الجامعة السورية الخاصة
SYRIAN PRIVATE UNIVERSITY

Dr. Nazir Ibrahim

MRCP, Hepatology & Gastroenterology
Associate professor

www.spu.edu.sy

CHB 2020

Transmission and disease
Transmission

- Among adolescents and adults major routes of infection are :
- sexual transmission by contact with :

semen or vaginal fluid .

- percutaneous transmission through the use of

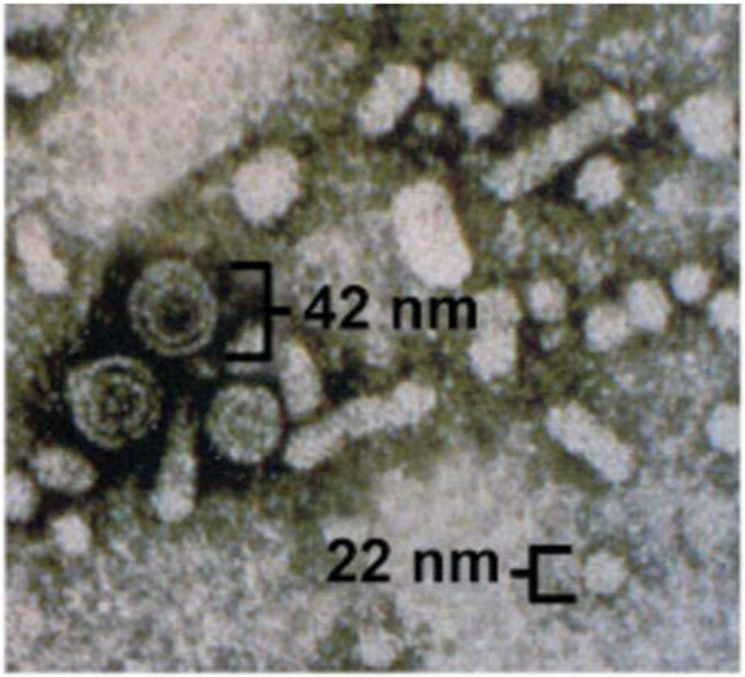
contaminated needles such as injecting drug use.

Pathogen

- HBV is sensitive to detergents and solvents:

which extract lipids from the viral envelope.

- HBV contains 3 important antigens:
- c, e and s .
- The hepatitis B core antigen (HBcAg):
- is present on the assembled capsids which enclose the viral DNA.



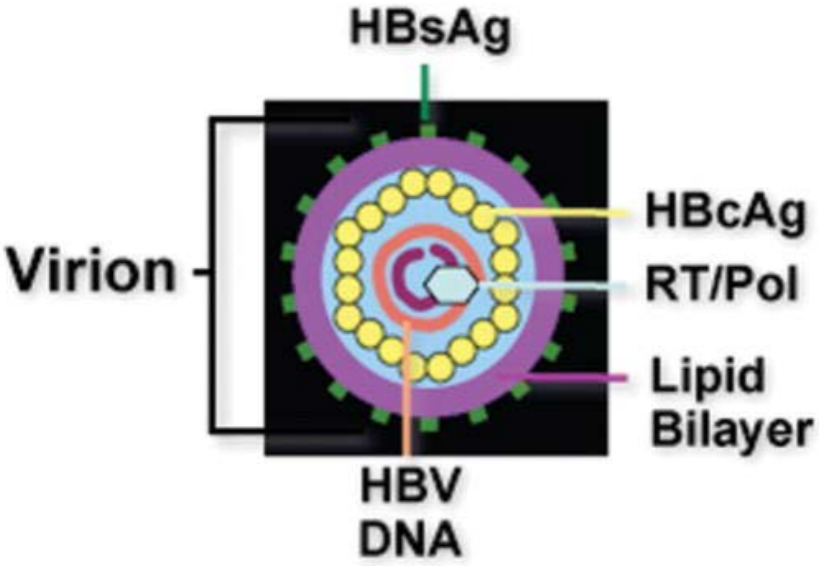
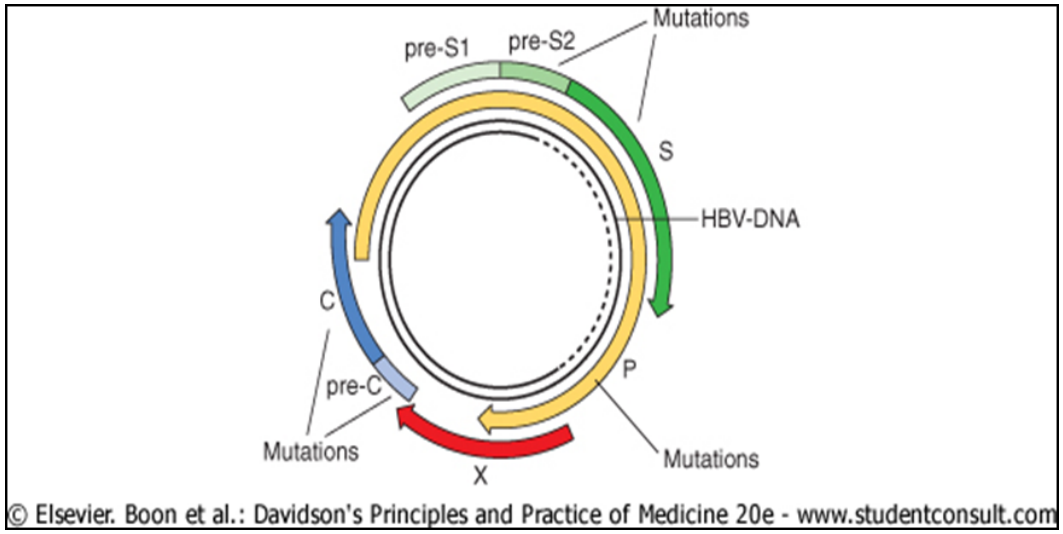


Figure 18.4 *HBV capsid.* Derived from cryo-electron microscopy images of capsids assembled in *E. coli* cells expressing HBV C protein. The bar represents 5 nm. From Watts *et al.* (2002) *The EMBO Journal*, **21**, 876. Reproduced by permission of Nature Publishing Group and the authors.



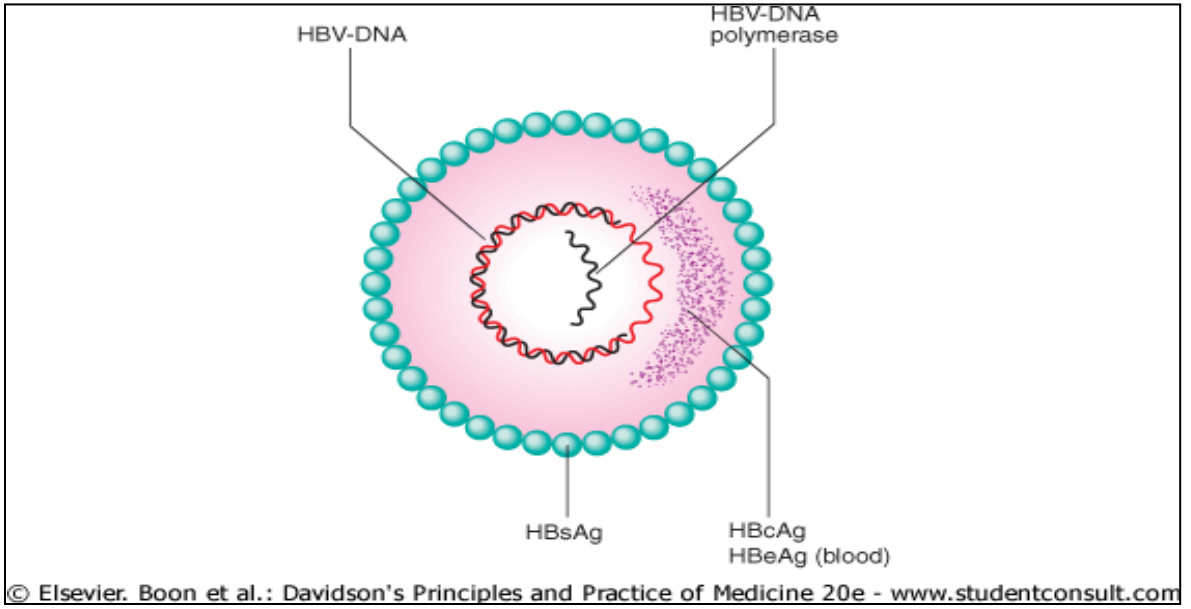


Figure 23.25 Schematic diagram of hepatitis B virus. Hepatitis B surface antigen (HBsAg) is a protein which makes up part of the viral envelope. Hepatitis B core antigen (HBcAg) is a protein which makes up the capsid or core part of the virus (found in the liver but not in blood). Hepatitis B e antigen (HBeAg) is part of the HBcAg which can be found in the blood and indicates infectivity.

Pathogen

- The viral envelope contains the HBsAg which includes 3 proteins :
  - small (SHBs)
  - middle (MHBs)
  - large surface proteins (LHBs)
- SHBs forms smaller non-infectious sub-viral particles

HBsAg

-Appears in the blood late in the incubation period and before the prodromal phase of acute type B hepatitis;

usually lasts for 3-4 weeks and can persist for

up to 5 months

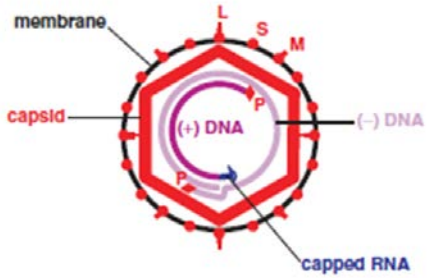


Figure 18.2 *The HBV virion.* S: small envelope protein. M: medium envelope protein. L: large envelope protein. P: polymerase (one molecule is covalently linked to the 5′ end of the (+) DNA; the virion may contain a second molecule of P, as indicated here).

