الجامعة السورية الخاصة
SYRIAN PRIVATE UNIVERSITY

VIRAL HEPATITIS

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2019

VIRAL HEPATITIS
NON-HEPATITIS VIRUSES

- Epstein Barr virus (mononucleosis)
- Cytomegalovirus
- Herpes simplex virus
- Varicella zoster (chicken pox)
- Measles
- Rubella
- Coxsackie
- Influenza

Most commonly seen in:
- Children
- Immune suppresed
  - HIV
  - Transplant recipients

	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
Virus					
Nucleic acid	RNA	DNA	RNA	RNA	RNA
Size (diameter)	27 nm	42 nm	30-38 nm	35 nm	27 nm
Incubation	2-4 w	4-20 w	2-26 w	6-9 w	3-8 w
Spread					
Faeces	Yes	No	No	No	Yes
Blood	Uncommon	Yes	Yes	Yes	No
Saliva	Yes	Yes	Yes	?	?
Sexual	Uncommon	Yes	Uncommon	Yes	?
Vertical	No	Yes	Uncommon	Yes	No
Chronic infection	No	Yes	Yes	Yes	No
Prevention					
Active	Vaccine	Vaccine	No	Prevented by	No
Passive	Immune serum	Hyperimmune	No	**hepatitis B**	No
	globulin	serum globulin		**vaccination**	

Five Causes of Acute Viral Hepatitis

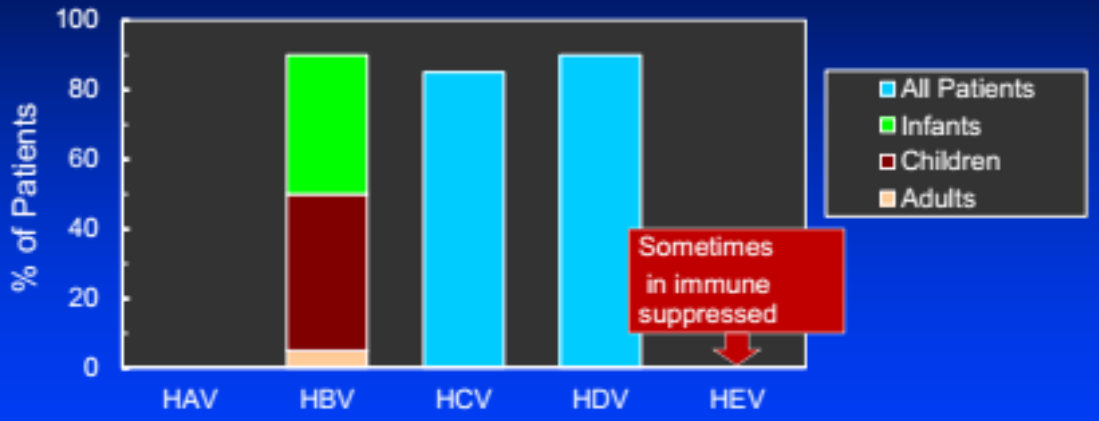
HEPATITIS VIRUS	SIZE (nm)	GENOME	SPREAD	INCUBATION PERIOD (DAYS)	FATALITY RATE	CHRONIC RATE	ANTIBODY
A	27	RNA	Fecal-oral	15–45 mean 25	1%	None	Anti-HAV
B	45	DNA	Parenteral Sexual	30–180 mean 75	1%	2–7%	Anti-HBs Anti-HBc Anti-HBe
C	60	RNA	Parenteral	15–150 mean 50	<0.1%	70–85%	Anti-HCV
D (delta)	40	RNA	Parenteral Sexual	30–150	2–10%	2–7% 50%	Anti-HDV
E	32	RNA	Fecal-oral	30–60	1%	None	Anti-HEV

Hepatitis A No chronic infection

Chronic Hepatitis E Just in immune suppressed patient

	Hepatitis A	Hepatitis E
Virus		
Nucleic acid	RNA	RNA
Size (diameter)	27 nm	27 nm
Incubation	2-4 w	3-8 w
Spread		
Faeces	Yes	Yes
Blood	Uncommon	No
Saliva	Yes	?
Sexual	Uncommon	?
Vertical	No	No
Prevention		
Active	Vaccine	No
Passive	Immune serum globulin	No

VIRAL HEPATITIS
CHRONIC INFECTION



ML Shiffman. Clin Liver Dis. 2010; 14:75-91.
A Regev and ER Schiff. Curr Opin Gastroenterol. 1999; 15:234-239.
U Navaneethan, et al. Liver Int. 2008; 28:1190-9

Bon Secours
Liver Institute of Virginia

	Hepatitis B	Hepatitis C	Hepatitis D
Virus			
Nucleic acid	DNA	RNA	RNA
Size (diameter)	42 nm	30-38 nm	35 nm
Incubation	4-20 w	2-26 w	6-9 w
Spread			
Faeces	No	No	No
Blood	Yes	Yes	Yes
Saliva	Yes	Yes	?
Sexual	Yes	Uncommon	Yes
Vertical	Yes	Uncommon	Yes
Chronic infection	Yes	Yes	Yes
Prevention			
Active	Vaccine	No	Prevented by
Passive	Hyperimmune globulin	No	**hepatitis B vaccine**

Acute hepatitis

- Acute viral hepatitis(A, B, C, D ,E)
- Drugs induced hepatitis
- Alcoholic acute hepatitis
- Toxic hepatitis

VIRAL HEPATITIS
MODES OF INFECTION

	HAV	HEV	HBV	HCV	Other
Food and water	Yes	Yes			
Seafood	Yes				
Person-person	Yes				Yes
IV drug use			Yes	Yes	
Blood transfusion			Rare	Rare	CMV
Men-sex-men	Yes		Yes		
Heterosexual activity			Yes		
Vertical transmission			Yes		

Adapted from: A Regev and ER Schiff
Curr Opin Gastroenterol 1999; 15:234-239

Bon Secours

VIRAL HEPATITIS
PRODROME

- Flu-like symptoms
  - Myalgias
  - Arthralgias
  - Fatigue
  - Nausea/vomiting
  - Loss of appetite
  - Fever may occur
- Mild tenderness over the liver
- Elevation in serum ALT
- Lasts for 3-5 days
- Serologic studies typically positive

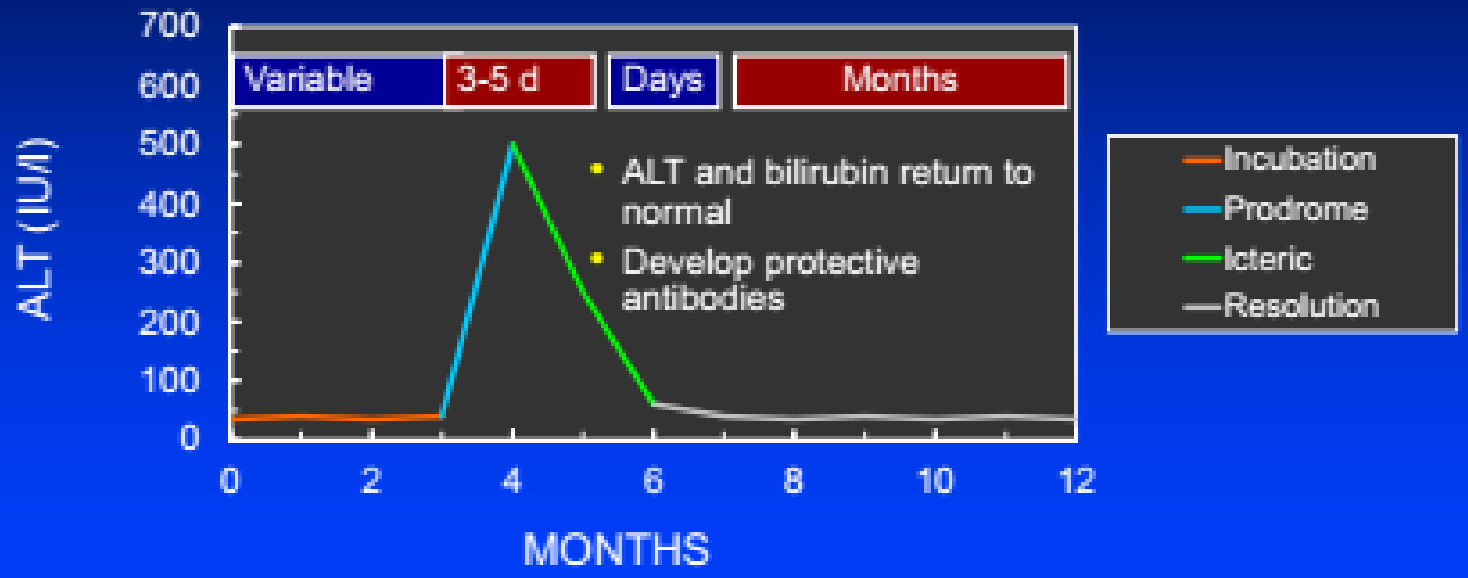
A Regev and ER Schiff
Curr Opin Gastroenterol. 1999; 15:234-239.

VIRAL HEPATITIS
EXTRAHEPATIC MANIFESTATIONS

HAV	HBV	HCV	HEV
Arthritis	Cryoglobulinemia	Cryoglobulinemia	Pancreatitis
Adult Still disease	Serum sickness	Glomerulonephritis	Guillian-Barre
Aplastic anemia	Glomerulonephritis	Type 2 DM	Neuralgic amyotrophy
Red cell aplasia	Polyarthritis	PCT	Hemolytic anemia
Interstitial nephritis	PAN	B cell NHL	Aplastic anemia
Acute tubular necrosis	Bullous Pemphigoid	Lichen planus	Cryoglobulinemia
Polymyositis	Lichen planus	Polyneuropathy	Glomerulonephritis
Rhabdomyolysis	Guillian Barre	Vasulitis	Thyroiditis
			Myocarditis
			Myositis

ML Shiffman. Clin Liver Dis. 2010; 14:75-91.
A Regev and ER Schiff. Curr Opin Gastroenterol. 1999; 15:234-239.
N Kamar N, et al. Liver Int. 2016; 36:467-72

VIRAL HEPATITIS
PHASES OF ACUTE DISEASE



Serologic Diagnosis of Acute Hepatitis

DIAGNOSIS	SCREENING ASSAYS	SUPPLEMENTAL ASSAYS
Hepatitis A	IgM anti-HAV	None needed
Hepatitis B	HBsAg, IgM anti-HBc	HBeAg, anti-HBe HBV DNA
Hepatitis C	Anti-HCV by EIA	HCV RNA by PCR; anti-HCV by Immunoblot
Hepatitis D	HBsAg	Anti-HDV
Hepatitis E	History	Anti-HEV
Mononucleosis	History, white blood cell differential counts	Monospot test Heterophil antibody
Drug-induced hepatitis	History	

COMPLICATIONS OF ACUTE VIRAL HEPATITIS

- Acute liver failure
- Cholestatic hepatitis
- Aplastic anaemia
- Chronic liver disease and cirrhosis (B and C)
- Relapsing hepatitis

Treatment of Acute viral hepatitis A

- Prevention
- Prevention
- Prevention
- Prevention
- Prevention
- Prevention
- Prevention
- Prevention

Managmemnt

Avoid Sedatives and narcotics.

