Hepatitis A-E Viruses

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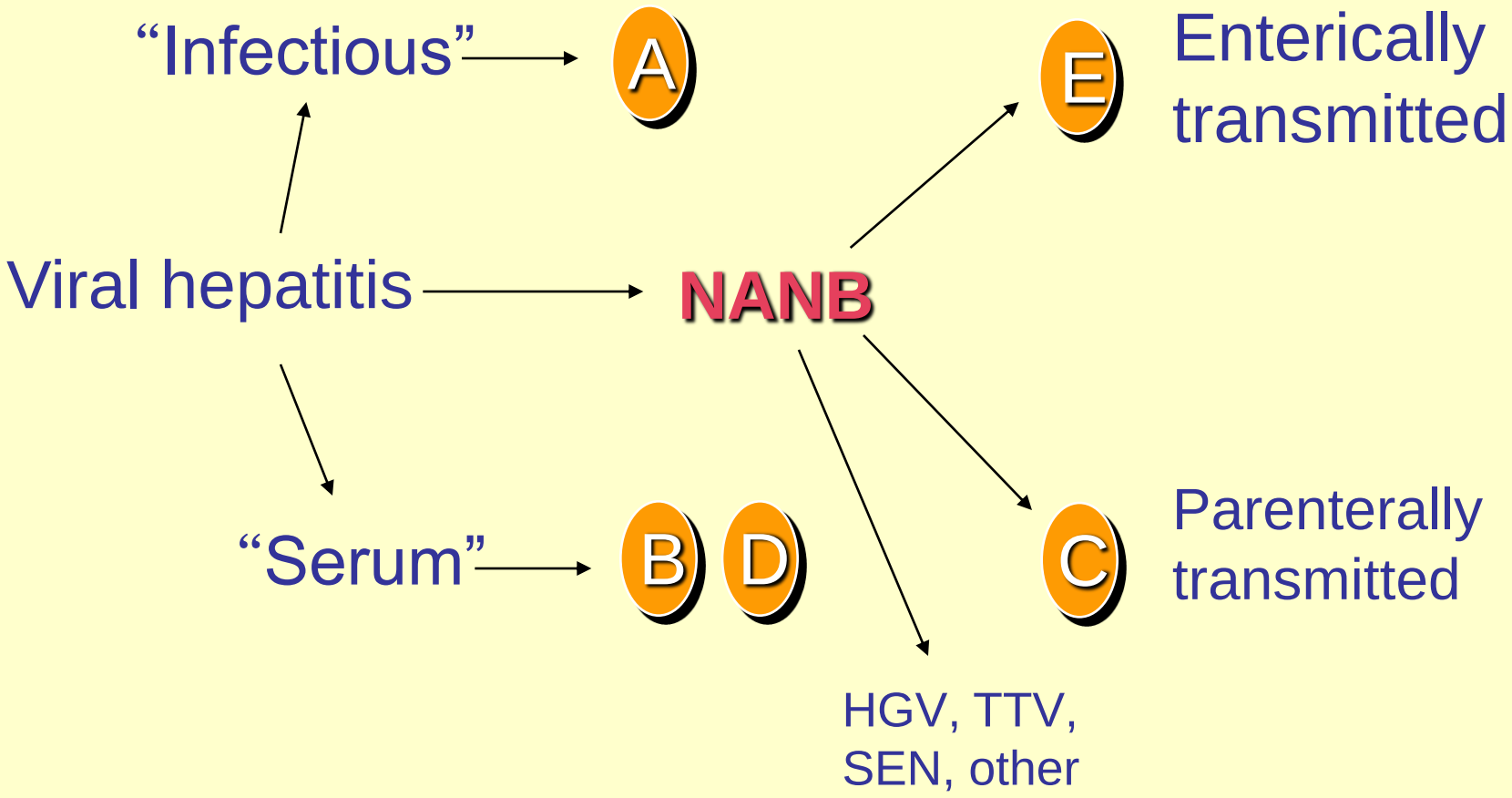
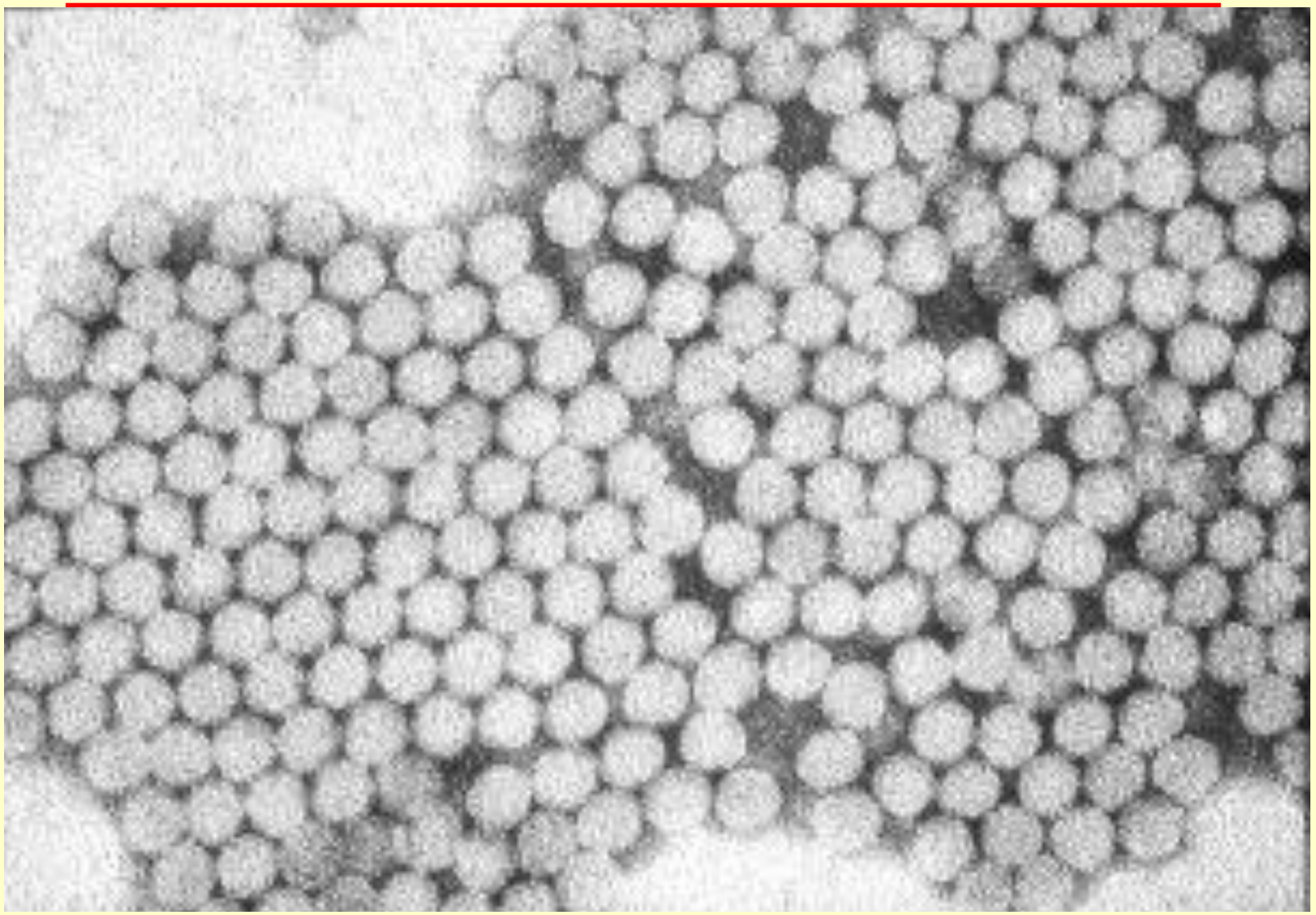
Viral Hepatitis - Historical Perspectives