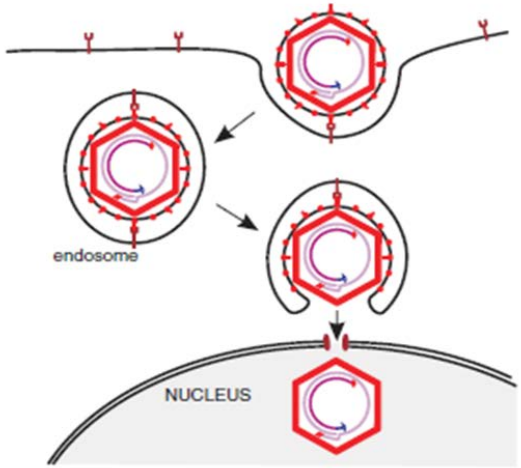


Figure 18.10 *Endocytosis of attached HBV virion followed by release of nucleocapsid and entry into the nucleus.*

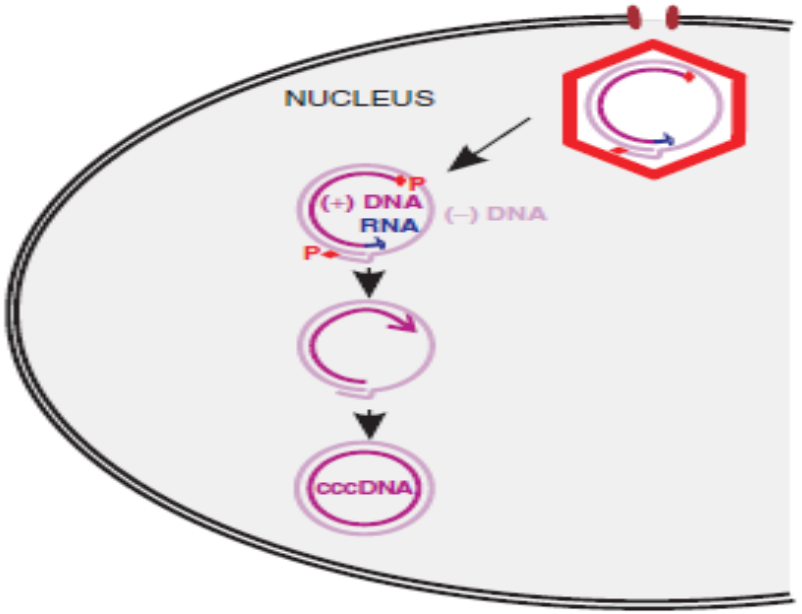
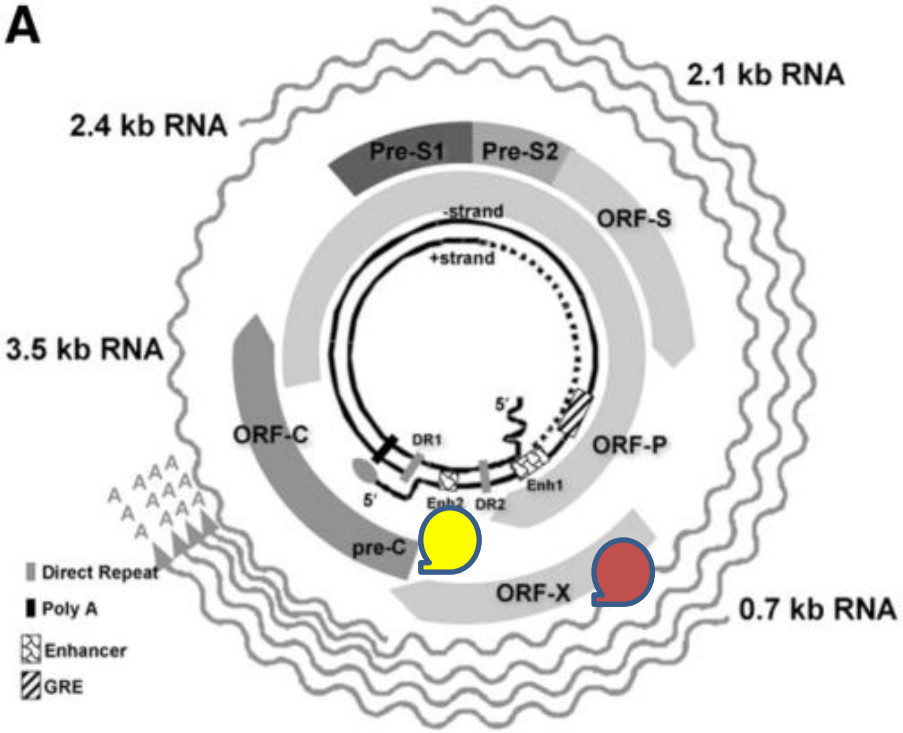
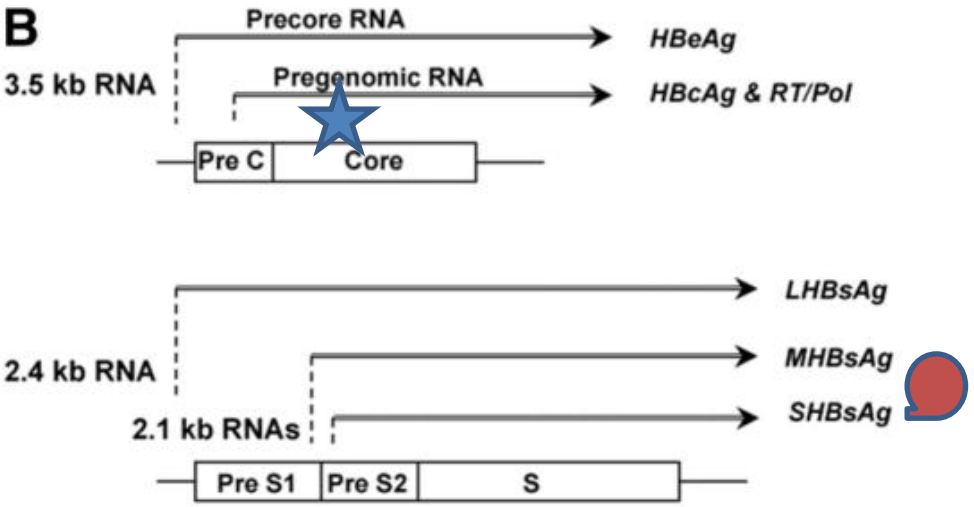


Figure 18.11 *Release of HBV genome from the capsid and conversion into cccDNA.*



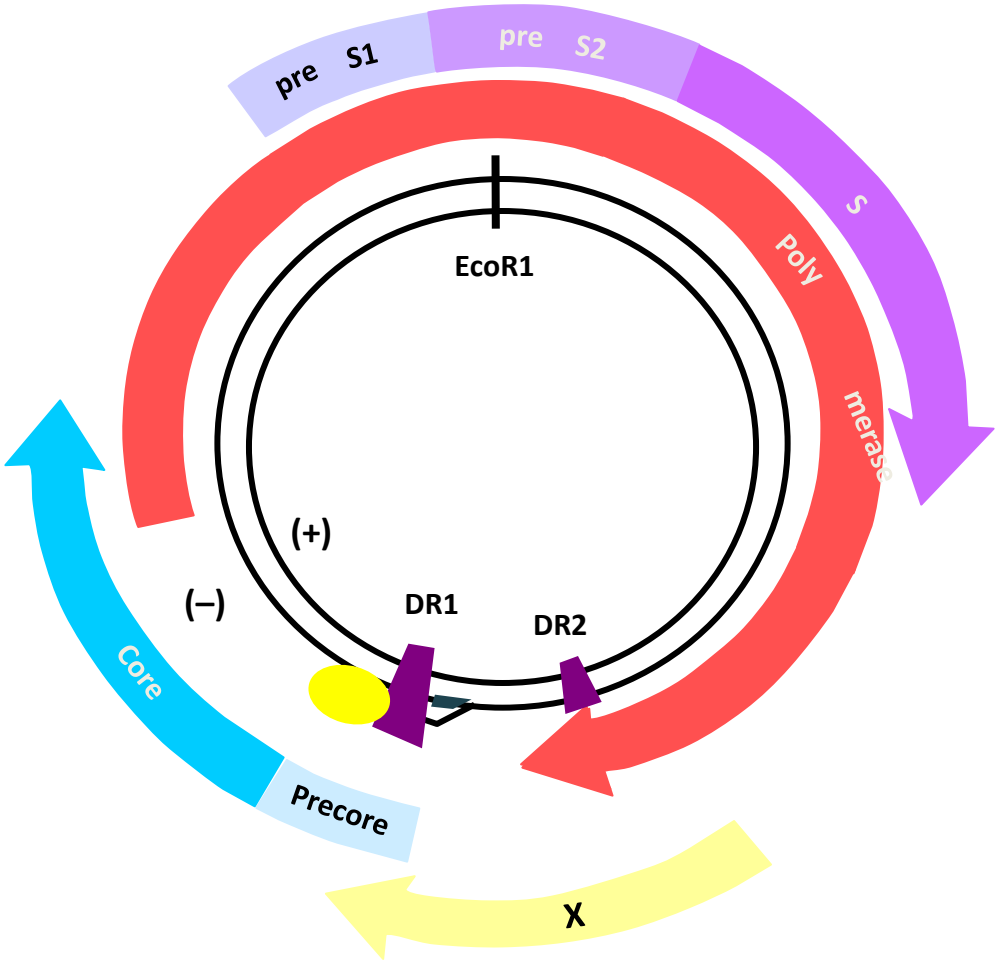
A non-structural protein HBx :

- and may contribute to the oncogenicity of HBV.



Pre C converts the core protein to a secreted protein. This protein does not form capsids or HBcAg but a new antigen specificity named hepatitis e antigen

Hepatitis B Virus Genome



In contrast, in those with low viral replication, HBsAg- and anti-HBe-positive, viral loads are less than 10^5 copies/ml

One exception mutation .

Pathogen

- HBcAg (anti-HBc) :

are readily formed at high titres during the course of infection

but **are not protective.**

SO WHAT

Pathogen

- A non-structural protein HBx :
  - supports the transcription of the viral DNA
  - and may contribute to the oncogenicity of HBV.

HB e

Ab

low viral replication

HBsAg +& anti-Hbe positive

viral loads are **less** than $<10^5$ copies/ml

One exception mutation

Ag

- **active viral replication**
- HBe Ag +ve.
- Viral loads are usually in **excess** of $>10^5$ copies/ml