No specific dietary modifications are needed

Elective surgery should be avoided

Not Just

HAV

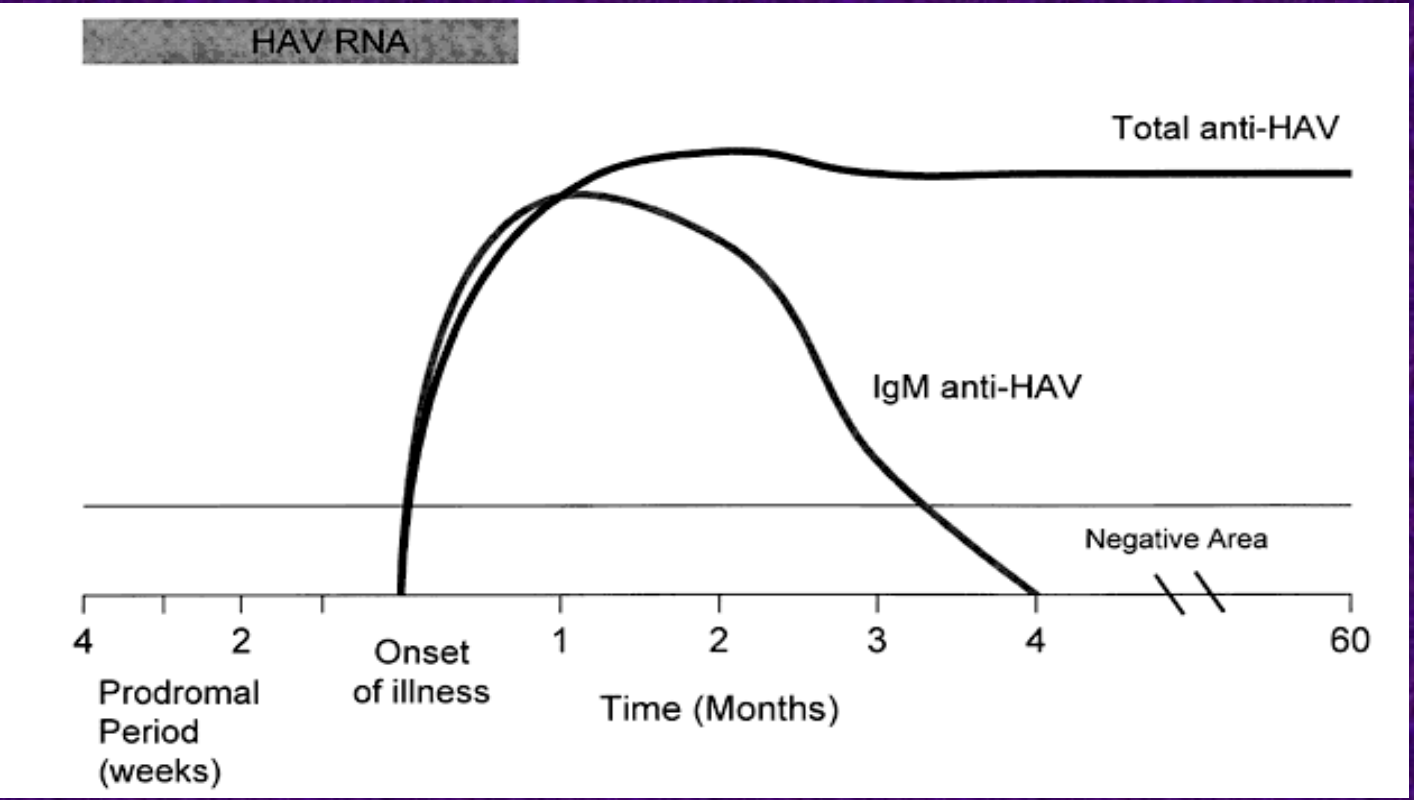
- excrete the virus in faeces for about
  2-3 weeks **before** symptoms
  2 weeks after
- May be asymptomatic, so up to 30% of adults will have serological evidence of past infection but give no history of jaundice.
- In occasional outbreaks water and shellfish have been the vehicles of transmission

Anti-HAV

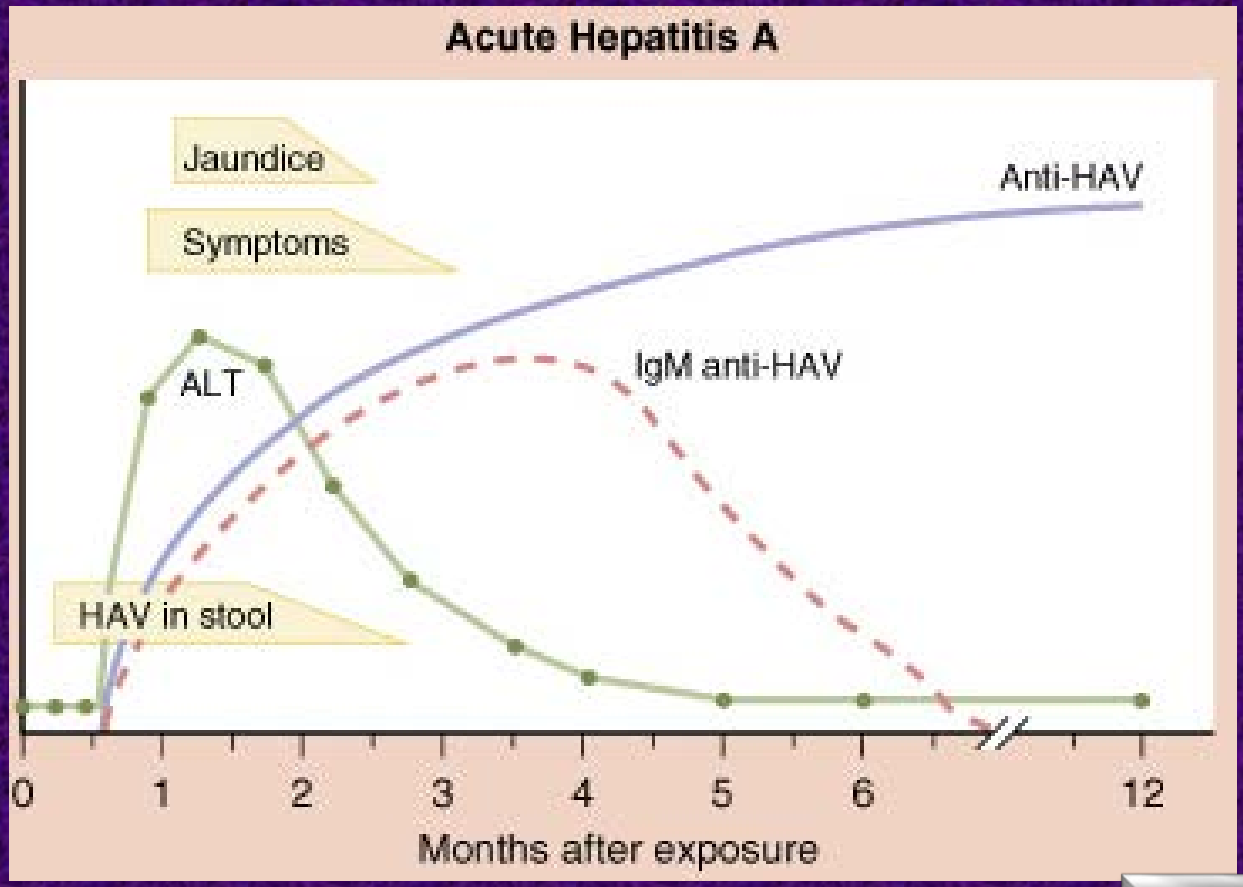
HAV is only present in the blood transiently during the incubation period. the virus cannot be grown readily.

Anti-HAV IgM type, is already present in the blood at the onset of the clinical illness and is diagnostic of an acute HAV infection.