Type of Hepatitis

	A	B	C	D	E
Source of virus	feces	blood/ blood-derived body fluids	blood/ blood-derived body fluids	blood/ blood-derived body fluids	feces
Route of transmission	fecal-oral	percutaneous permucosal	percutaneous permucosal	percutaneous permucosal	fecal-oral
Chronic infection	no	yes	yes	yes	no
Prevention	pre/post-exposure immunization	pre/post-exposure immunization	blood donor screening; risk behavior modification	pre/post-exposure immunization; risk behavior modification	ensure safe drinking water

Hepatitis A Virus



Hepatitis A Virus

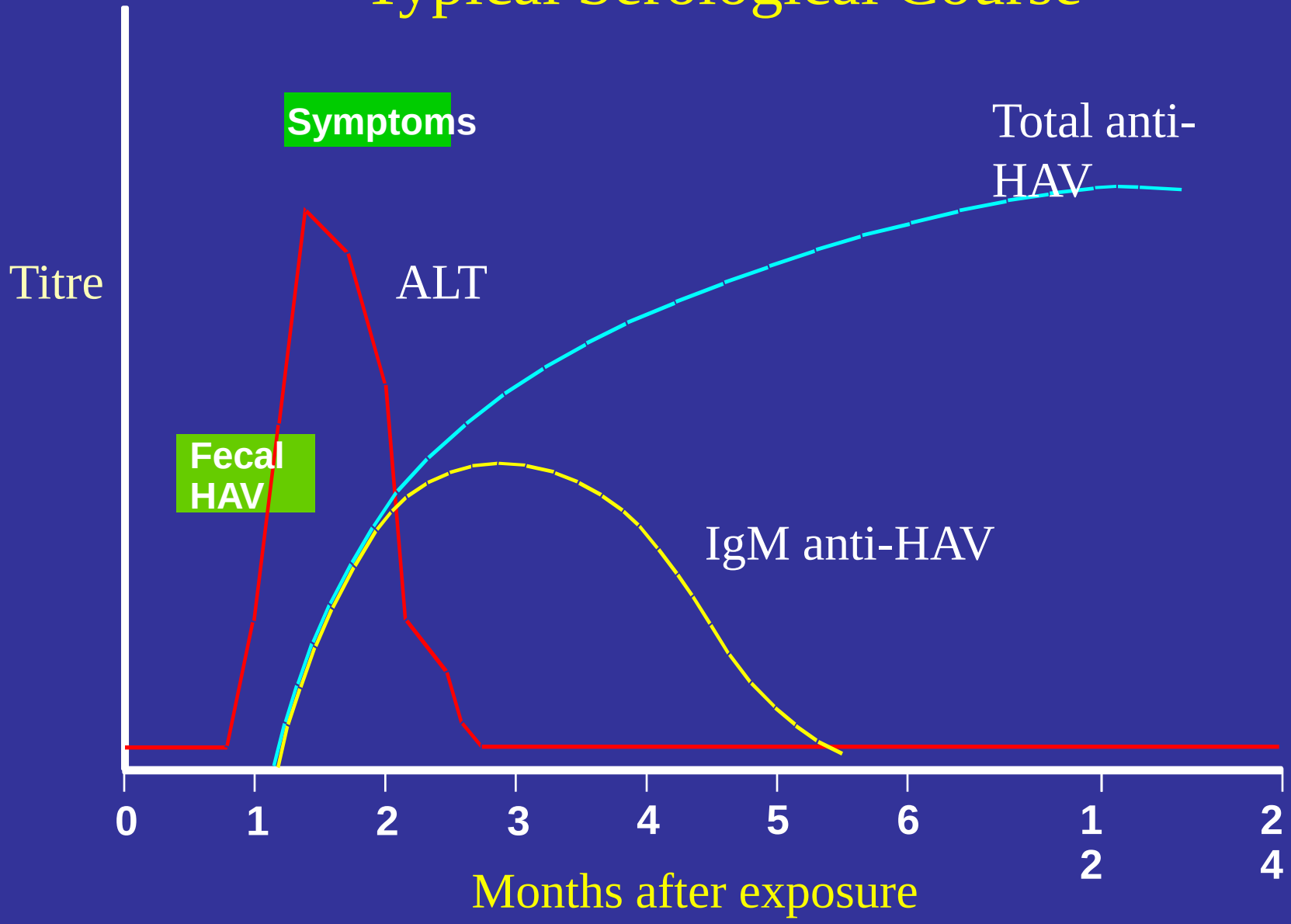
- Naked RNA virus
- Related to enteroviruses, formerly known as enterovirus 72, now put in its own family: heptovirus
- One stable serotype only
- Difficult to grow in cell culture: primary marmoset cell culture and also in vivo in chimpanzees and marmosets
- 4 genotypes exist, but in practice most of them are group 1