HB e mutation

- which means

- they cannot secrete e antigen into serum

HB e mutation

Such individuals will be

anti-HBe-positive

but

have a high viral load and often evidence of chronic hepatitis

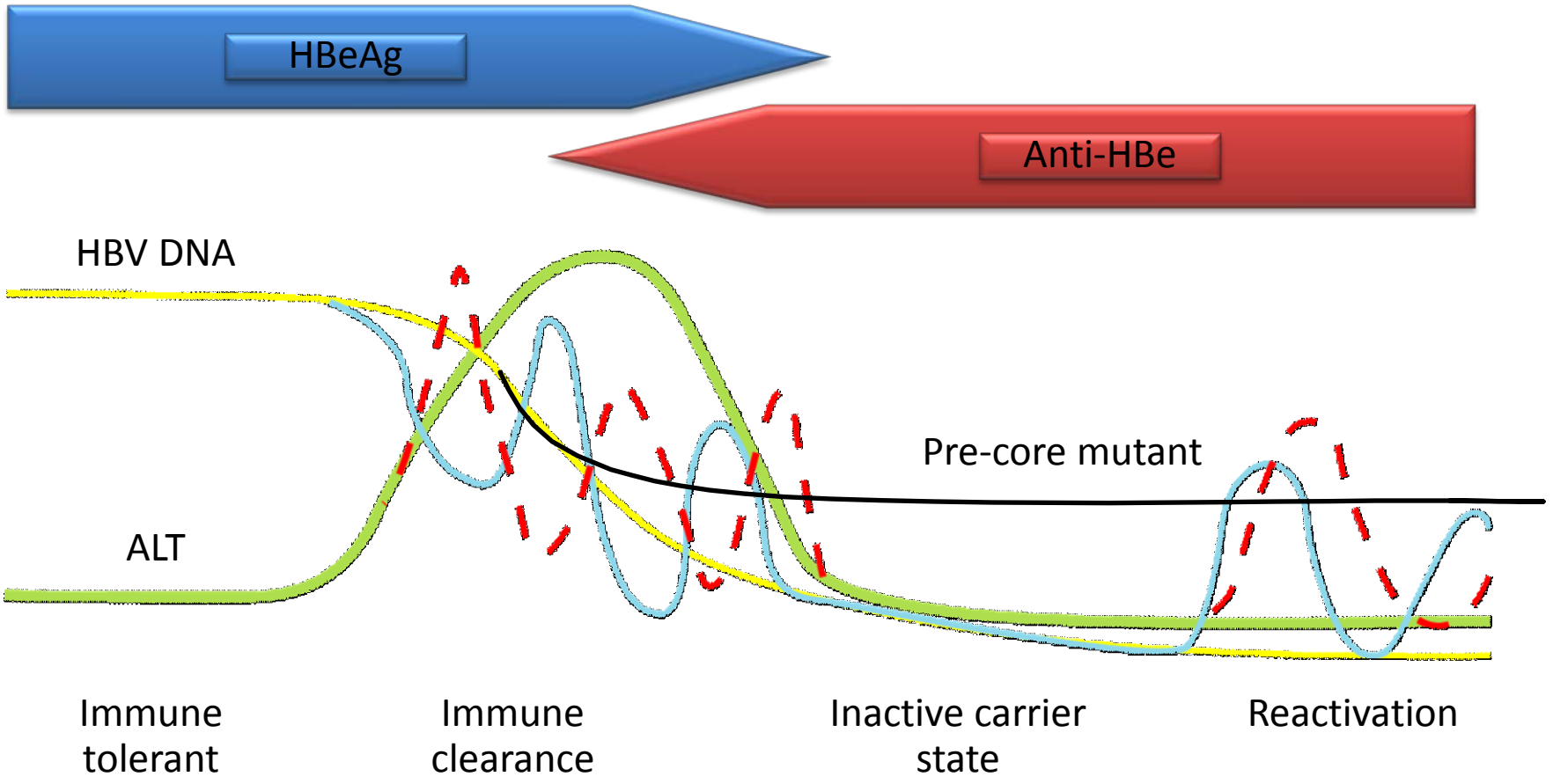
HB e mutation

They respond differently to antiviral drugs from those with classical e antigen-positive chronic hepatitis.

Chronic hepatitis B

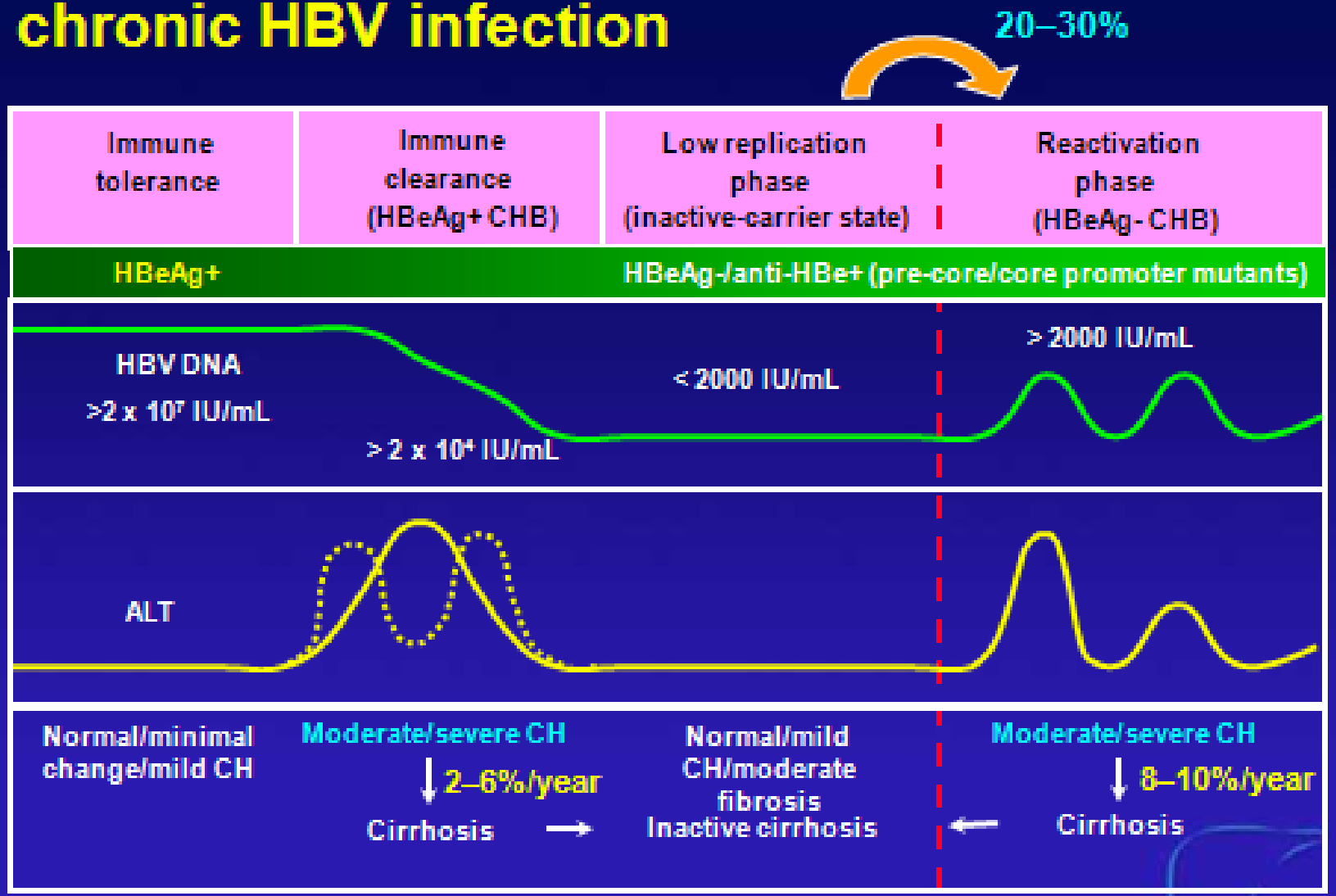
- the presence of detectable HBsAg in the blood or serum for longer than 6 months .

Phases of chronic HBV infection



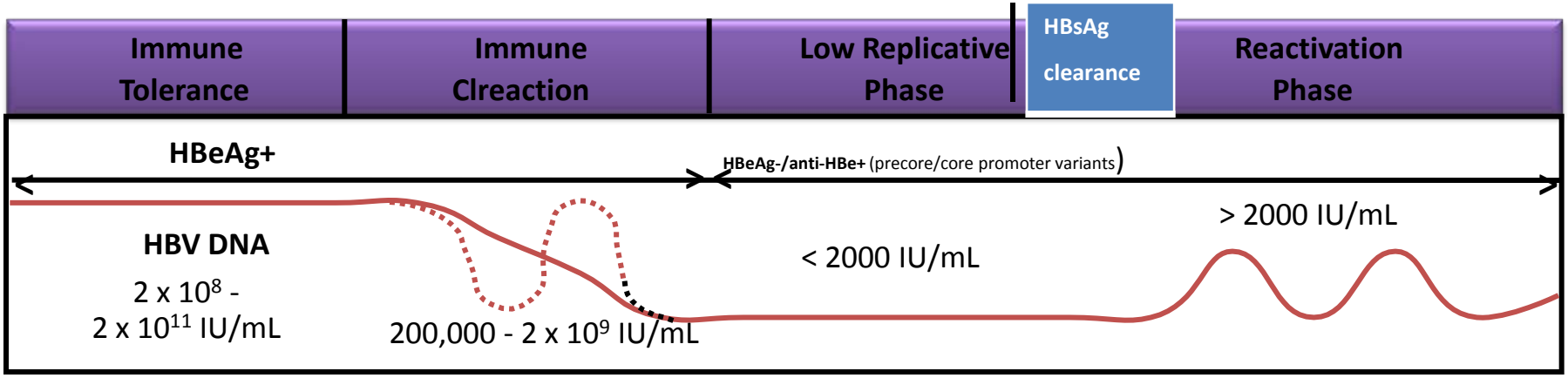
Adapted from Yim JY, Lok ASF. *Hepatology* 2006; 43: S173–81.

Natural history of perinatally acquired chronic HBV infection



Modified from Lok AS *et al. Hepatology* 2007; 45: 507–39; Pungpapong S *et al. Mayo Clin Proc* 2007; 82: 967–75.