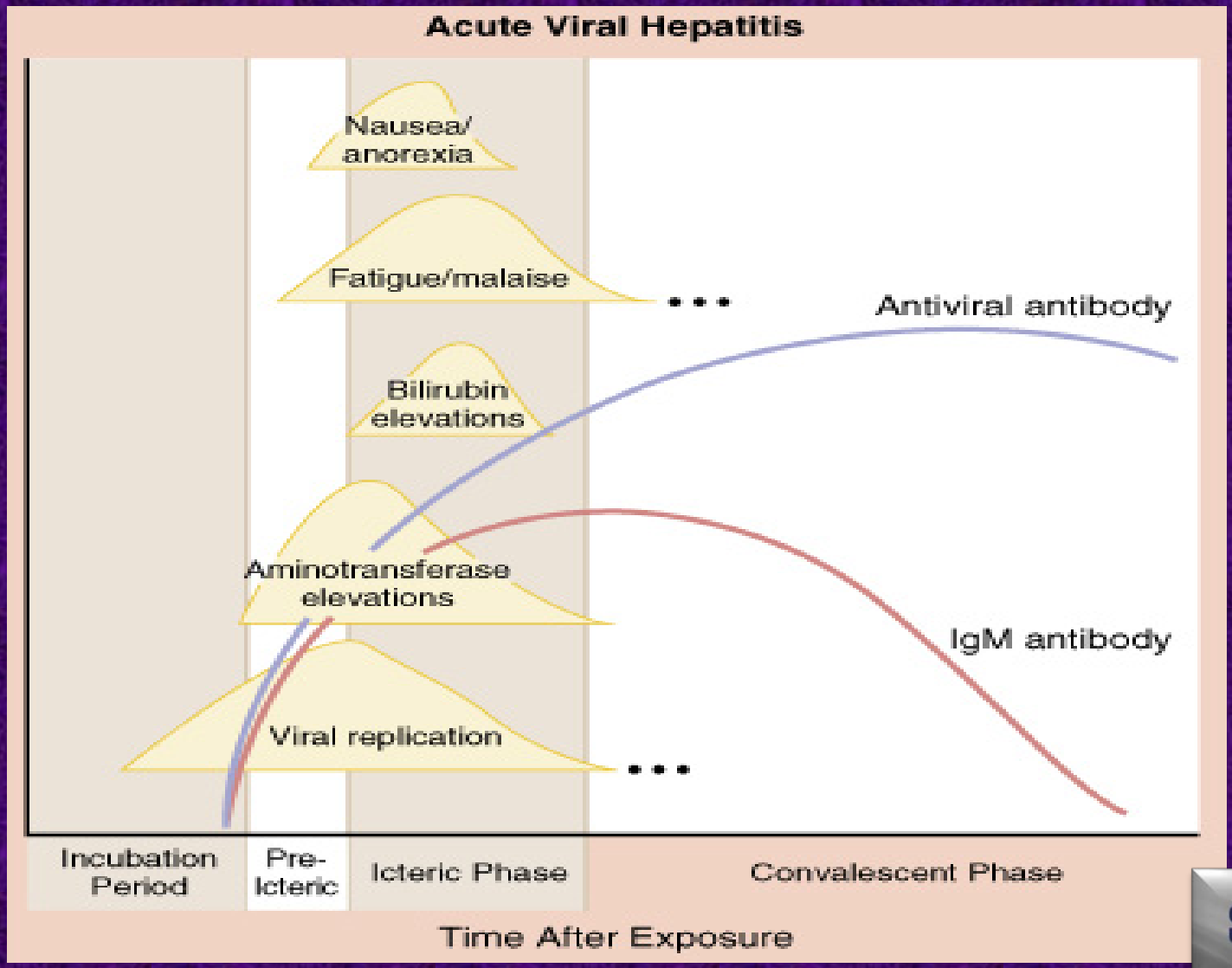
الاختبارات المصلية لالتهاب الكبد الفيروسي الحاد A



الاختبارات المصلية لالتهاب الكبد الفيروسي الحاد أ



الشكل السريري الوصفي لالتهاب الكبد الفيروسي الحاد



Investigation

Anti-HAV

HAV Blood

HAV stool

Anti-HAV of IgM type

diagnostic of an acute HAV infection.

Investigation

Diagnostic of an acute HAV infection

Anti-HAV of IgM type

Anti-HAV of IgG type

is of no diagnostic value

-it can be used to measure the prevalence of HAV infection.

Its presence indicates immunity to HAV

Prognosis

- Acute liver failure complicates acute hepatitis A in only 0.1% of cases
- chronic infection does not occur.
- However, HAV infection in patients with chronic liver disease may be life-threatening disease.

Immunization HAV

<u>should be considered for individuals with</u>

-chronic hepatitis B or C infections.

-particular risk such as

1-close contacts

2- Elderly

3-Those with other major disease

4- ?pregnant women

5- People travelling to endemic areas

Route of transmission	Risk of chronic infection
Horizontal transmission	10%
Injection drug use	
Infected unscreened blood products	
Tattoos/acupuncture needles	
Sexual (homosexual and heterosexual)	
Vertical transmission	90%
HbsAg-positive mother	

Global Burden of Viral Hepatitis (Estimates)

- 2000 million (2 billion) infected with hepatitis B (> 250 million chronically)
- 150 million chronically infected with hepatitis C
- ~800,000 deaths annually – hepatitis B+C

Hepatitis C prevalence in people who inject drugs

- People who inject drugs – the most affected population group
- Prevalence estimates
  - 30% to 98% in EU countries (2002)
  - 21% to 86% in 9 EU countries (2012)

Sources: Roy K, et al 2002. Monitoring hepatitis C virus infection among injecting drug users in the European Union: a review of the literature. *Epidemiology & Infection*. 129: 577-85; Rondy M, et al 2012. Hepatitis C prevalence in injecting drug users in Europe, 1990-2007: impact of study recruitment setting. *Epidemiology & Infection*

Prevalence in Syria

4% of the population

ندوة التهابات الكبد الفيروسية ـالمجلس الأعلى للعلوم

2003

CHRONIC HEPATITIS B
THE PERSISTENCE OF HBsAg FOR LONGER THAN 6 MONTHS.

Infectivity

Like AIDS but

Hep B 100 times more concentrated in blood

It is ability to remain stable outside and infective in dried blood at room temperature for more than a week

HCV

It is ability to remain stable outside and infective in dried blood at room temperature for **16 hours**

When the serum HBV DNA level is under 200,000 IU/ml vertical transmission can be prevented simply by administering HBIG and HBV vaccine to the newborn.

Hep.B &Pregnancy

- Babies born to Mothers with HBsAg+ve &HBV DNA have *20 to 95%* risk of becoming Infected
- infectivity depends on HBV DNA level

- Babies of HBsAg+ve M others and HBeAg -ve ***uncommon*** to be chronic hepatitis B BUT at risk of severe acute neonatal hepatitis &acute liver failure

Recommendations (2009)

Accordingly, all infants should receive the first dose of hepatitis B vaccine as soon as possible (<24 hours) after birth.

This should be followed by 2 or 3 doses to complete the series

- **The risk of HCV transmission after percutaneous exposure is low, approximately 1.8%**

The risk of HBV seroconversion after a percutanous injury ranges from 32% to 62% in unvaccinated person and is dependent on the hepatitis B e antigen status of the source ,DNA ---

Mode of Transmission of HBV

Infected blood transfusion or blood products

Needle stick injuries: HCW - injection drug users

Hemodialysis

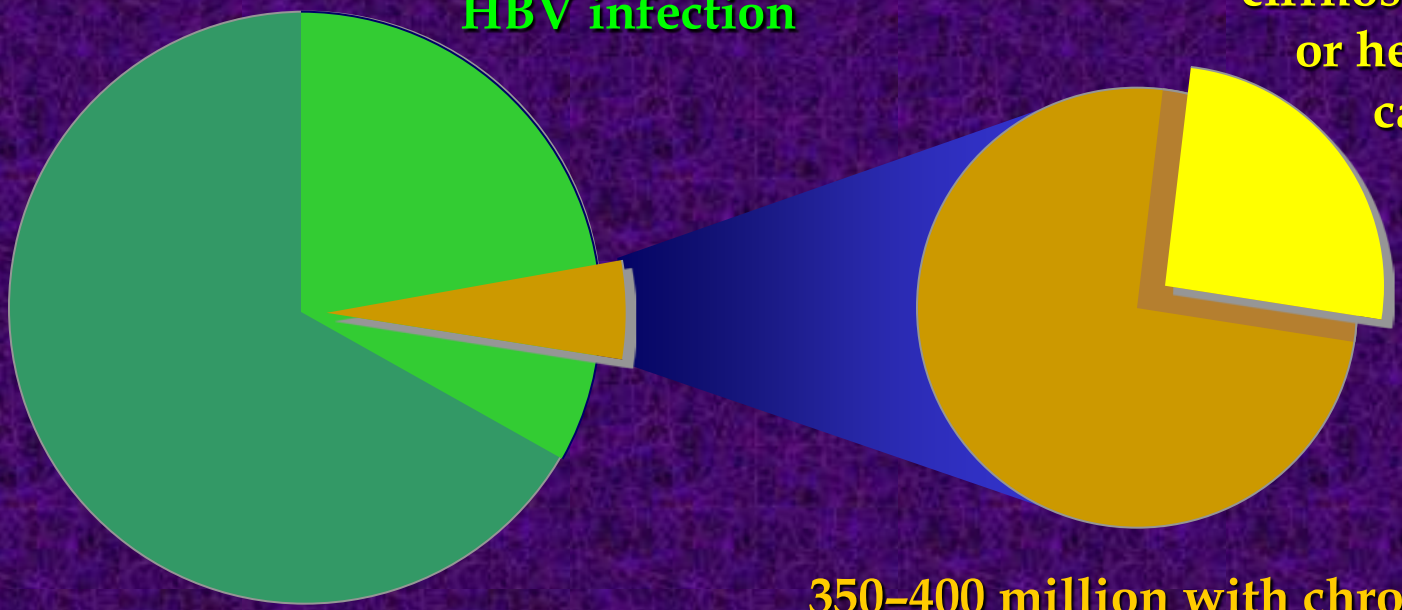
Sexual transmission: heterosexual - homosexual

Horizontal transmission: childhood - family member

Vertical Transmission (mother to newborn)

Unsafe Procedures: ear piercing - tattooing - barbering

Global Impact Of Hepatitis B Infection



Worldwide: ~1 million / year die from HBV-associated liver disease

نسبة المعدل الوطني للإصابات المكتشفة بالفحوص بالنسبة للحمى B و C ومقارنتها مع نسبة الإصابات المكتشفة بالدم لبقية الأمراض

السنة	1996	1997	1998	1999	2000	2001	2002
B	%7.01	%5	%4.46	%3.94	%3.85	% 3.69	%3.61
C	%2.53	%1.81	%1.77	%1.74	%1.19	%0.74	%0.46
HIV	%0.07	%0.10	%0.15	%0.13	%0.10	%0.10	%0.16
CMV IgM	%0.41	%0.32	%0.21	%0.42	%0.11	%0.65	%0.33