Hepatitis A - Clinical Features

Incubation period:	Average 30 days Range 15-50 days
Jaundice by age group:	<6 yrs, <10% 6-14 yrs, 40%-50% >14 yrs, 70%-80%
Complications:	Fulminant hepatitis Cholestatic hepatitis Relapsing hepatitis
Chronic sequelae:	None

Hepatitis A Infection

Typical Serological Course



Hepatitis A Virus Transmission

- Close personal contact
  (e.g., household contact, sex contact, child day care centers)
- Contaminated food, water
  (e.g., infected food handlers, raw shellfish)
- Blood exposure (rare)
  (e.g., injecting drug use, transfusion)

Global Patterns of Hepatitis A Virus Transmission

Endemicity	Disease Rate	Peak Age of Infection	Transmission Patterns
High	Low to High	Early childhood	Person to person; outbreaks uncommon
Moderate	High	Late childhood/ young adults	Person to person; food and waterborne outbreaks
Low	Low	Young adults	Person to person; food and waterborne outbreaks
Very low	Very low	Adults	Travelers; outbreaks uncommon

Laboratory Diagnosis

- Acute infection is diagnosed by the detection of HAV-IgM in serum by EIA.
- Past Infection i.e. immunity is determined by the detection of HAV-IgG by EIA.
- Cell culture – difficult and take up to 4 weeks, not routinely performed
- Direct Detection – EM, RT-PCR of faeces. Can detect illness earlier than serology but rarely performed.

Hepatitis A Vaccination Strategies
Epidemiologic Considerations

- Many cases occur in community-wide outbreaks
  - no risk factor identified for most cases
  - highest attack rates in 5-14 year olds
  - children serve as reservoir of infection
- Persons at increased risk of infection
  - travelers
  - homosexual men
  - injecting drug users

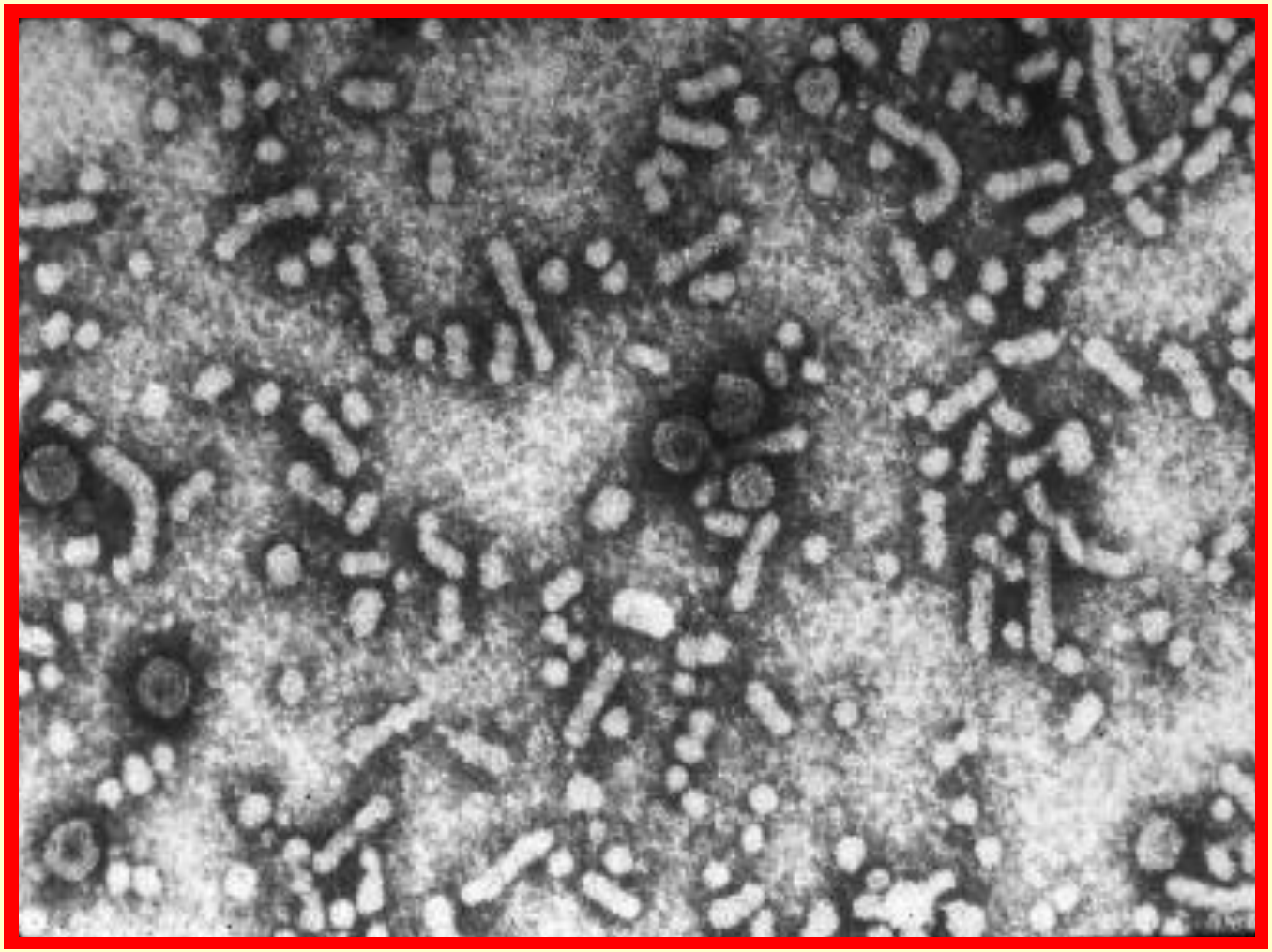
Hepatitis A Prevention - Immune Globulin