Phases of Chronic HBV Infection



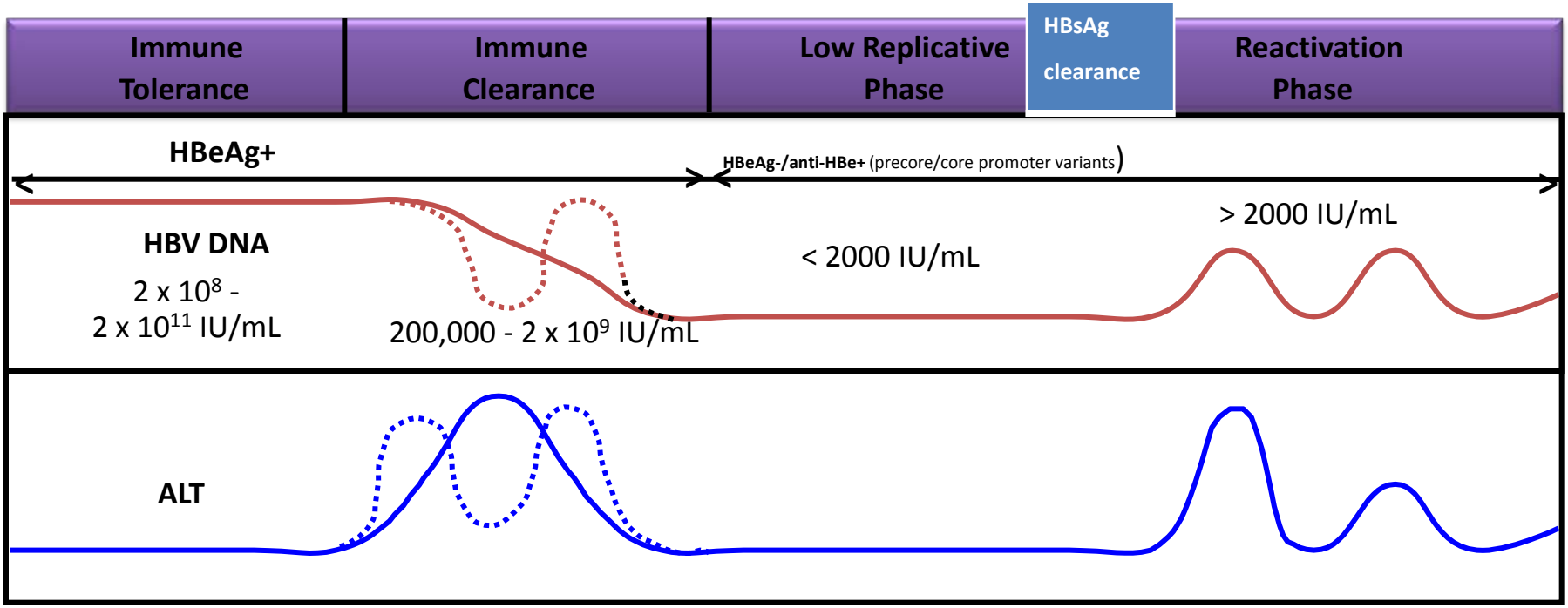
Immune tolerance phase

- In perinatally infected persons

  May persist 10 -30 years

Short lived or absent in childhood or adult-aquired HBV infection

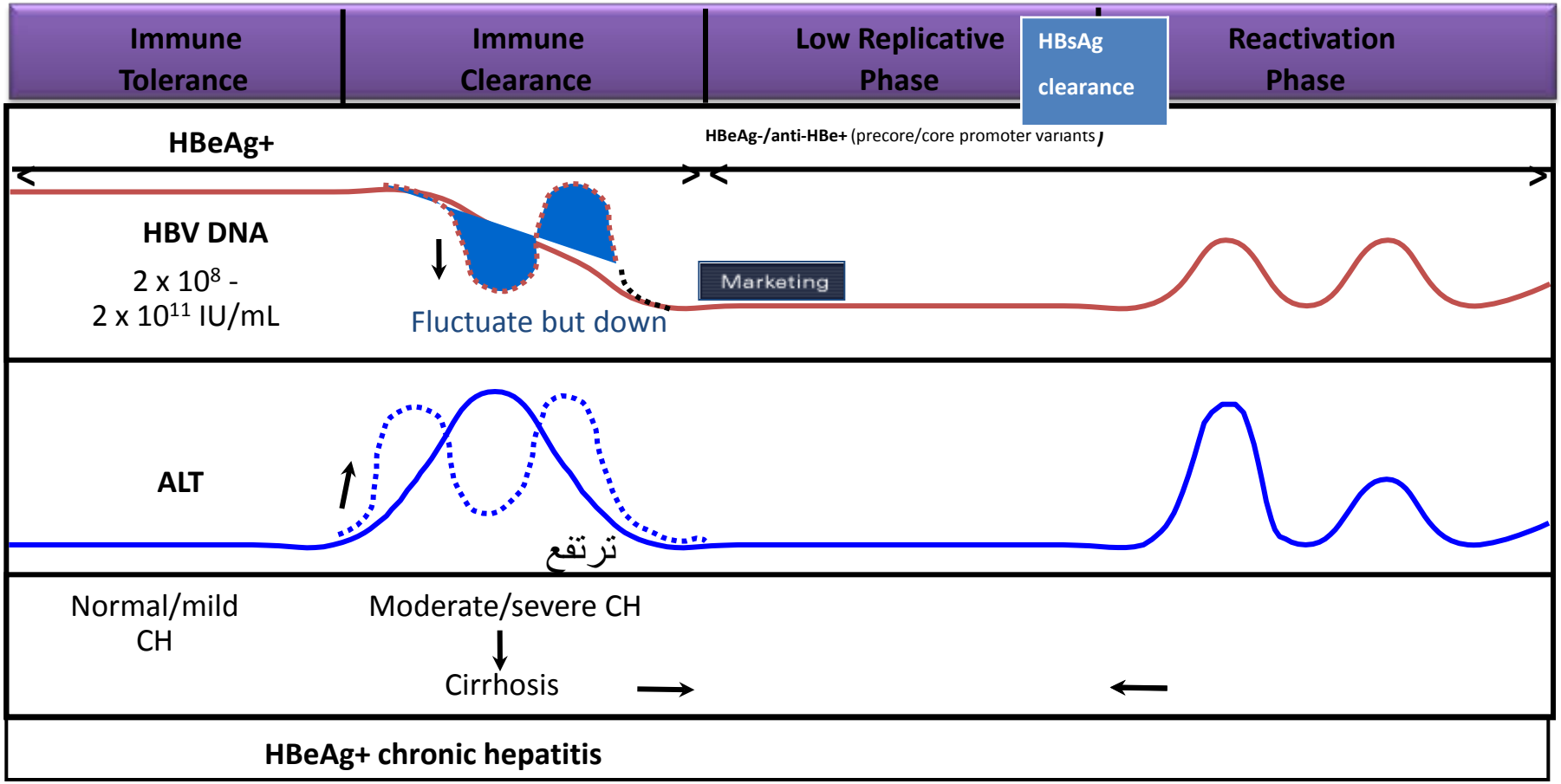
Phases of Chronic HBV Infection



Immune clearance

- Immune system mount an attack on infected hepatocytes

Phases of Chronic HBV Infection



HBeAg-positive chronic HBV infection

previously termed

‘‘immune tolerant’’ phase

These patients are highly contagious due to the high levels of HBV DNA.

a high level of HBV DNA integration and clonal hepatocyte expansion suggesting that hepatocarcinogenesis could be already underway in this early phase of the infection.[1,1]

Phase 3: HBeAg-negative chronic HBV infection

previously termed ‘inactive carrier’ phase

is characterised by the presence of serum antibodies to HBeAg (anti-HBe), undetectable or low (\2,000 IU/ml) HBV DNA levels and normal ALT according to traditional cut-off values (ULN 40 IU/L).

Phase 5: HBsAg-negative phase

This phase is also known as ‘‘occult HBV infection

is characterised by serum negative HBsAg and positive antibodies to HBcAg (anti-HBc), with or without detectable antibodies to HBsAg (anti-HBs).”

Inactive carrier

- 15 -24 % develop HBeAg chronic disease
- 1-17 %sustained reversion back to HBeAg positivity

Immune Reaction (clearance)

- Immune system mount an attack on infected hepatocytes

Liver biopsy

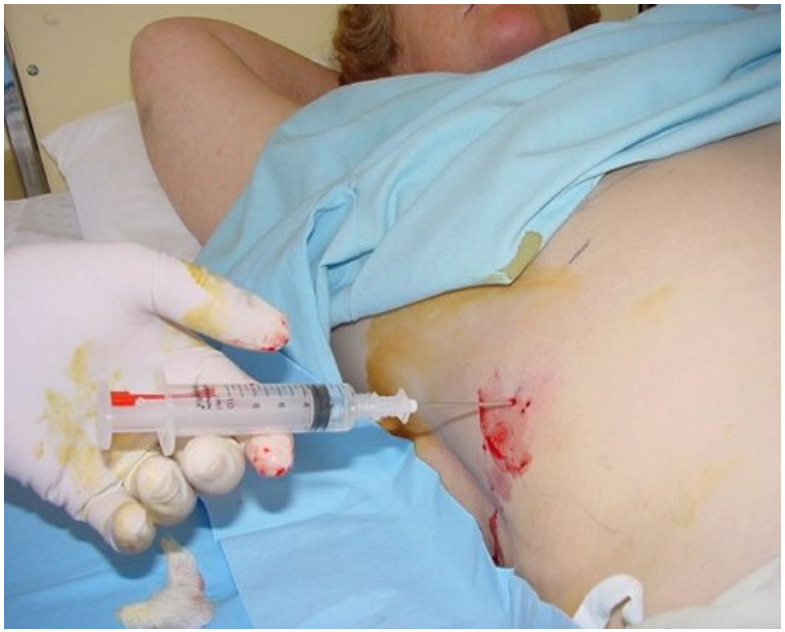
Why?

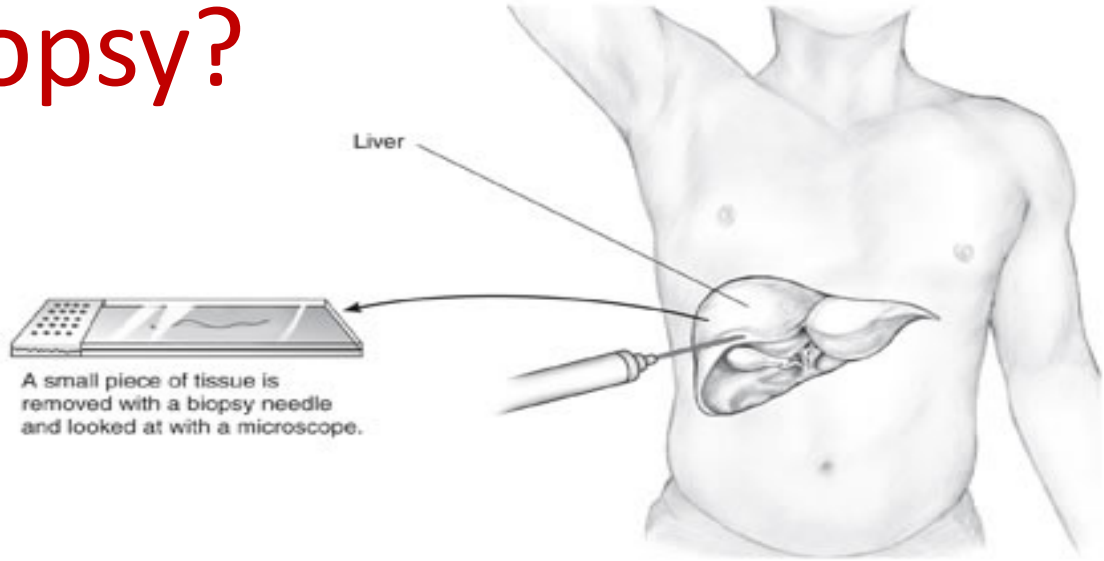
- a liver biopsy is often required to stage the degree of liver damage.