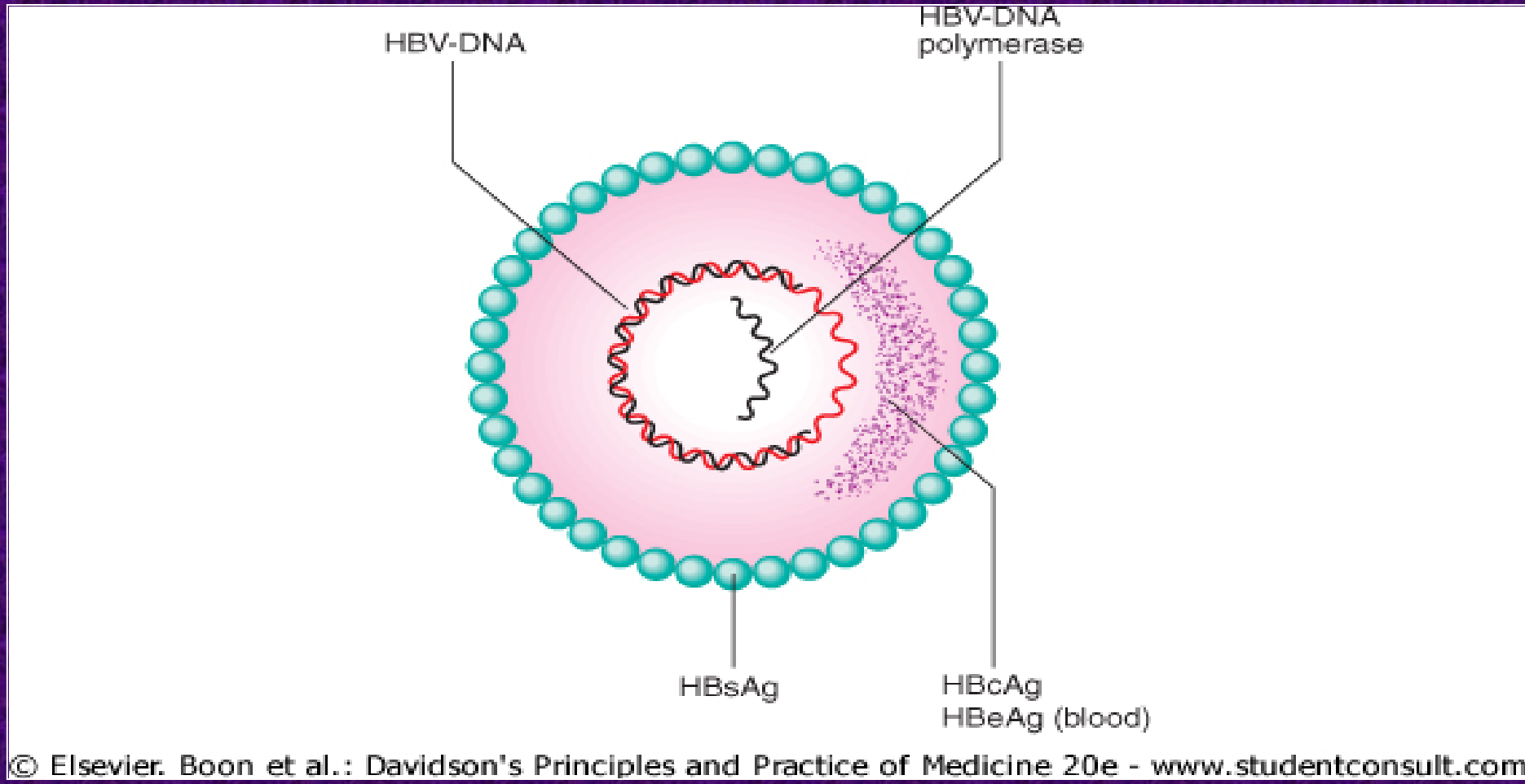
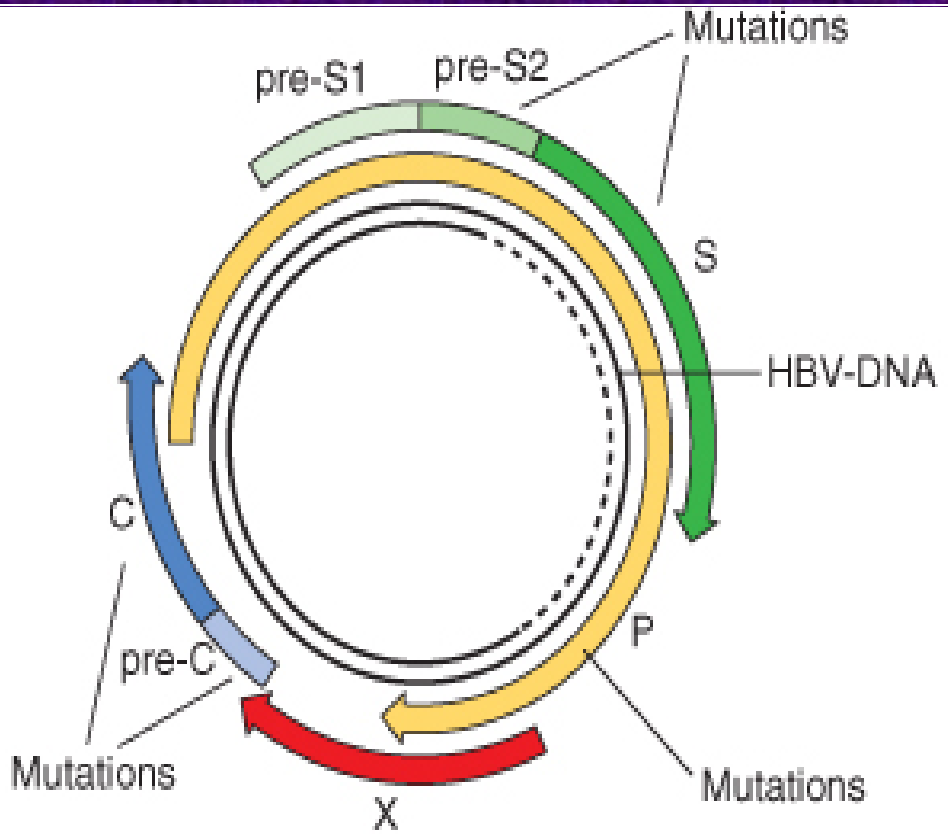


Figure 23.25 Schematic diagram of hepatitis B virus. Hepatitis B surface antigen (HBsAg) is a protein which makes up part of the viral envelope. Hepatitis B core antigen (HBcAg) is a protein which makes up the capsid or core part of the virus (found in the liver but not in blood). Hepatitis B e antigen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