- Pre-exposure
  - travelers to intermediate and high HAV-endemic regions
- Post-exposure (within 14 days)

  Routine
  - household and other intimate contacts

  Selected situations
  - institutions (e.g., day care centers)
  - common source exposure (e.g., food prepared by infected food handler)

Hepatitis B Virus



Hepatitis B Virus - Virology

- Double stranded DNA virus,the + strand not complete
- Replication involves a reverse transcriptase.
- Complete Dane particle 42 nm, 28 nm electron dense core, containing HBcAg and HBeAg. The coat and the 22 nm free particles contain HBsAg
- At least 4 phenotypes of HBsAg are recognized;
  adw, adr, ayw and ayr.
- The HBcAg is of a single serotype
- Hepatitis B virus (HBV) has been classified into 8 genotypes (A-H).
  - Genotypes A and C predominate in the US and Europe. However, genotypes B and D are also present in the US. Genotype F predominates in South America and in Alaska, while A, D and E predominate in Africa. Genotype D predominates in Russia and in all its prior dominions, while in Asia, genotypes B and C predominate.
  - Available data suggests that genotype A produces a milder disease, respond better to IFN therapy, and is less likely to develop hepatocellular carcinoma.
- It has not yet been possible to propagate the virus in cell culture.

Hepatitis B - Clinical Features

Incubation period:	Average 60-90 days Range 45-180 days
Clinical illness (jaundice):	<5 yrs, <10% 5 yrs, 30%-50%
Acute case-fatality rate:	0.5%-1%
Chronic infection:	<5 yrs, 30%-90% 5 yrs, 2%-10%
Premature mortality from chronic liver disease:	15%-25%

Spectrum of Chronic Hepatitis B Diseases

1 Chronic Persistent Hepatitis - asymptomatic

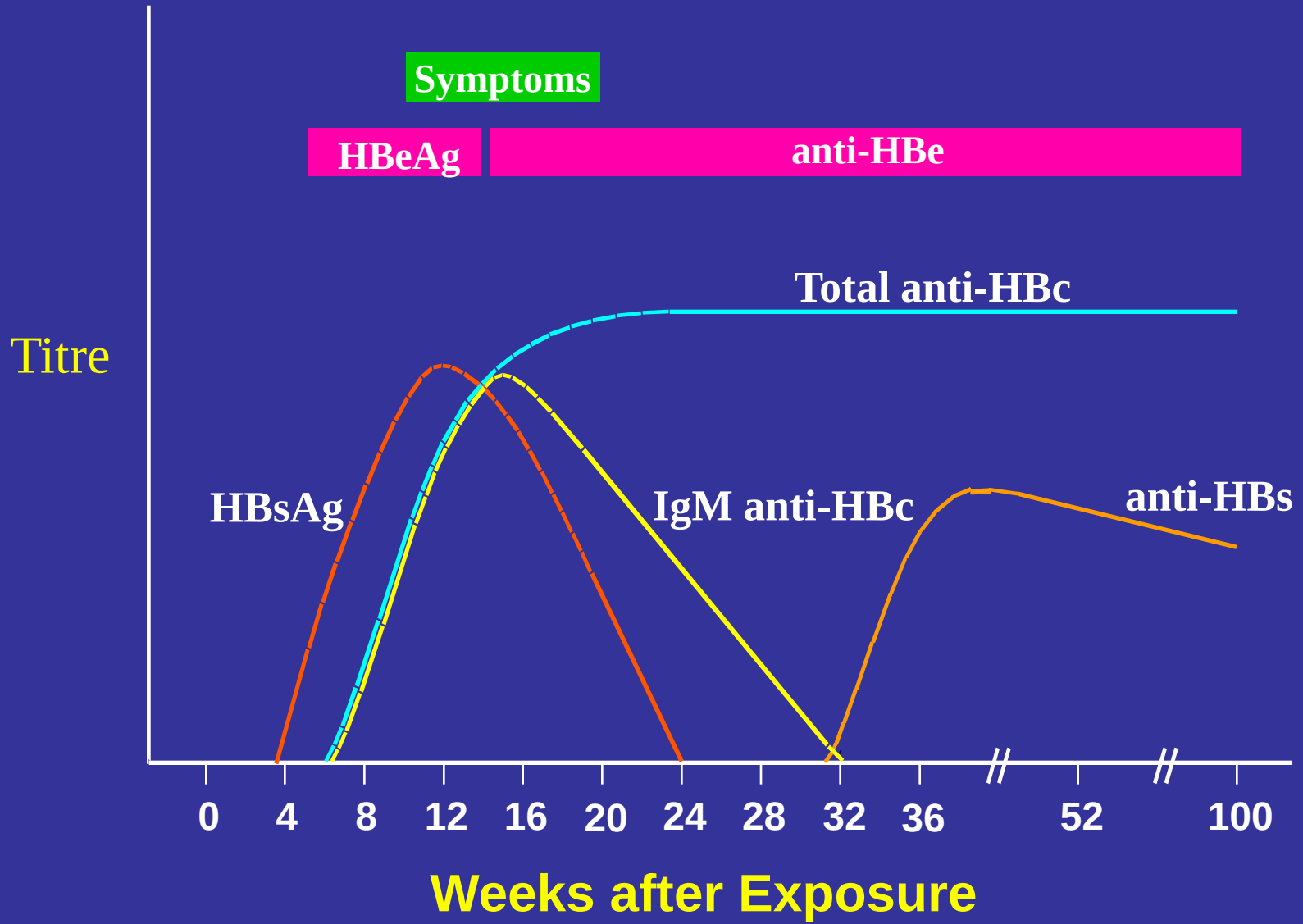
2. Chronic Active Hepatitis - symptomatic exacerbations of hepatitis