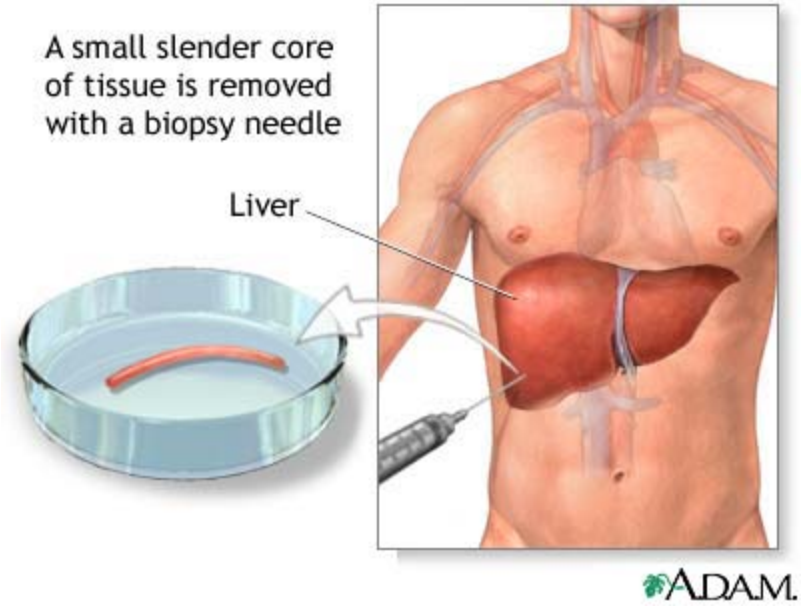
Scoring system

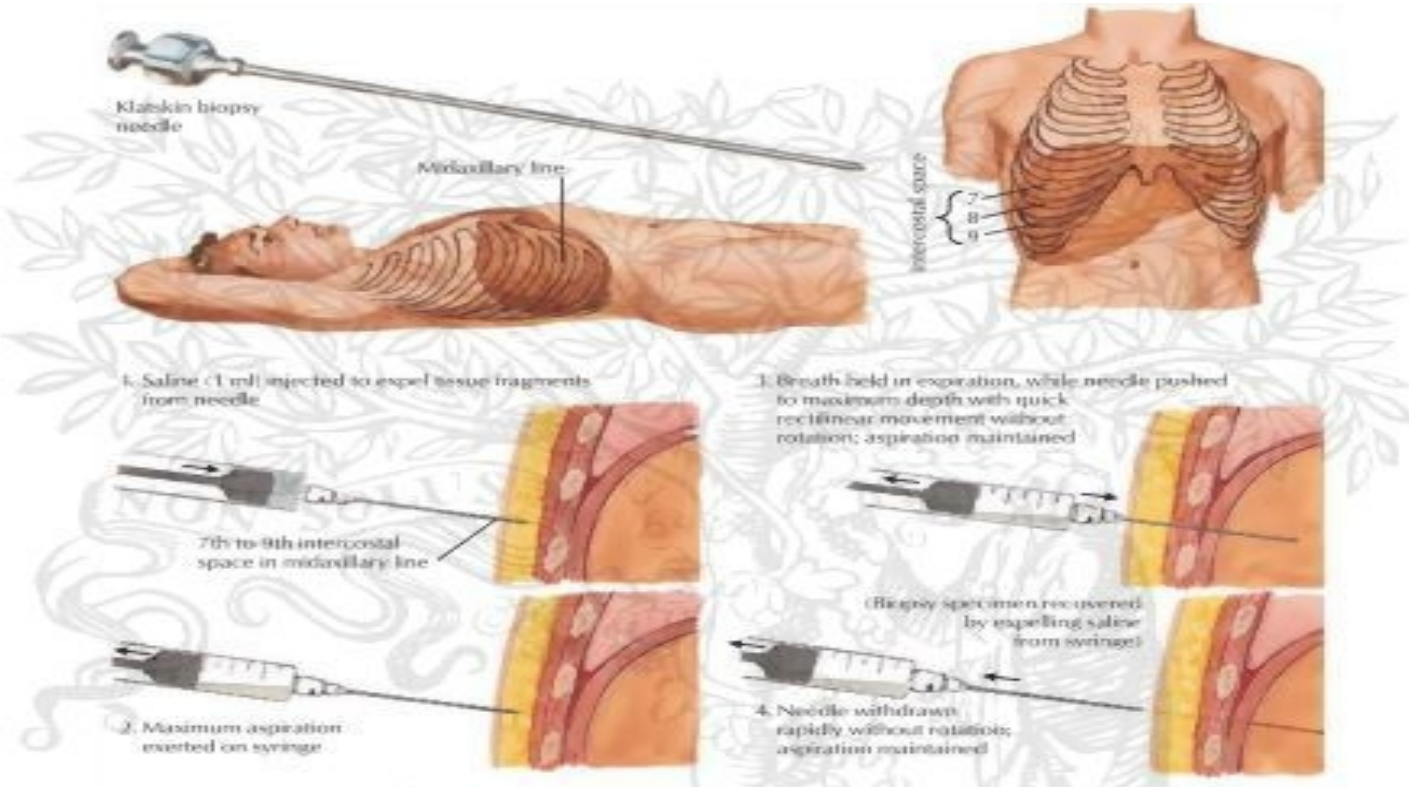
- The most common scoring system used is the Metavir system,
- which scores fibrosis from 1 to 4, the
- latter equating to cirrhosis

What is a Liver Biopsy?

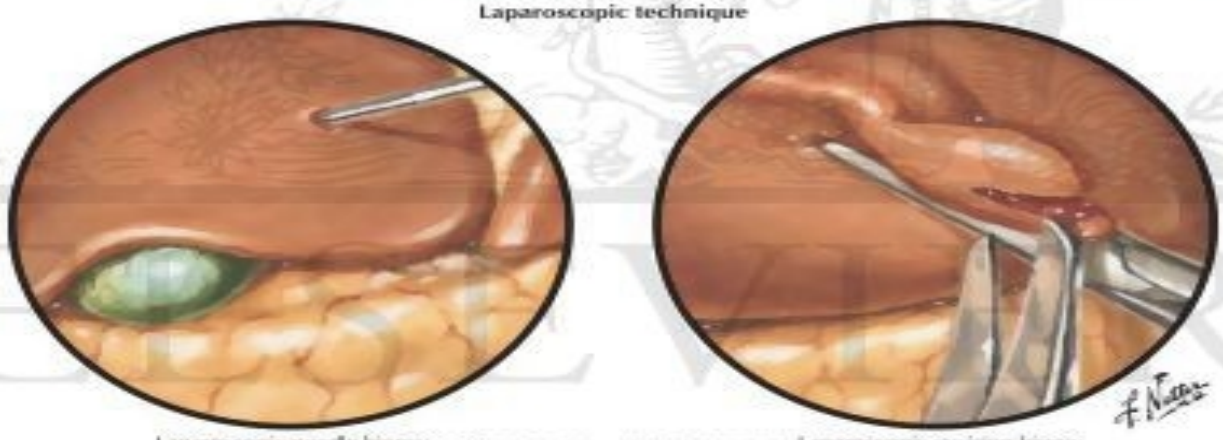








Laparoscopic technique



Laparoscopic needle biopsy

Laparoscopic excision biopsy

Vaccines

- since 1982 :
- Safe and effective vaccines against hepatitis B have been available
- The active substance in the hepatitis B vaccine is :
- the viral surface protein HBsAg

- Additionally a combined hepatitis B
- and hepatitis A vaccine is also available

HCV -Health acre workers /Syria

• SPU 2016	0.0	small
• WHO 2016	0.8	1990
• Othman, Monem 2001	3.0	small

Vaccines/ recombinant

- in 1986 :Recombinant vaccines they contain SHBs
- The recombinant HBsAg particles differ from natural particles in :

lacking : 1-pre S domain of HBsAg

- 2-Glycosylation due to their production in yeast.

Vaccines

- Target groups also include :
  - health-care workers
  - patients with renal failure
  - patients with non-HBV chronic liver disease

Vaccines

Vaccine	Adults	paediatric	immunocompromised & dialysis
standard dose 10 –20 µg	X 1 10 –20	½ of adult dose (5-10 µg)	**x2 adult** (40 µg dose)

Vaccines

- there is no international standard for vaccine potency

due to the diversity in the reactivity of vaccines

- produced by :
  - different manufacturing techniques
  - differences in the adjuvants used for the formulation

Administration, manufacturers stipulated schedules

- Administration into the **gluteal muscle is not recommended**

  has been associated with :

1- decreased concentrations of protective antibody

2-injury to the sciatic nerve.

Administration, manufacturers stipulated schedules and storage

- dose followed by either 2 doses

of monovalent or hepatitis B-containing combination vaccine

- administered during the same visits as the first and third doses of DTP-containing vaccines.
- 4 doses of hepatitis B vaccine may be given for programmatic reasons

Administration, manufacturers stipulated schedules

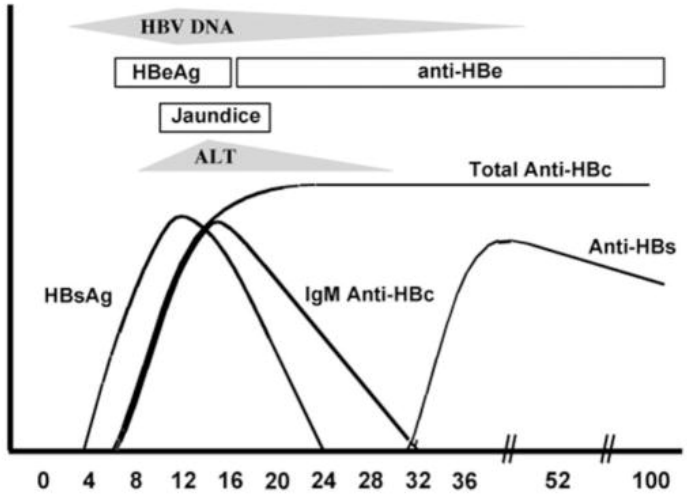
- Among infants or adults randomized to

receive vaccine stored in or outside the cold chain

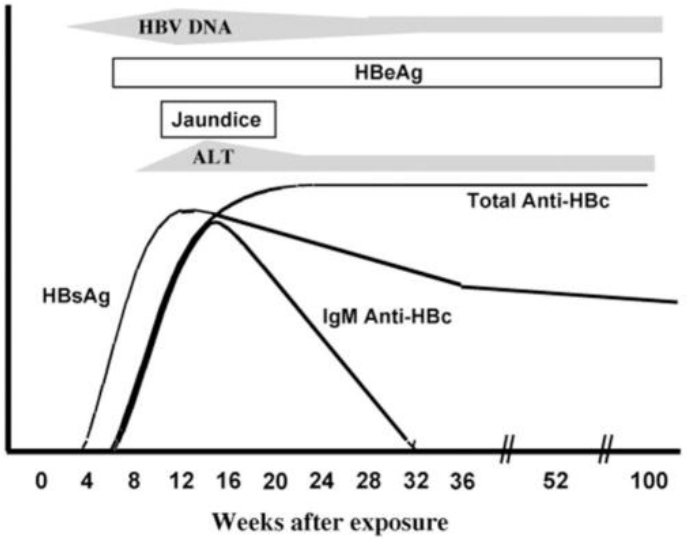
no difference was found in

- anti-HBs antibody
- the proportions achieving anti-HBs seroprotection

A Acute Hepatitis B



B Chronic Hepatitis B



Vaccine immunogenicity, efficacy and effectiveness

- The protective efficacy of hepatitis B vaccine depends on :

➢ the presence of :

IgG antibodies to HBsAg (anti-HBs) after completion of vaccination.

- A primary 3-dose series induces

protective antibody concentrations in >95% of healthy infants

Duration of protection

- It was estimated that approximately 90% of vaccinees protected
- at least 30 years
- (Irrespective of the presence or absence of measurable anti-HBV anti body)
- among a group had not received booster dose anti-HBV antibody titers >10 mIU\ml at 30 years.

Duration of protection

- it was concluded that individuals adequately vaccinated in

3-dose or 4-dose schedule do not require a booster dose.

Duration of protection

- since 2002
- A review examined studies on the need for booster doses against hepatitis B published
- it was concluded that booster do are not necessary in immunologically competent persons
- who had received a full primary course,
- up to 20 years after the primary vaccination.

Pre-vaccination and post-vaccination testing

- Immunocompromised people should be tested annually to

Assess anti-HBs concentration

- Those found to have :

anti-HBs concentration < 10 mlU/ml

- After the primary vaccination series should be revaccinated

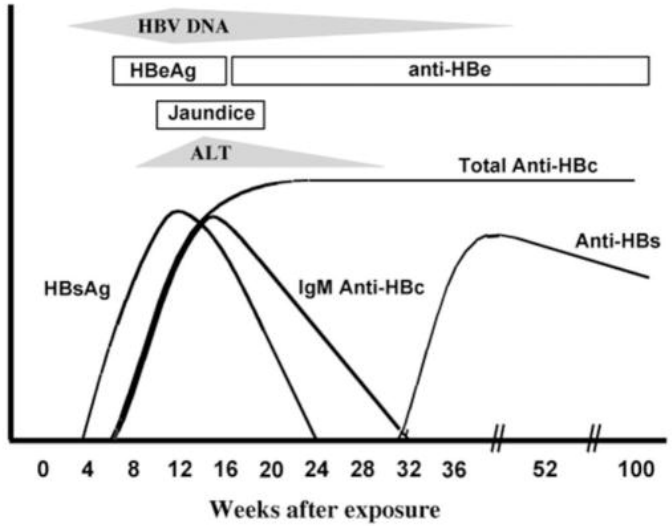
Post-exposure prophylaxis and passive immunization

- As a rule, HBIG should be used as an adjunct to hepatitis B vaccine .