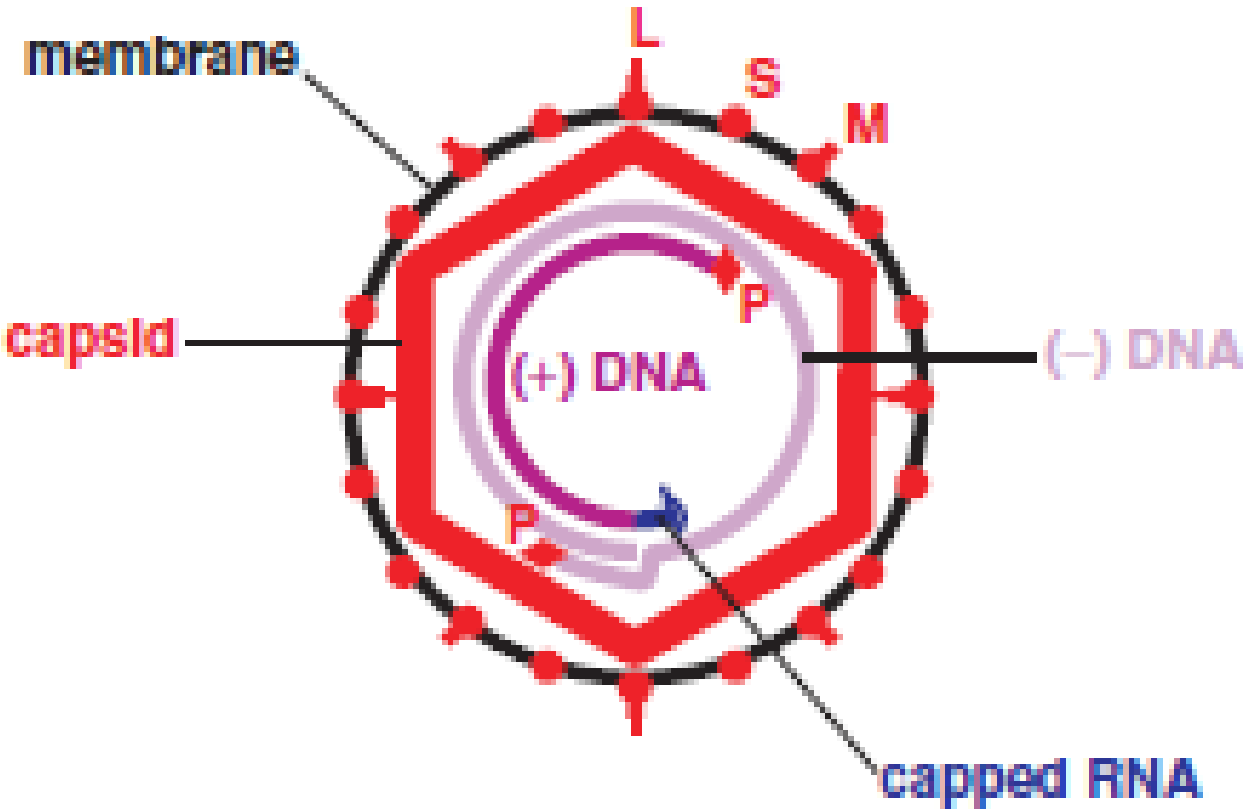
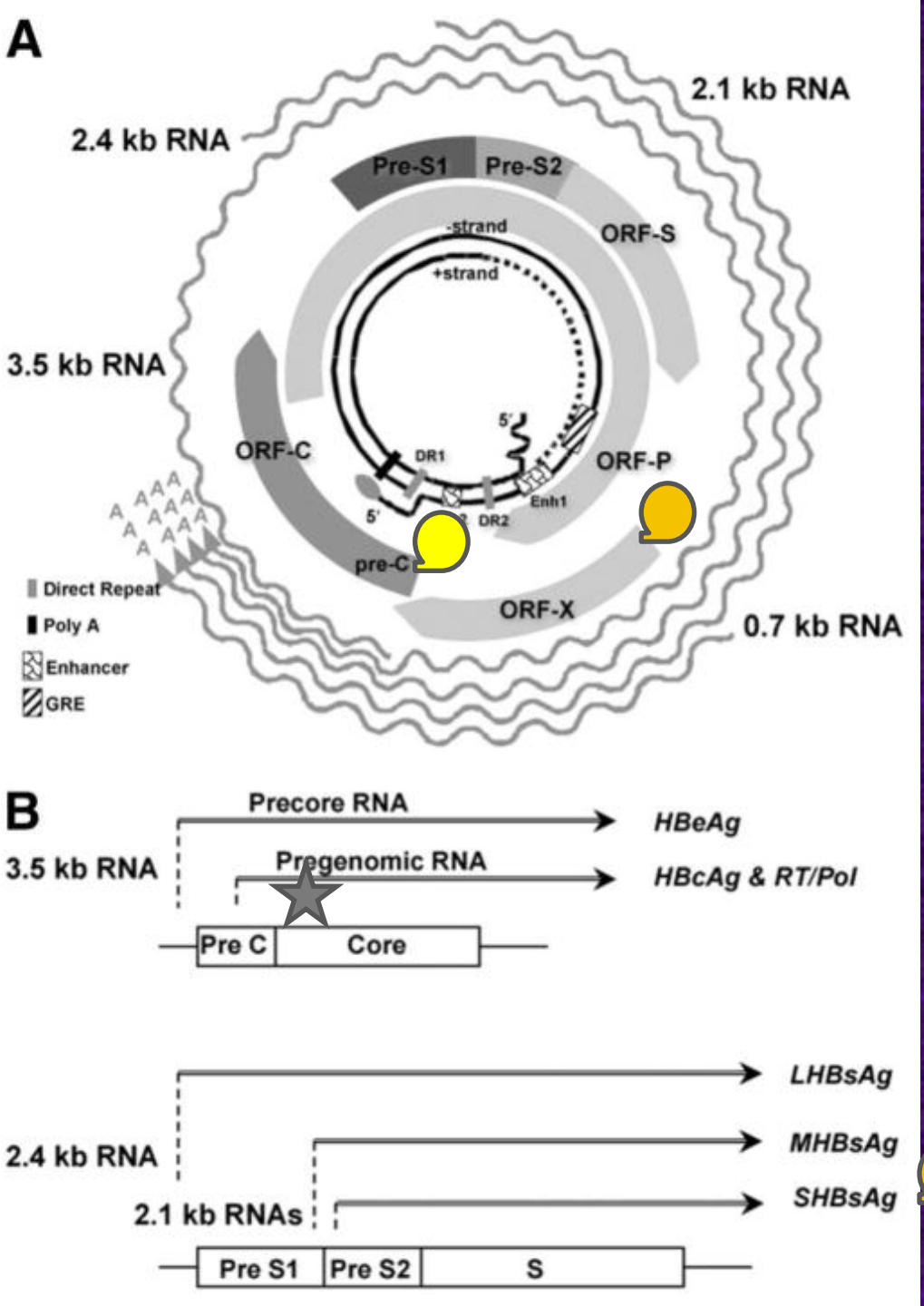
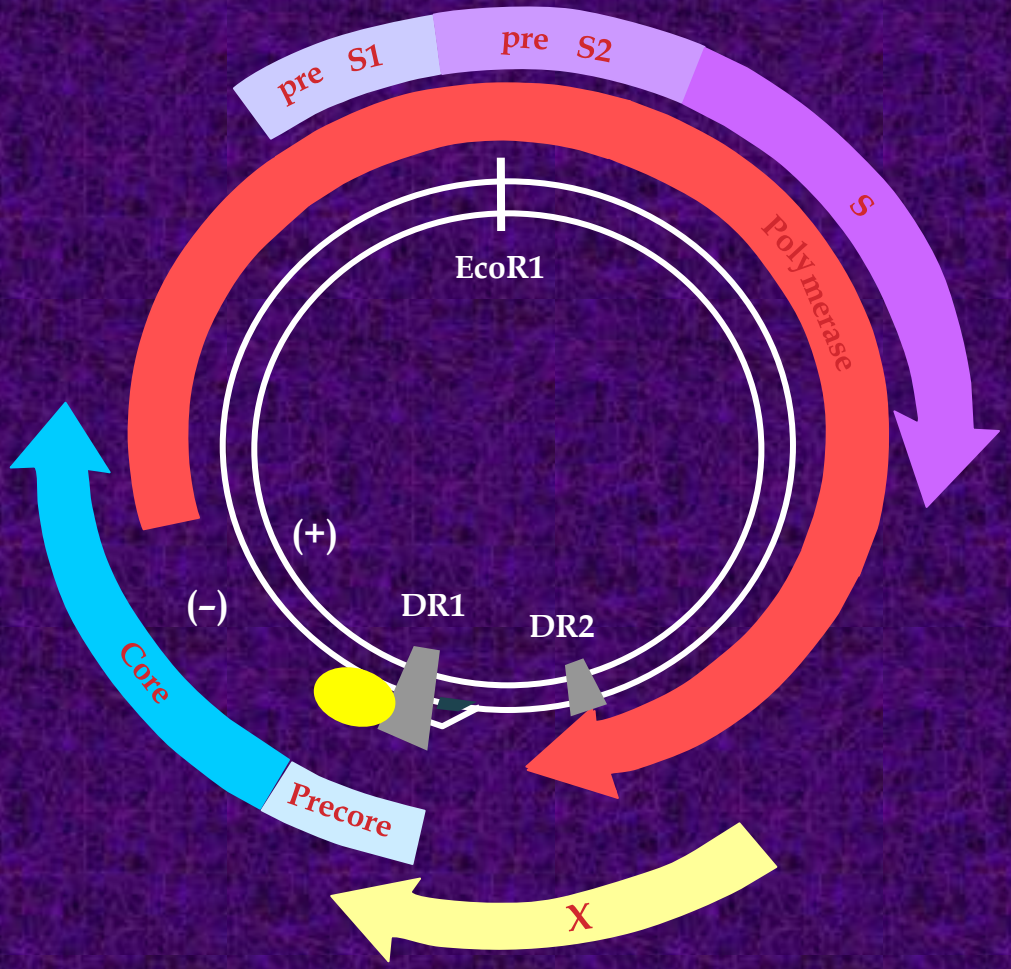


Figure 18.2 *The HBV virion.* S: small envelope protein. M: medium envelope protein. L: large envelope protein. P: polymerase (one molecule is covalently linked to the 5′ end of the (+) DNA; the virion may contain a second molecule of P, as indicated here