3. Cirrhosis of Liver

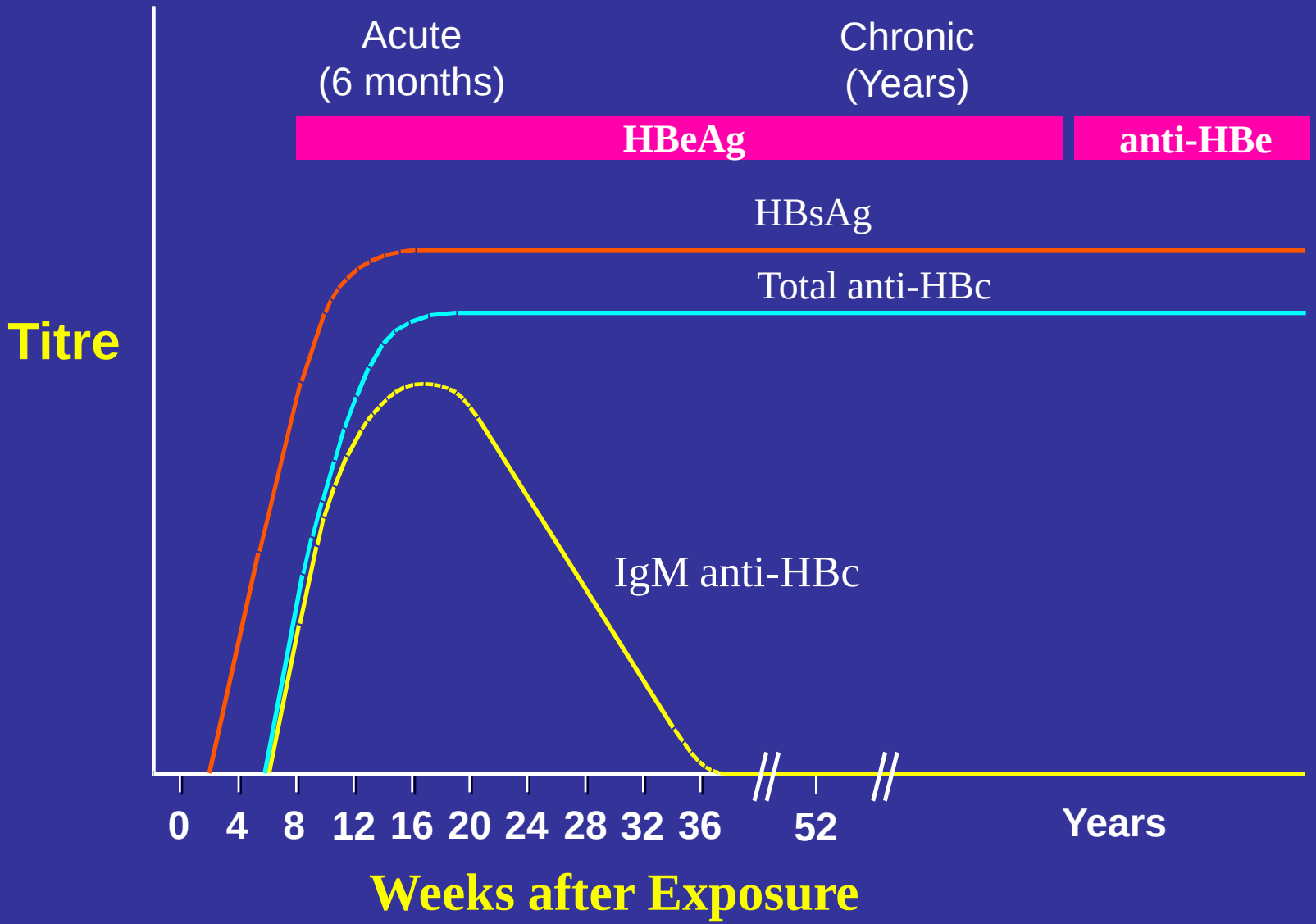
4. Hepatocellular Carcinoma

Acute Hepatitis B Virus Infection with Recovery

Typical Serologic Course



Progression to Chronic Hepatitis B Virus Infection
Typical Serologic Course



Global Patterns of Chronic HBV Infection

- High (>8%): 45% of global population
  - lifetime risk of infection >60%
  - early childhood infections common
- Intermediate (2%-7%): 43% of global population
  - lifetime risk of infection 20%-60%
  - infections occur in all age groups
- Low (<2%): 12% of global population
  - lifetime risk of infection <20%
  - most infections occur in adult risk groups