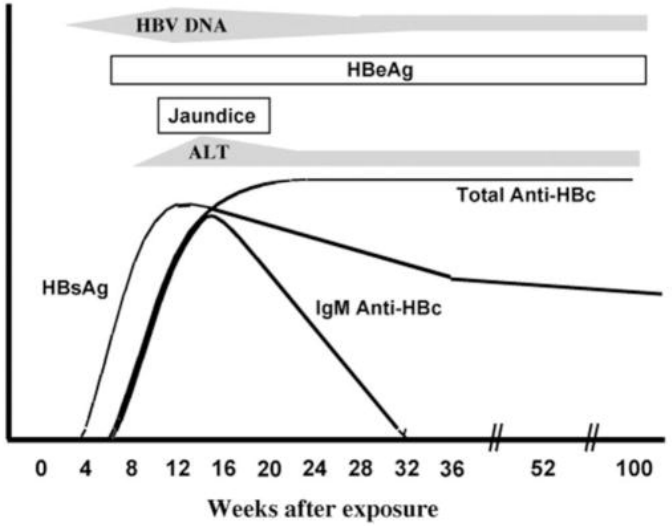
Hepatitis B Virus Serological and Virological Markers

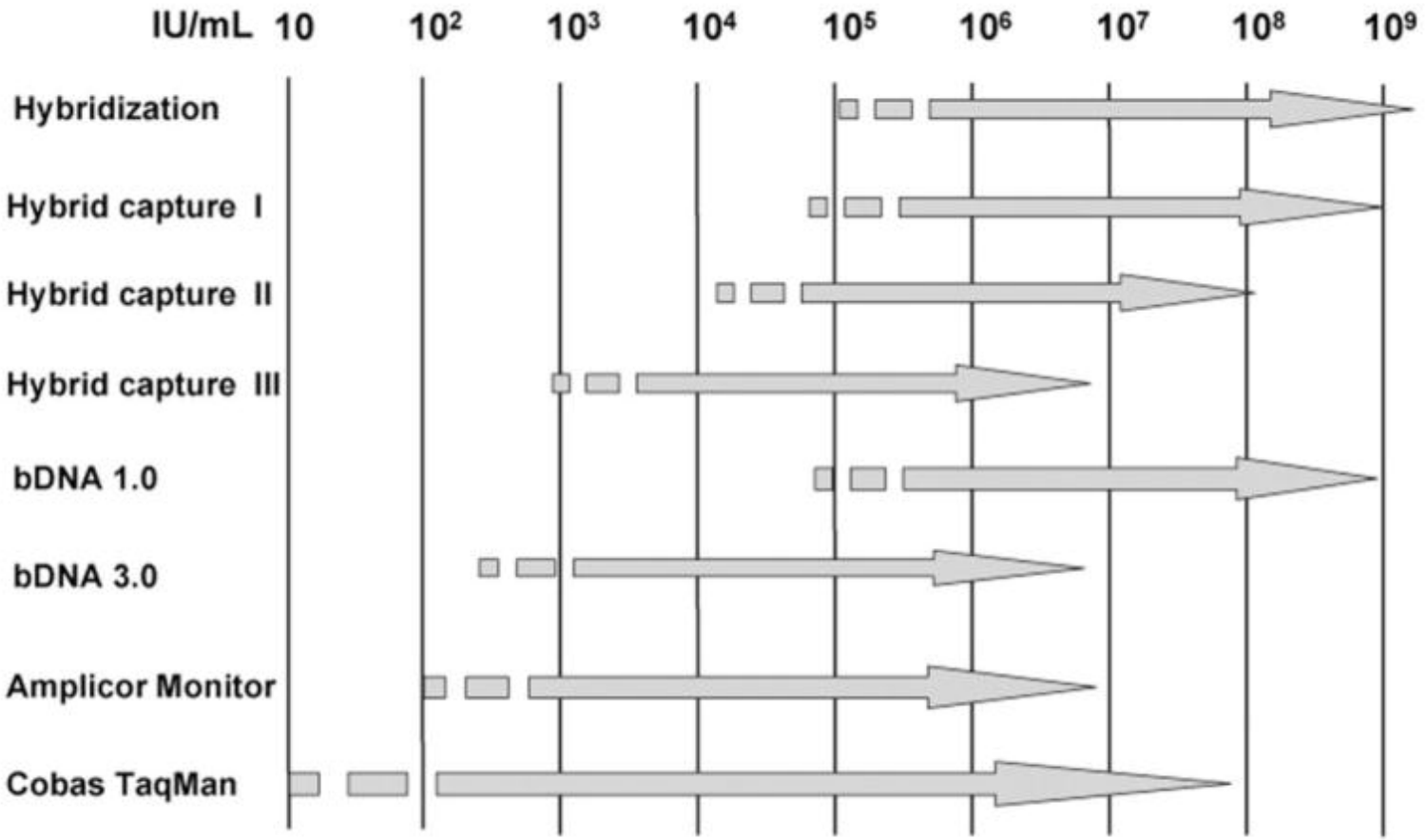
HBsAg	HBV infection, both acute and chronic
HBeAg	High-level HBV replication and infectivity; marker for treatment response
HBV DNA	Level of HBV replication; primary virologic marker for treatment response
Anti-HBc (IgM)	Acute HBV infection; could be seen in flare of chronic hepatitis B
Anti-HBc (IgG)	Recovered or chronic HBV infection
Anti-HBs	Recovered HBV infection or marker of HBV vaccination; immunity to HBV infection (titer can be measured to assess vaccine efficacy)
Anti-HBe	Low-level HBV replication and infectivity; marker for treatment response
Anti-HBc (IgG) and anti-HBs	Past HBV infection; could lose anti-HBs
Anti-HBc (IgG) and HBsAg	Chronic HBV infection
Anti-HBc (IgG) and/or anti-HBs and HBV DNA (PCR)	Latent or occult HBV infection

A Acute Hepatitis B



B Chronic Hepatitis B




IU/mL
10
10²
10³
10⁴
10⁵
10⁶
10⁷
10⁸
10⁹
Hybridization
Hybrid capture I
Hybrid capture II
Hybrid capture III
bDNA 1.0
bDNA 3.0
Amplicor Monitor
Cobas TaqMan

Definitions of cure
(Off treatment)

Sterilising cure:

- HBsAg and HBV DNA negative
- No cccDNA
- No integrated DNA

No active liver disease
No risk of recurrence
No HCC risk
No need for surveillance

Complete cure:

- HBsAg and HBV DNA negative
- No cccDNA
- Integrated DNA not cleared

No active liver disease
No risk of recurrence
HCC risk
Need for surveillance

Functional cure:

- HBsAg and HBV DNA negative
  - cccDNA not cleared
  - Integrated DNA not cleared

No active liver disease

Risk of recurrence

HCC risk

Need for surveillance

Partial cure:

- HBV DNA negative
- HBsAg positive
- cccDNA not cleared
- Integrated DNA not cleared

No active liver disease

High risk of recurrence

HCC risk

Need for surveillance

Suboptimal-partial cure:

- ***HBV DNA low level***
- HBsAg positive
- cccDNA not cleared
- Integrated DNA not cleared

No active liver disease

High risk of recurrence

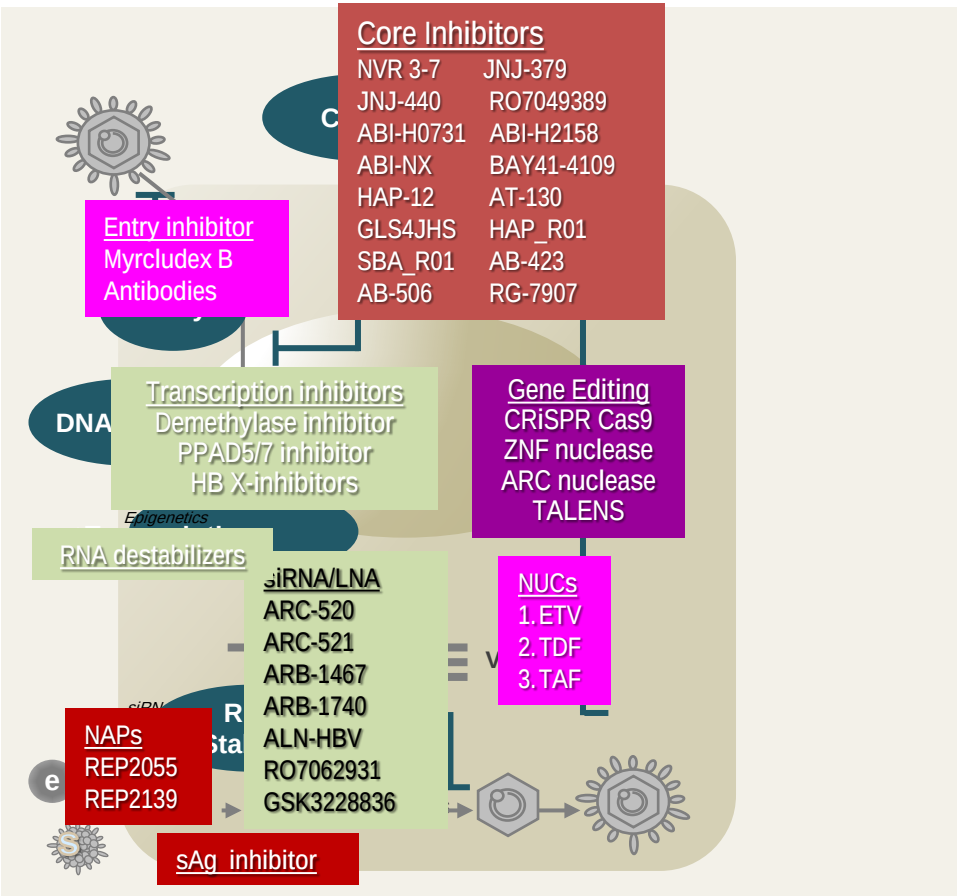
HCC risk

Need for surveillance

Cure strategies

- Decrease viral burden
- Immunological approaches
- Approaches targeting directly ccc DNA