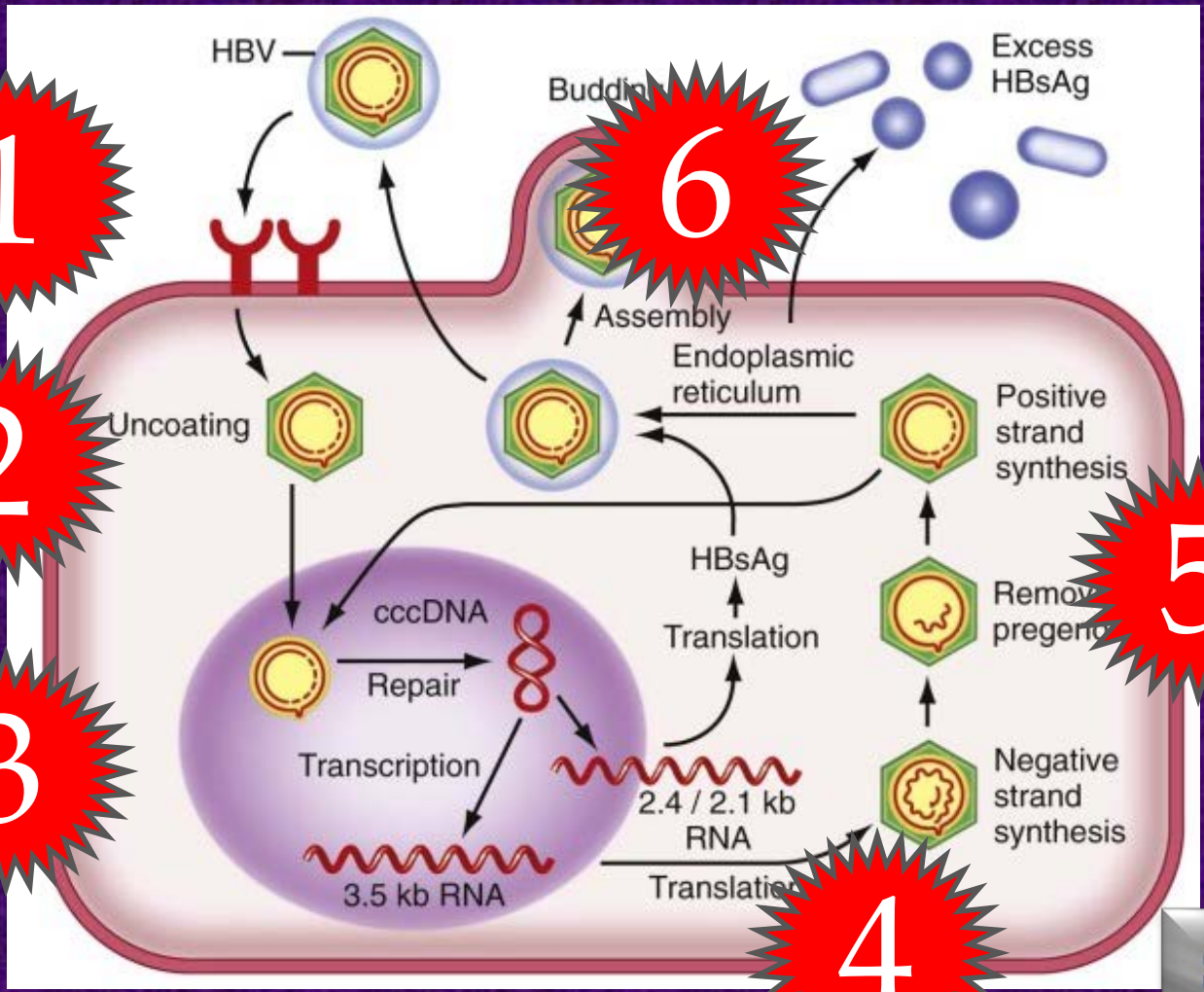
DNA PCR



Hepatitis B Virus Genome



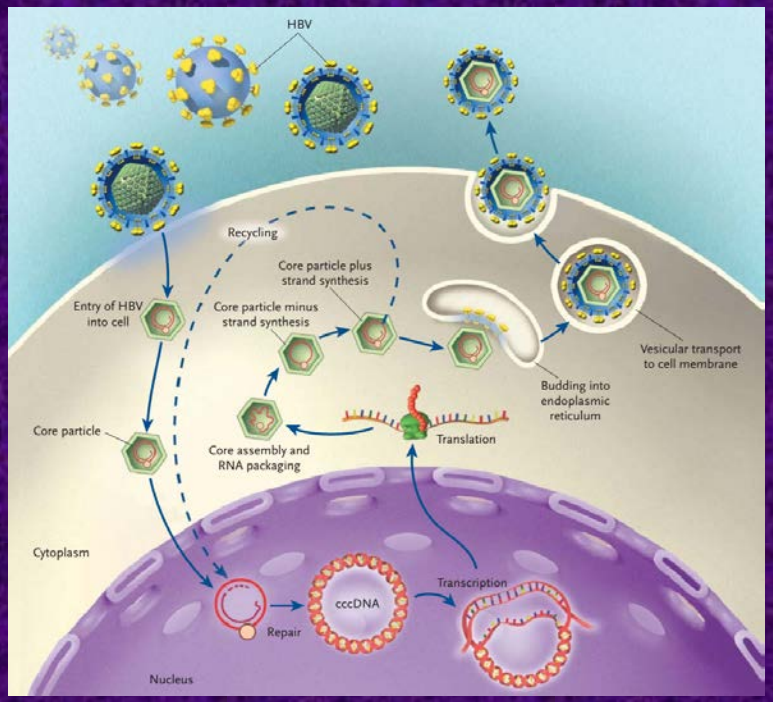
Life cycle of the hepatitis B virus (HBV)



Covalently Closed Circular DNA (cccDNA)

A

cccDNA



Covalently Closed Circular DNA (cccDNA)

- **Very stable within the hepatocyte**
- **Persist after antiviral therapy and even after clearance of HBsAg**
- **Plays a significant role in reactivation of disease**

Werle-Lapostolle et al (2004) Gastroenterology 126:1750

N Engl J Med 2004;350:1118-29

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.

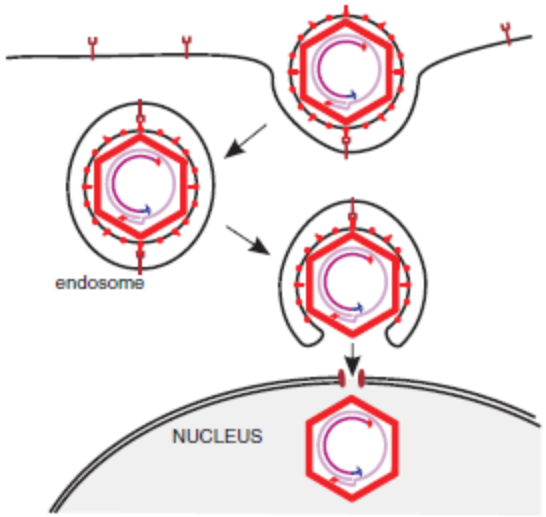


Figure 18.10 *Endocytosis of attached HBV virion followed by release of nucleocapsid and entry into the nucleus.*

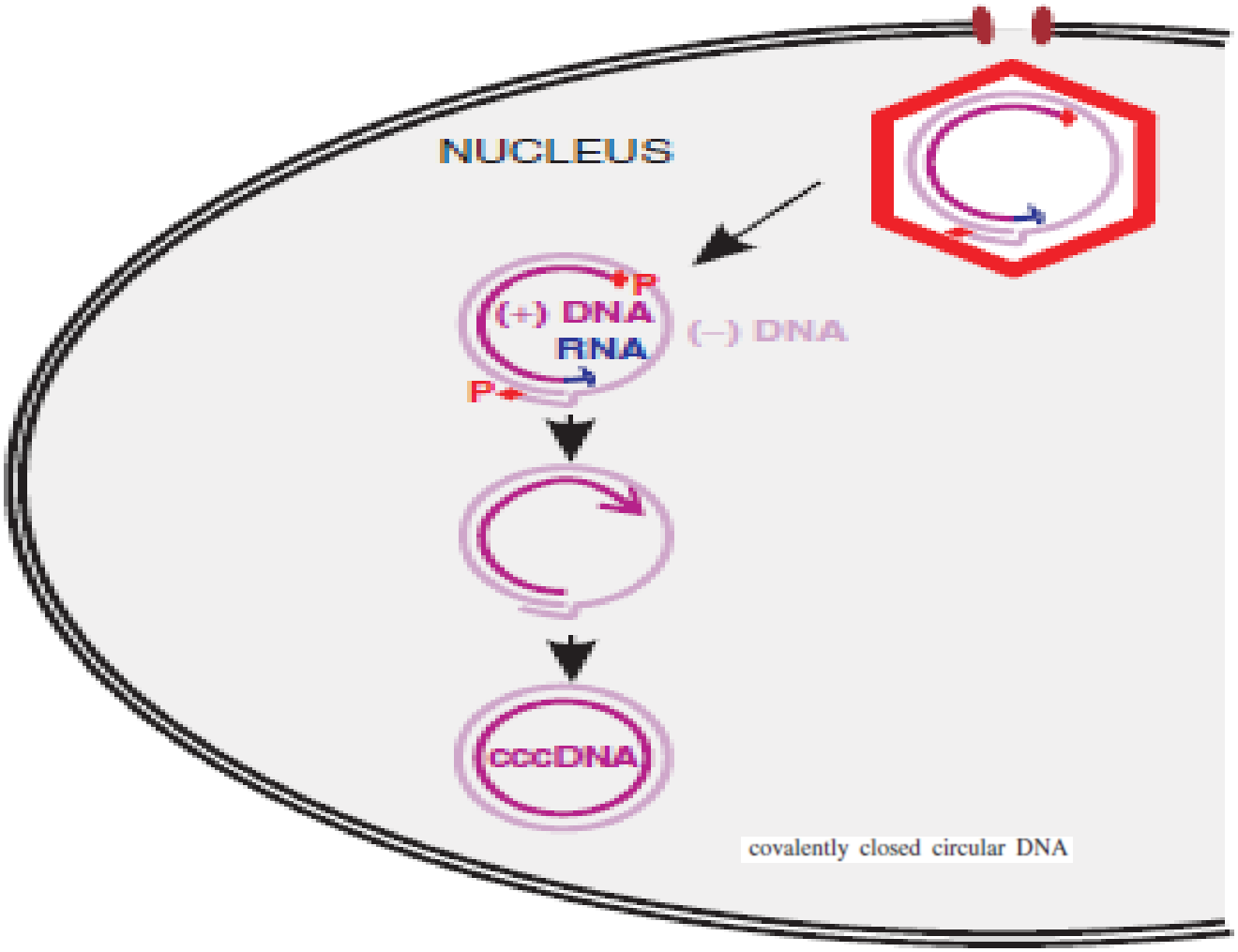


Figure 18.11 *Release of HBV genome from the capsid and conversion into cccDNA.*

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

Viral loads are usually in excess of 10^5 copies/ml in the presence of active viral replication, as indicated by the presence of e antigen.

.

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 .

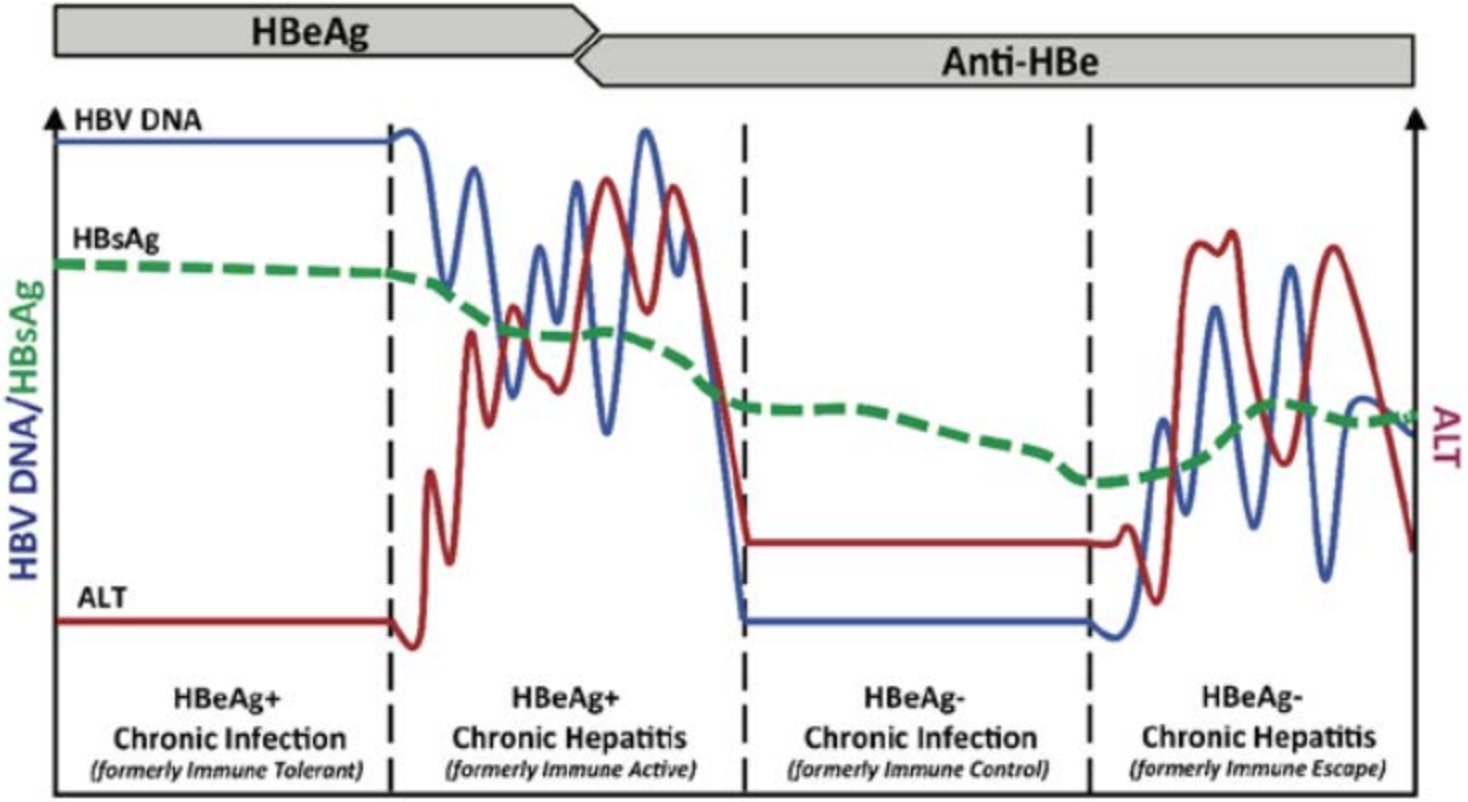


Fig. 1. Disease phases of chronic hepatitis B infection reflecting the updated

Table 1. Phases of chronic HBV as proposed by the EASL Guidelines [2].