Concentration of Hepatitis B Virus in Various Body Fluids

High	Moderate	Low/Not Detectable
blood	semen	urine
serum	vaginal fluid	feces
wound exudates	saliva	sweat
		tears
		breastmilk

Hepatitis B Virus
Modes of Transmission

- Sexual - sex workers and homosexuals are particular at risk.
- Parenteral - IVDA, Health Workers are at increased risk.
- Perinatal - Mothers who are HBeAg positive are much more likely to transmit to their offspring than those who are not. Perinatal transmission is the main means of transmission in high prevalence populations.

Diagnosis

- A battery of serological tests are used for the diagnosis of acute and chronic hepatitis B infection.
- HBsAg - used as a general marker of infection.
- HBsAb - used to document recovery and/or immunity to HBV infection.
- anti-HBc IgM - marker of acute infection.
- anti-HBcIgG - past or chronic infection.
- HBeAg - indicates active replication of virus and therefore infectiveness.
- Anti-Hbe - virus no longer replicating. However, the patient can still be positive for HBsAg which is made by integrated HBV.
- HBV-DNA - indicates active replication of virus, more accurate than HBeAg especially in cases of escape mutants. Used mainly for monitoring response to therapy.

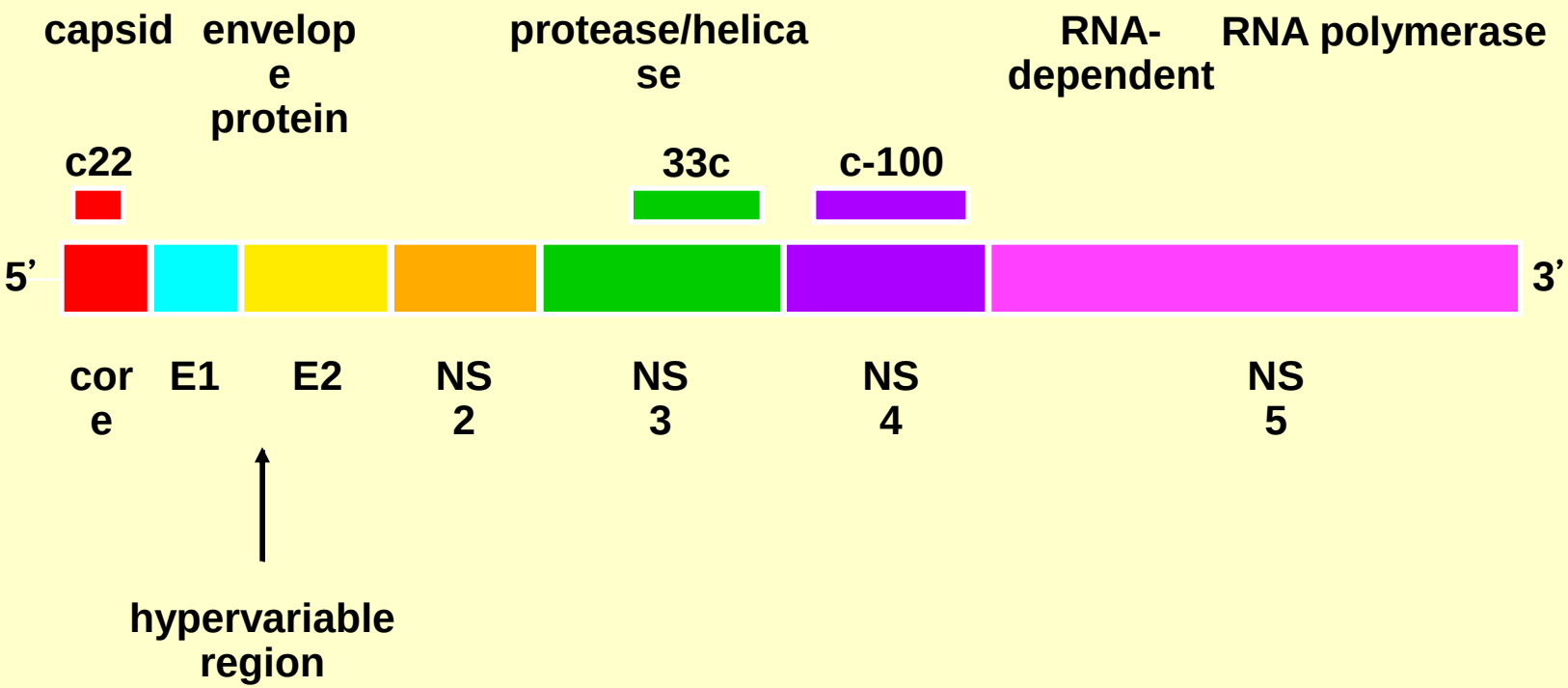
Treatment

- Interferon - for HBeAg +ve carriers with chronic active hepatitis. Response rate is 30 to 40%.
  - alpha-interferon 2b (original)
  - alpha-interferon 2a (newer, claims to be more efficacious and efficient)
- Lamivudine - a nucleoside analogue reverse transcriptase inhibitor. Well tolerated, most patients will respond favorably. However, tendency to relapse on cessation of treatment. Another problem is the rapid emergence of drug resistance.
- Adefovir – less likely to develop resistance than Lamivudine and may be used to treat Lamivudine resistance HBV. However more expensive and toxic
- Entecavir – most powerful antiviral known, similar to Adefovir
- Successful response to treatment will result in the disappearance of HBsAg, HBV-DNA, and seroconversion to HBeAg.