Targets for Viral Inhibitors

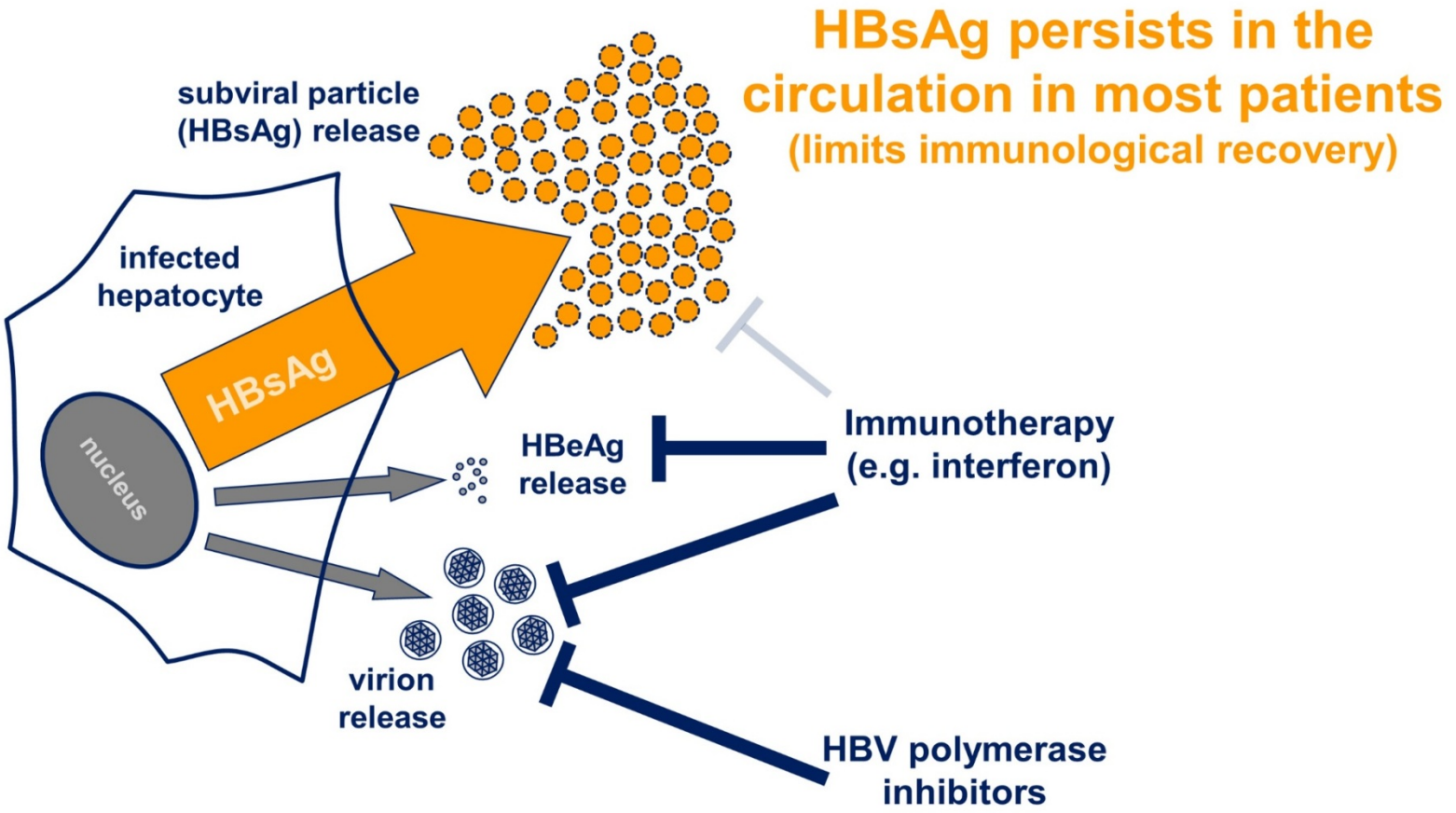


Nucleic acid polymers

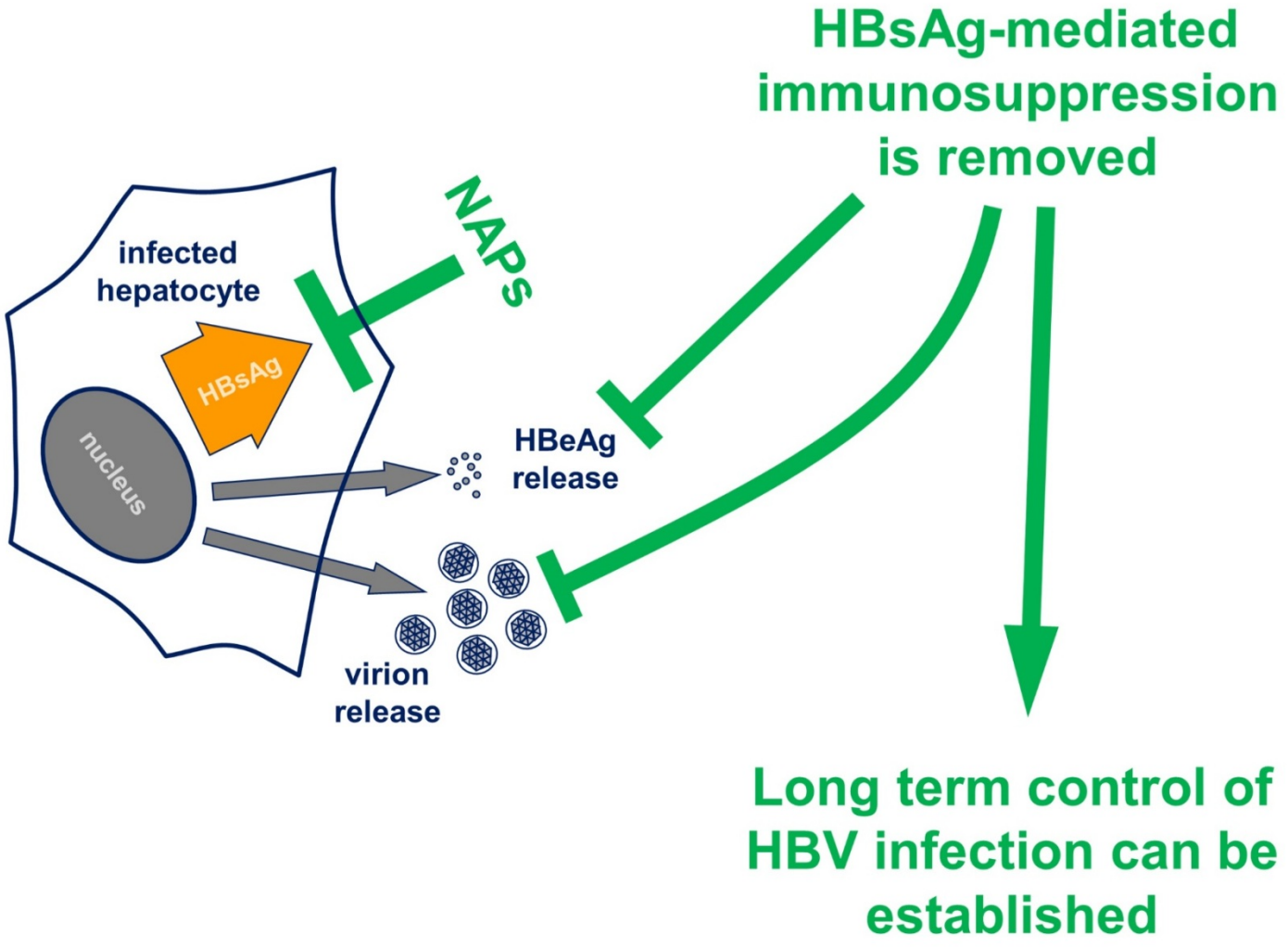
- Nucleic acid polymers (NAPs) are sequence-independent phosphorothioated oligonucleotides which exert their pharmacological effect in a sequence independent manner.

- Their mechanism of action is not entirely clear but it is suggested that NAPs inhibit assembly and/or secretion of subviral particles.

Limitation of current HBV antiviral therapies



NAPs block the release of subviral particles



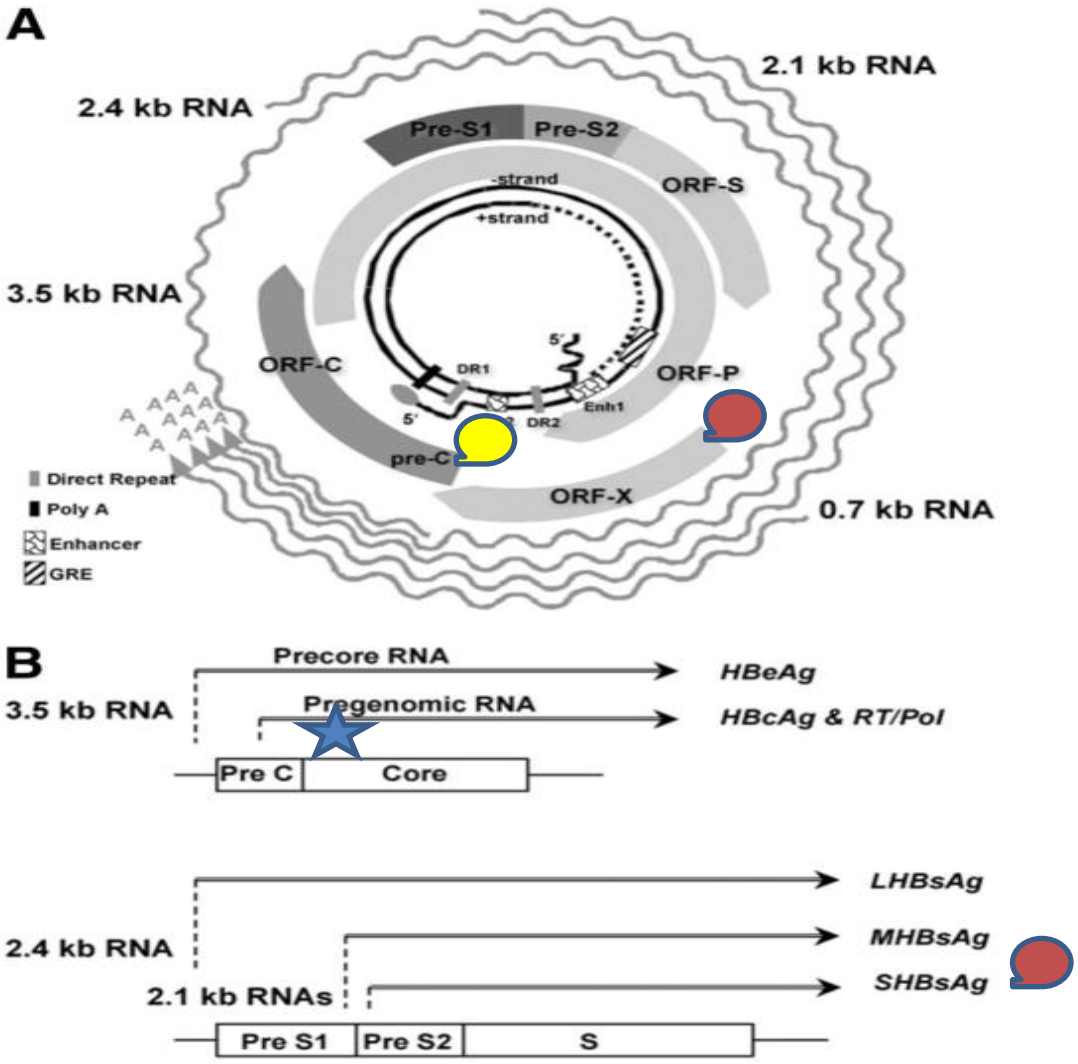
Summary and Conclusions

- Functional cure is rare. Both add-on Peg IFN approaches and NA dc should aim a suboptimal partial cure- can lead to functional cure

- Infants born to mothers who are positive for both HBsAg and HBeAg are at a higher risk of acquiring infection

Position paper 2017 WHO

DNA PCR


A
2.1 kb RNA
2.4 kb RNA
Pre-S1
Pre-S2
-strand
+strand
ORF-S
3.5 kb RNA
ORF-C
DR1
5'
ORF-P
Enh1
5'
DR2
pre-C
ORF-X
0.7 kb RNA
Direct Repeat
Poly A
Enhancer
GRE
B
Precore RNA
HBeAg
3.5 kb RNA
Pregenomic RNA
HBcAg & RT/Pol
Pre C
Core
LHBsAg
2.4 kb RNA
MHBsAg
2.1 kb RNAs
SHBsAg
Pre S1
Pre S2
S

How to mange pregnant women to minimize the risk of transmission??