	HBeAg positive		HBeAg negative	
	Chronic infection	Chronic hepatitis	Chronic infection	Chronic hepatitis
HBsAg	High	High/intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	$>10^7$ IU/ml	10^4-10^7 IU/ml	<2,000 IU/ml**	>2,000 IU/ml
ALT	Normal	Elevated	Normal	Elevated*
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis

*Persistently or **intermittently HBV DNA levels can be between 2,000 and 20,000 IU/ml in some patients without signs of chronic hepatitis.

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

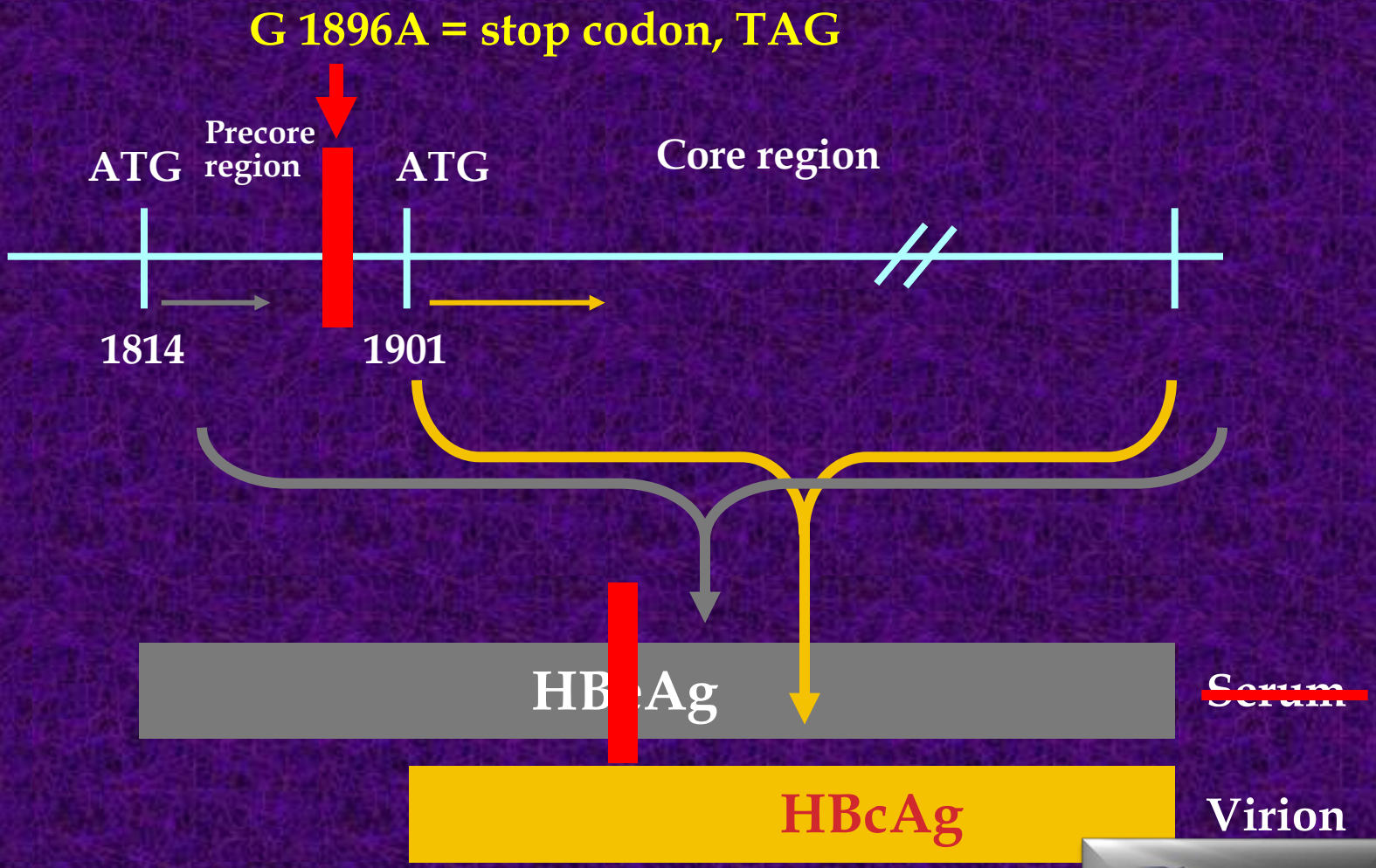
have a high viral load and often evidence of chronic hepatitis

.