Prevention

- Vaccination - highly effective recombinant vaccines are now available. Vaccine can be given to those who are at increased risk of HBV infection such as health care workers. It is also given routinely to neonates as universal vaccination in many countries.
- Hepatitis B Immunoglobulin - HBIG may be used to protect persons who are exposed to hepatitis B. It is particular efficacious within 48 hours of the incident. It may also be given to neonates who are at increased risk of contracting hepatitis B i.e. whose mothers are HBsAg and HBeAg positive.
- Other measures - screening of blood donors, blood and body fluid precautions.

Hepatitis C Virus



Hepatitis C Virus

- Genome resembled that of a flavivirus positive stranded RNA genome of around 10,000 bases
- 1 single reading frame, structural genes at the 5' end, the non-structural genes at the 3' end. enveloped virus, virion thought to 30-60nm in diameter
- morphological structure remains unknown
- HCV has been classified into a total of six genotypes (type 1 to 6) on the basis of phylogenetic analysis
- Genotype 1 and 4 has a poorer prognosis and response to interferon therapy,
- In Hong Kong, genotype 1 accounts for around 67% of cases and genotype 6 around 25%.

Terminology

Family → Genus → Species → Genotype → Subtype → Quasispecies

Term	Definition	% Nucleotide Similarity
Genotype	Genetic heterogeneity among different HCV isolates	65.7-68.9
Subtype	Closely related isolates within each of the major genotypes	76.9-80.1
Quasispecies	Complex of genetic variants within individual isolates	90.8-99

Hepatitis C - Clinical Features

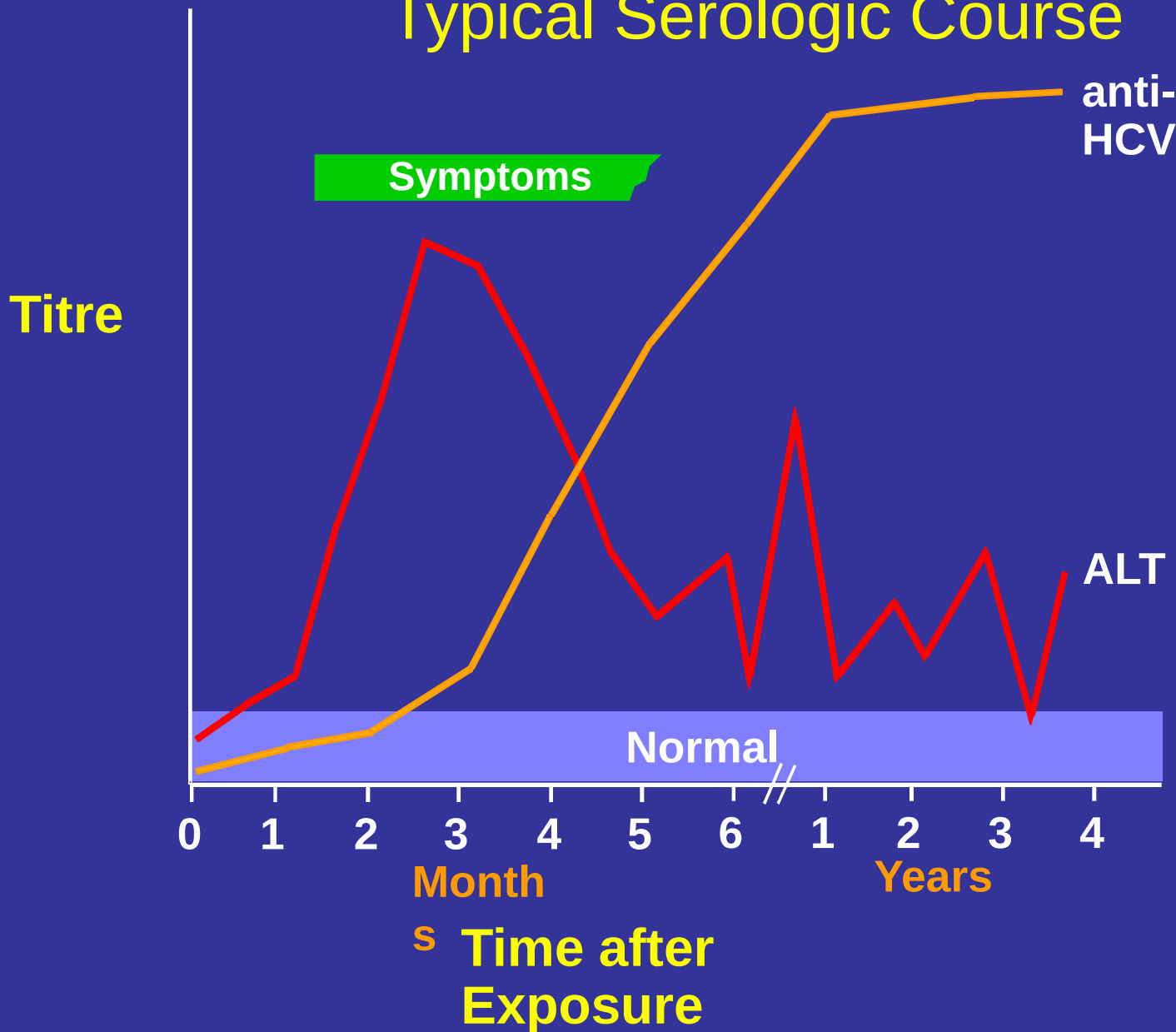
Incubation period:	Average 6-7 wks Range 2-26 wks
Clinical illness (jaundice):	30-40% (20-30%)
Chronic hepatitis:	70%
Persistent infection:	85-100%
Immunity:	No protective antibody response identified

Chronic Hepatitis C Infection

- The spectrum of chronic hepatitis C infection is essentially the same as chronic hepatitis B infection.
- All the manifestations of chronic hepatitis B infection may be seen, albeit with a lower frequency i.e. chronic persistent hepatitis, chronic active hepatitis, cirrhosis, and hepatocellular carcinoma.

