chemotherapy and continued at least 12 wks after the end of chemotherapy.

Patient With Acute Severe Hepatitis

- > 95-99% of adult with severe HBV infection will recover spontaneously
- Lamivudine, Entecavir or Tenofovir may be used
- Duration- at least 3 months after seroconversion to anti HBS or 6 months after HBe seroconversion without HBsAg loss

Liver Transplantation

- Liver transplantation has become a cost – effective treatment of liver failure and HCC with excellent 5 – yr survival.
- Lamivudine, entacavir and adefovir can be used before transplantation.
- Combination of lamivudine + low dose I.M. HB1g prophylaxis (400-800 U daily for 1 wk, then monthly reduces recurrence rate of HBV to < 5%.
- 5-yr patient survival - 85%
- 5-yr graft survival – 80%.

Treatment of resistant HBV

- Patients failed to respond to IFN alfa may be treated with NUCs
- In case of primary nonresponse therapy should be changed to more potent antiviral like- Entecavir or Tenofovir at wk 12
- In partial virological response at wk 24, change to a more potent drug or add nucleoside analogue to nucleotide analogue & vice versa

- In patients receiving Entecavir or Tenofovir with a partial virological response at wk 48 may be added the other drug but long term safety of combination of Entecavir & Tenofovir in unkown

- In case of viral breakthrough rescue therapy by adding- on a second drug without having coss-resistance

Treatment options after NA failure

Resistance to	**Treatment options**
Entecavir	Add adefovir or Add tenfovir
Telbivudine	Add adefovir or Add tenofovir

Rapti I et al Hepatology 2007

Lampertico P et al Hepatology 2006

Treatment options after NA failure

Resistance to	**Treatment options**
Lamivudine	Add adefovir or Add tenofovir Or Switch to entecavir 1 mg/d
Adefovir	Add Lamivudine or Add Entecavir or Switch to entecavir or Switch to tenofovir + emtricitabine

Switching to IFN based therapy is an option

Duration of Treatment

- For Interferon
  - 6 months for HBeAg positive patients
  - 12 months for HBeAg negative patients

Duration of Treatment

For NUCs :

- In HBeAg positive patients:

  - Treatment can be stopped when HBeAg Seroconvertion with undetectable HBV-DNA has been documented on two separate occasions at least 6 months apart

Duration of Treatment

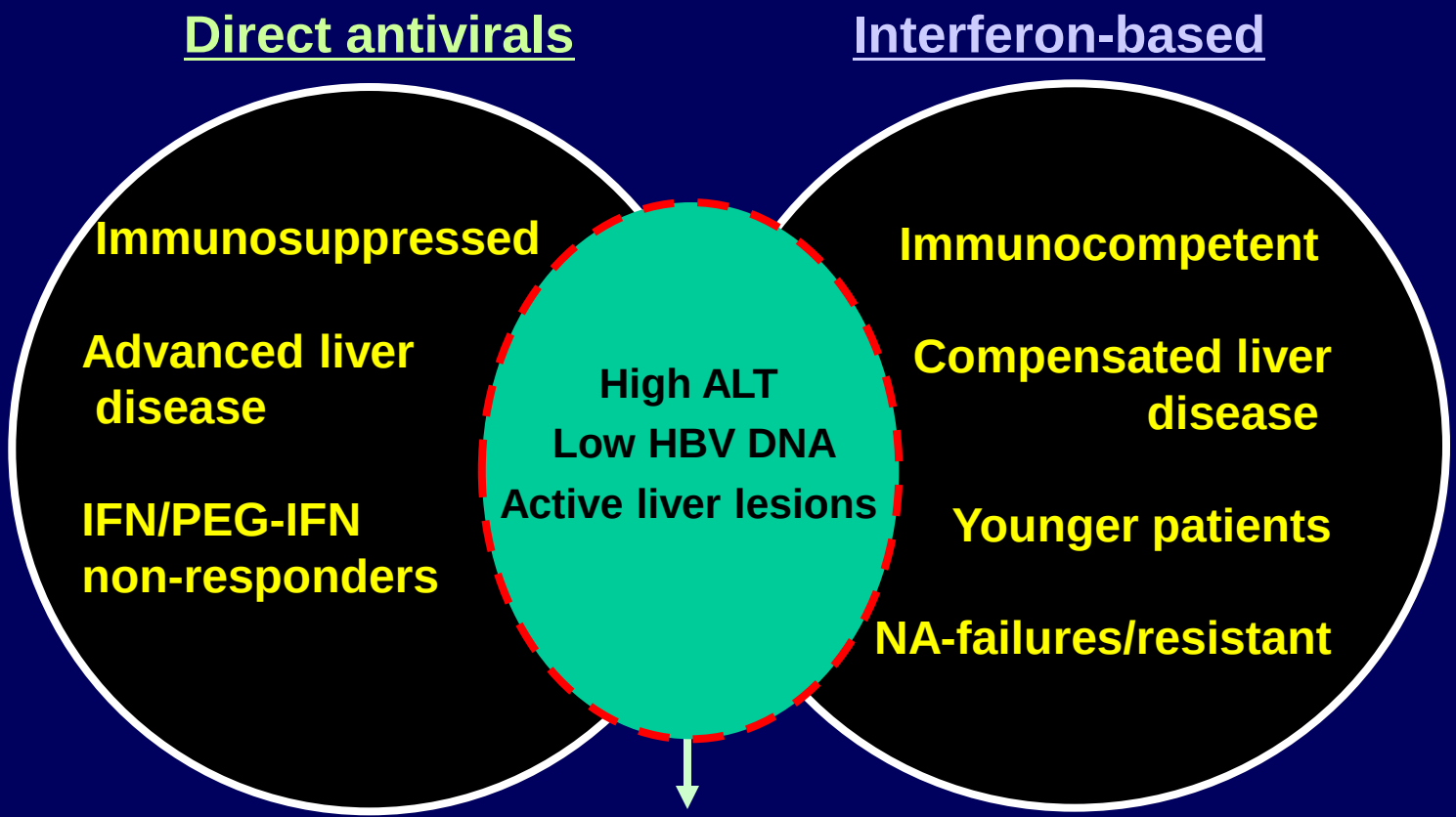
- In HBeAg negative patient:

  - It is not clear how long treatment should be continued but treatment discontinuation can be considered if undetectable HBV DNA has been documented on three separate occasions 6 months apart

Patient monitoring & follow-up

- Every 3- 6 monthly
- ALT, PT, HBeAg, Anti HBe, HBV DNA, USG to be done at each visit

Who should be treated with what?



NA treatment should not be prescribed until the PATIENT understands that they CANNOT be stopped abruptly for any reason

Conclusions

- IFN, Entecavir & Tenofovir are 1st line drugs
- NUCs have good antiviral effect but cannot eleminate HBsAg & cccDNA
- NUCs have high resistance rate except Entecavir & Tenofovir
- IFN – based treatment has no resistance & higher HBsAg clearance rate but costly

Conclusions

- All drugs are safe & effective & can reduce the progression of disease and even prevent or delay cirrhosis & HCC
- But none are suitable to eradicate the disease
- We are looking for new drugs


THANK YOU