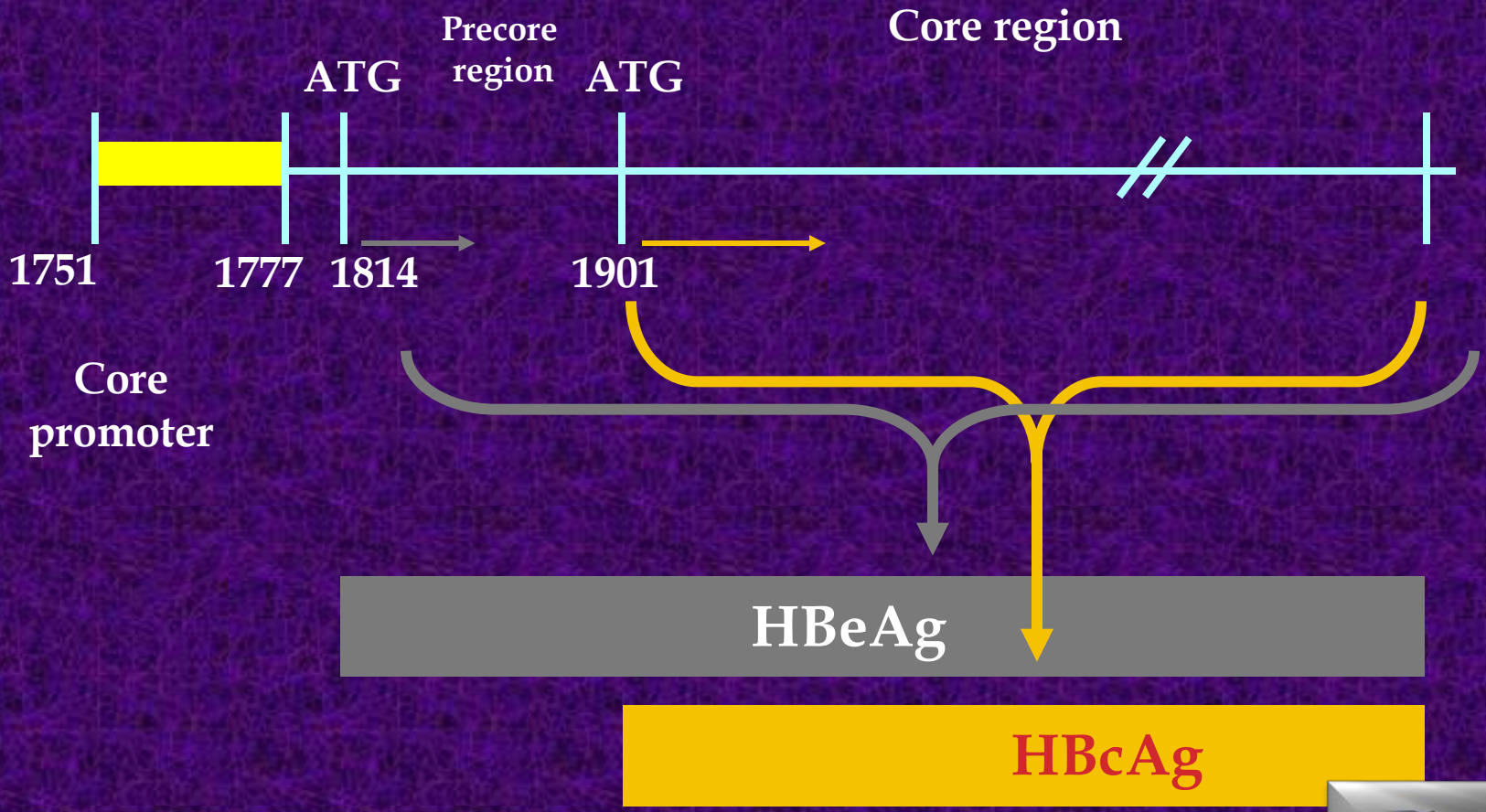
HB e mutation

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

HBeAg and Precore Mutation

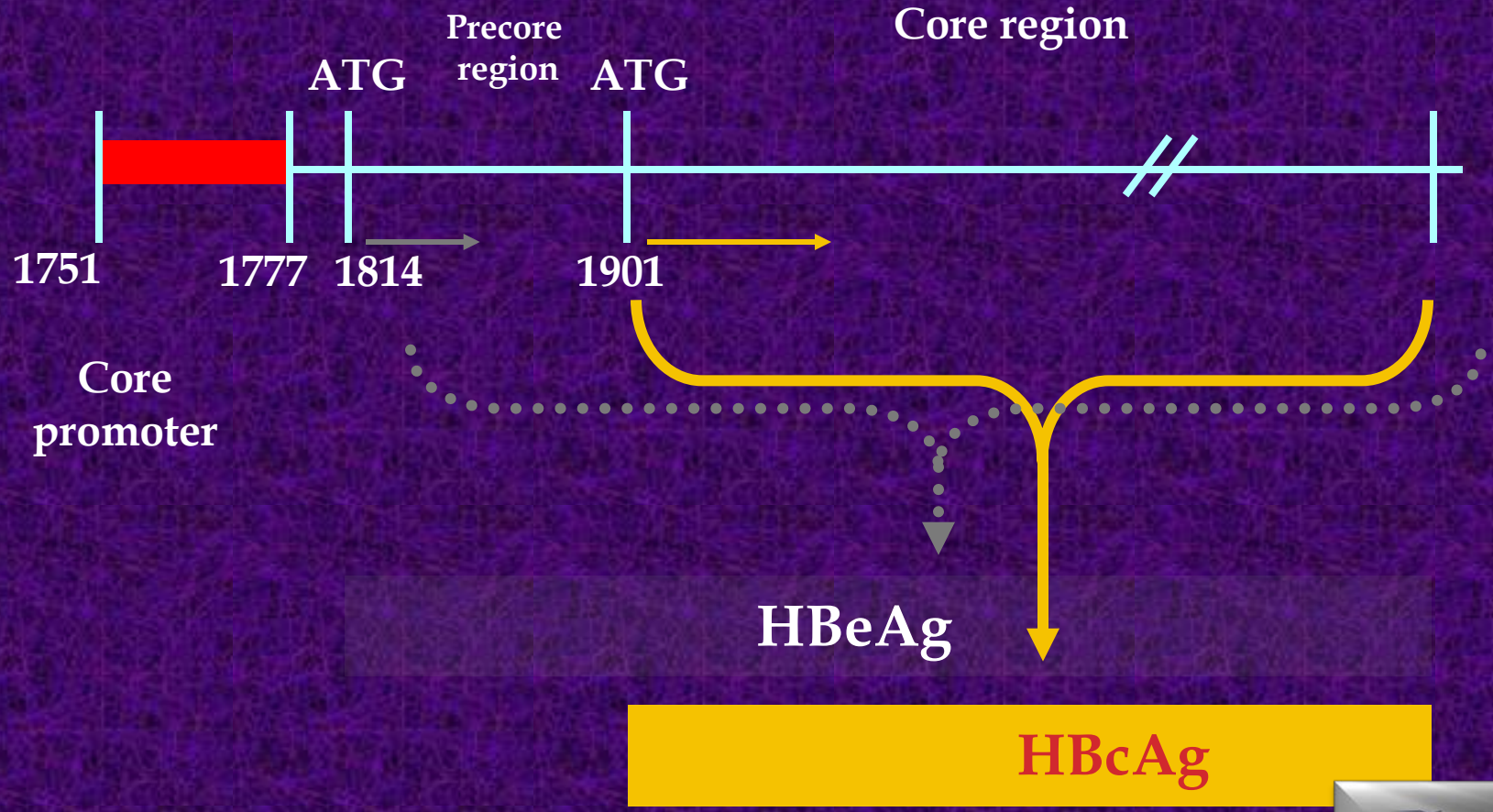


HBeAg and Core Promoter Mutation



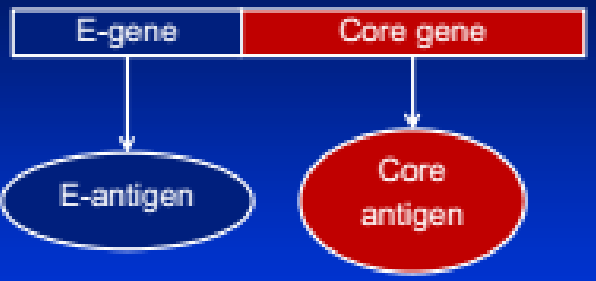
HBeAg and Core Promoter Mutations

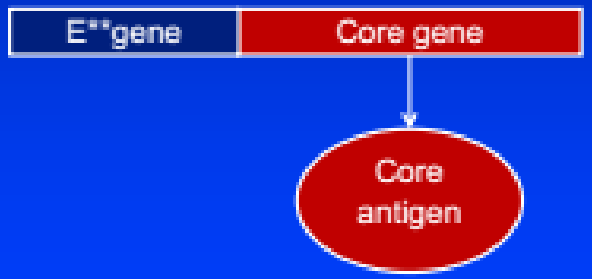
A1762T, G1764A
T1753C, C1766T etc



CHRONIC HBV
WHAT IS E-NEGATIVE ACTIVE HBV

- E-gene located in the pre-core region of HBV
- Not necessary for replication
- Target of the immune response to inactivate HBV





- Mutation of the E-gene
- No detectable E-antigen
- Does not prevent replication
- Prevents the immune response from inactivating HBV

Adapted from: S Ahn et al
Gastroenterol 2003; 125:1370-1378.

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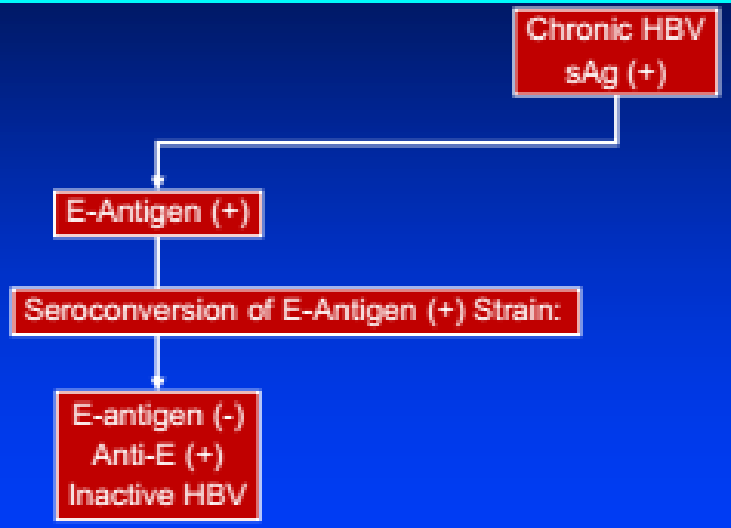
Liver Institute of Virginia

E-ANTIGEN NEGATIVE CHRONIC HBV EVOLUTION



Adapted from: JH Hoofnagle et al.
Hepatology 2007; 45:1056-1075.

The impact of treatment on chronic viral hepatitis

This includes

- **1-improved quality of life**
- **2-regression of fibrosis**
- **3- a reduction in the risk of HCC**
- **4-a reduction in mortality**

Patients with E-antigen negative HBV cannot seroconvert to an inactive state and therefore viral suppression must be considered life long.

- Patients with cirrhosis are at high risk to develop hepatic decompensation if HBV reactivates and liver transaminases flair.

  For this reason it is recommended that all patients with chronic HBV and cirrhosis be treated.
- This includes patients with inactive disease and low levels of HBV DNA

- optimal treatment for a patient with cirrhosis and chronic HBV is an oral antiviral agent.

pregnant women

- If they are HBsurface antigen positive
- HBV DNA should be measured

and

- if this is greater than 200,000 IU/ml

Consider oral antiviral therapy at the start of the third trimester

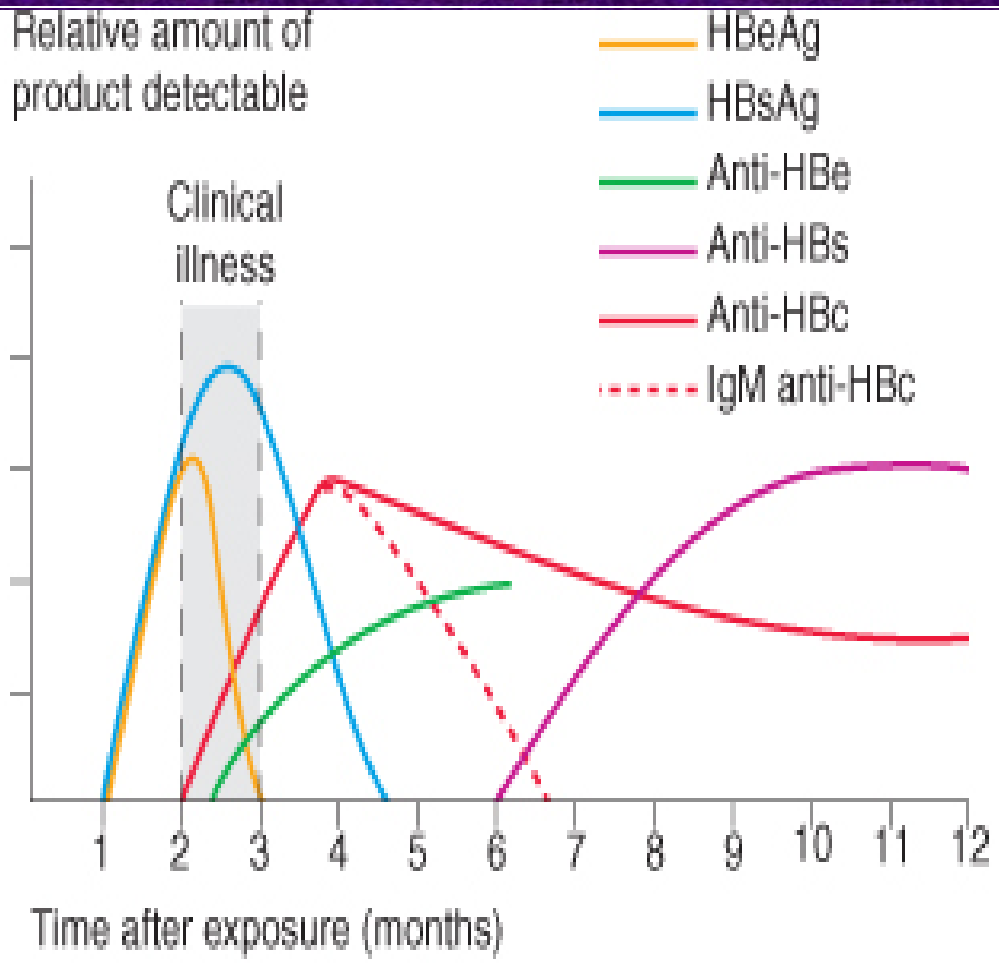


Figure 23.27 Serological responses to hepatitis B virus infection. (HBsAg = hepatitis B surface antigen; anti-HBs = antibody to HBsAg; HBeAg = hepatitis B e antigen; anti-HBe = antibody to HBeAg; anti-HBc = antibody to hepatitis B core antigen)