- **MOTHER**
- Vaccine
- HBIG during pregnancy(antenatal)
- Anti viral treatment
- ***Baby***
- Vaccine
- HBIG

Pregnant women with HBsAg (+)

The prevention of HBV perinatal transmission is based on the combination of **HBIG and vaccination given within 12 h of birth**

Pregnant women with CHB and Treatment not Indicated

If High HBV DNA levels > 200,000 IU/ml **or**

HBsAg levels > 4 log10 IU/ml

Antiviral prophylaxis with TDF should start at week 24–28 of gestation and continue for up to 12 weeks after delivery

EASL (Evidence level 1, grade of recommendation 1)

Breast feeding is not contraindicated in HBsAg-positive untreated women or on TDF-based treatment or prophylaxis

EASL (Evidence level III, grade of recommendation 2)

Opinions, descriptive epidemiology

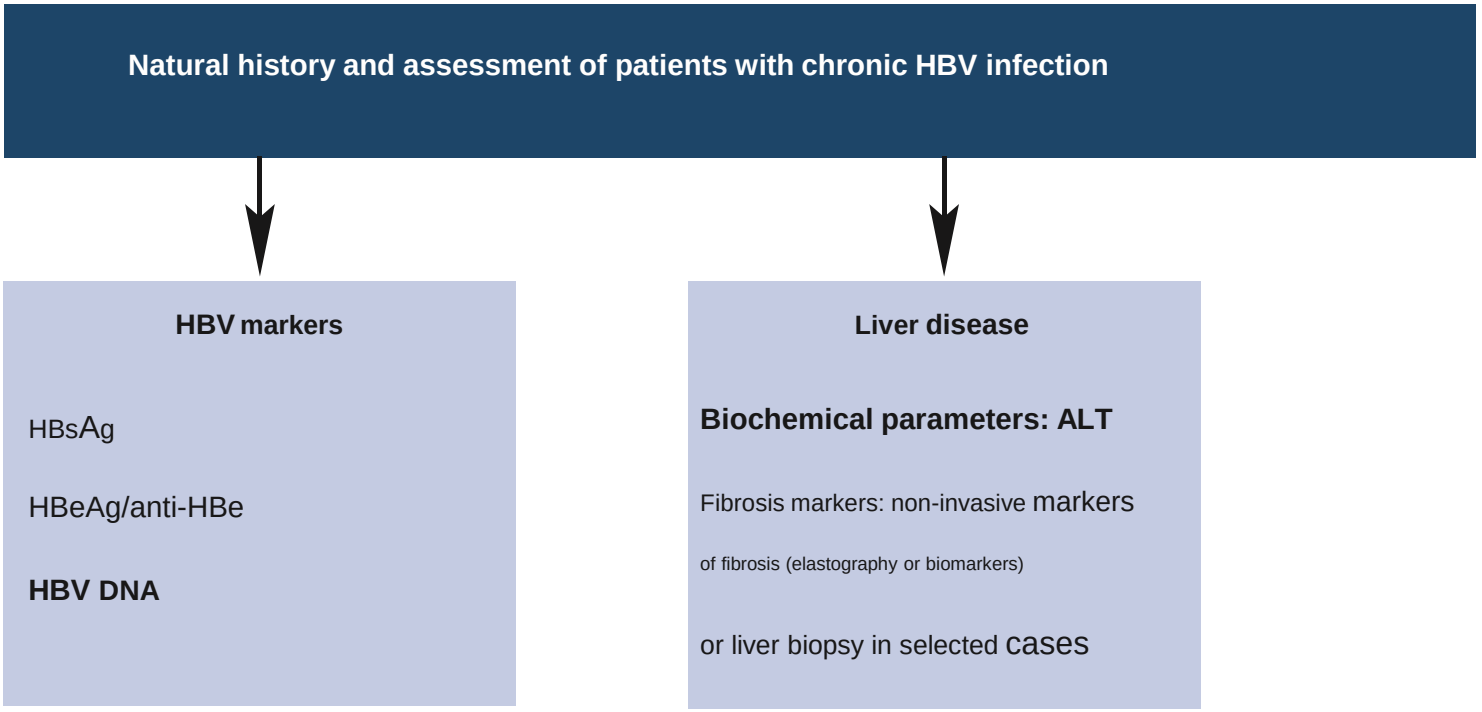
Screening for HBsAg in the first trimester of pregnancy is strongly recommended

Vaccination against HBV is both safe and efficacious during pregnancy

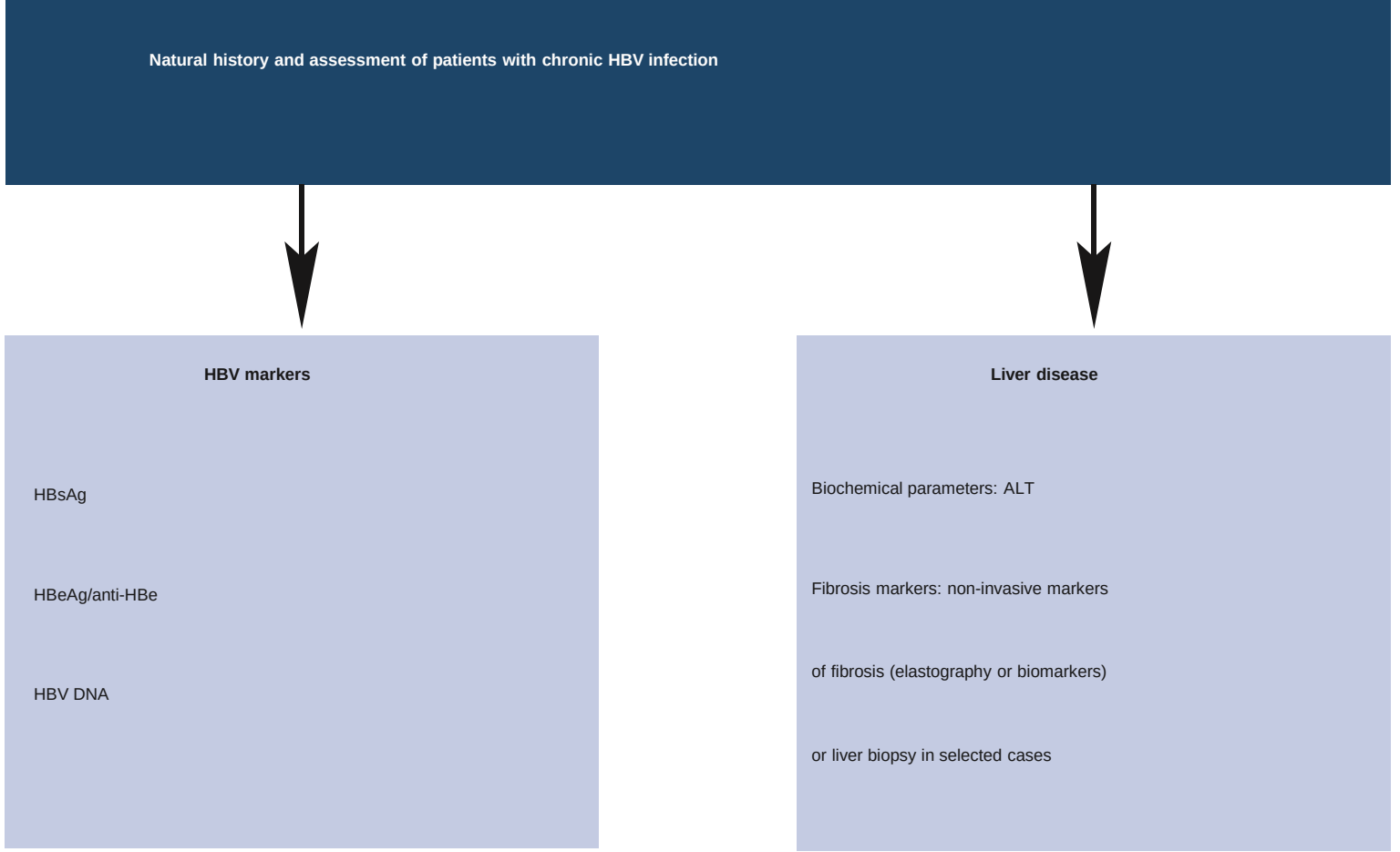
EASL (Evidence level 1, grade of recommendation 1)

Impact of pregnancy

- **Liver disease :**
  - no worsening of liver disease in majority of women


Natural history and assessment of patients with chronic HBV infection
HBV markers
HBsAg
HBeAg/anti-HBe
HBV DNA
Liver disease
Biochemical parameters: ALT
Fibrosis markers: non-invasive markers
of fibrosis (elastography or biomarkers)
or liver biopsy in selected cases
HBeAg positive
HBeAg negative

characterised by the presence of serum HBeAg, very high levels of HBV DNA and ALT persistently within the normal range according to traditional cut-off values [upper limit of normal (ULN) approximately 40 IU/L].1 In the liver, there is


Natural history and assessment of patients with chronic HBV infection
HBV markers
HBsAg
HBeAg/anti-HBe
HBV DNA
Liver disease
Biochemical parameters: ALT
Fibrosis markers: non-invasive markers
of fibrosis (elastography or biomarkers)
or liver biopsy in selected cases
HBeAg positive
HBeAg negative

Natural history and assessment of patients with chronic HBV infection HBV markers Biochemical parameters: ALT Fibrosis markers: non-invasive markers of fibrosis (elastography or biomarkers) or liver biopsy in selected cases HBsAg HBeAg/anti-HBe HBV DNA Liver disease HBeAg negative HBeAg positive				
	Chronic infection	Chronic hepatitis	Chronic infection	Chronic hepatitis
HBsAg HBeAg	High Positive 7	High/intermediate Positive 4 7	Low Negative	Intermediate Negative
HBV DNA ALT	>10 IU/ml Normal	10 -10 IU/ml Elevated	<2,000 IU/ml°° Normal	>2 ,000 IU/ml Elevated*
Liver disease Old terminology	None/minimal Immune tolerant	Moderate/severe Immune reactive HBeAg positive	None Inactive carrier	Moderate/severe HBeAg negative chronic hepatitis

Fig. 1. Natural history and assessment of patients with chronic HBV infection based upon HBV and liver disease markers.
*Persistentlyorintermittently. HBVDNA levelscanbebetween2,000and20,000IU/mlinsomepatientswithoutsingsofchronichepatitis.

THANK YOU FOR YOUR TIME .