Hepatitis C Virus Infection

Typical Serologic Course



Risk Factors Associated with Transmission of HCV

- Transfusion or transplant from infected donor
- Injecting drug use
- Hemodialysis (yrs on treatment)
- Accidental injuries with needles/sharps
- Sexual/household exposure to anti-HCV-positive contact
- Multiple sex partners
- Birth to HCV-infected mother

Laboratory Diagnosis

- HCV antibody - generally used to diagnose hepatitis C infection. Not useful in the acute phase as it takes at least 4 weeks after infection before antibody appears.
- HCV-RNA - various techniques are available e.g. PCR and branched DNA. May be used to diagnose HCV infection in the acute phase. However, its main use is in monitoring the response to antiviral therapy.
- HCV-antigen - an EIA for HCV antigen is available. It is used in the same capacity as HCV-RNA tests but is much easier to carry out.

Prognostic Tests

- Genotyping – genotype 1 and 4 have a worse prognosis overall and respond poorly to interferon therapy. A number of commercial and in-house assays are available.
  - Genotypic methods – DNA sequencing, PCR-hybridization e.g. INNO-LIPA.
  - Serotyping – particularly useful when the patient does not have detectable RNA.
- Viral Load – patients with high viral load are thought to have a poorer prognosis. Viral load is also used for monitoring response to IFN therapy. A number of commercial and in-house tests are available.

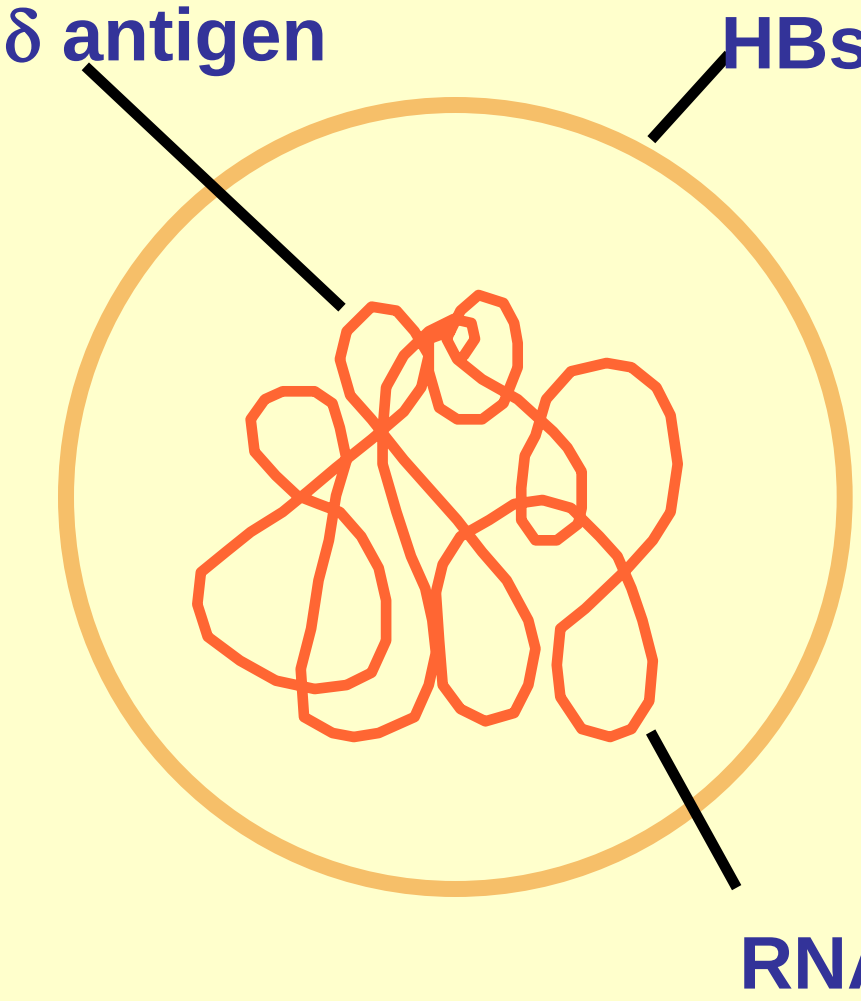
Treatment

- Interferon - may be considered for patients with chronic active hepatitis. The response rate is around 50% but 50% of responders will relapse upon withdrawal of treatment.
- Ribavirin - there is less experience with ribavirin than interferon. However, recent studies suggest that a combination of interferon and ribavirin is more effective than interferon alone.

Prevention of Hepatitis C

- Screening of blood, organ, tissue donors
- High-risk behavior modification
- Blood and body fluid precautions

Hepatitis D (Delta) Virus



Hepatitis D Virus

- The delta agent is a defective virus which shows similarities with the viroids in plants.
- The agent consists of a particle 35 nm in diameter consisting of the delta antigen surrounded by an outer coat of HBsAg.
- The genome of the virus is very small and consists of a single-stranded RNA

Hepatitis D - Clinical Features

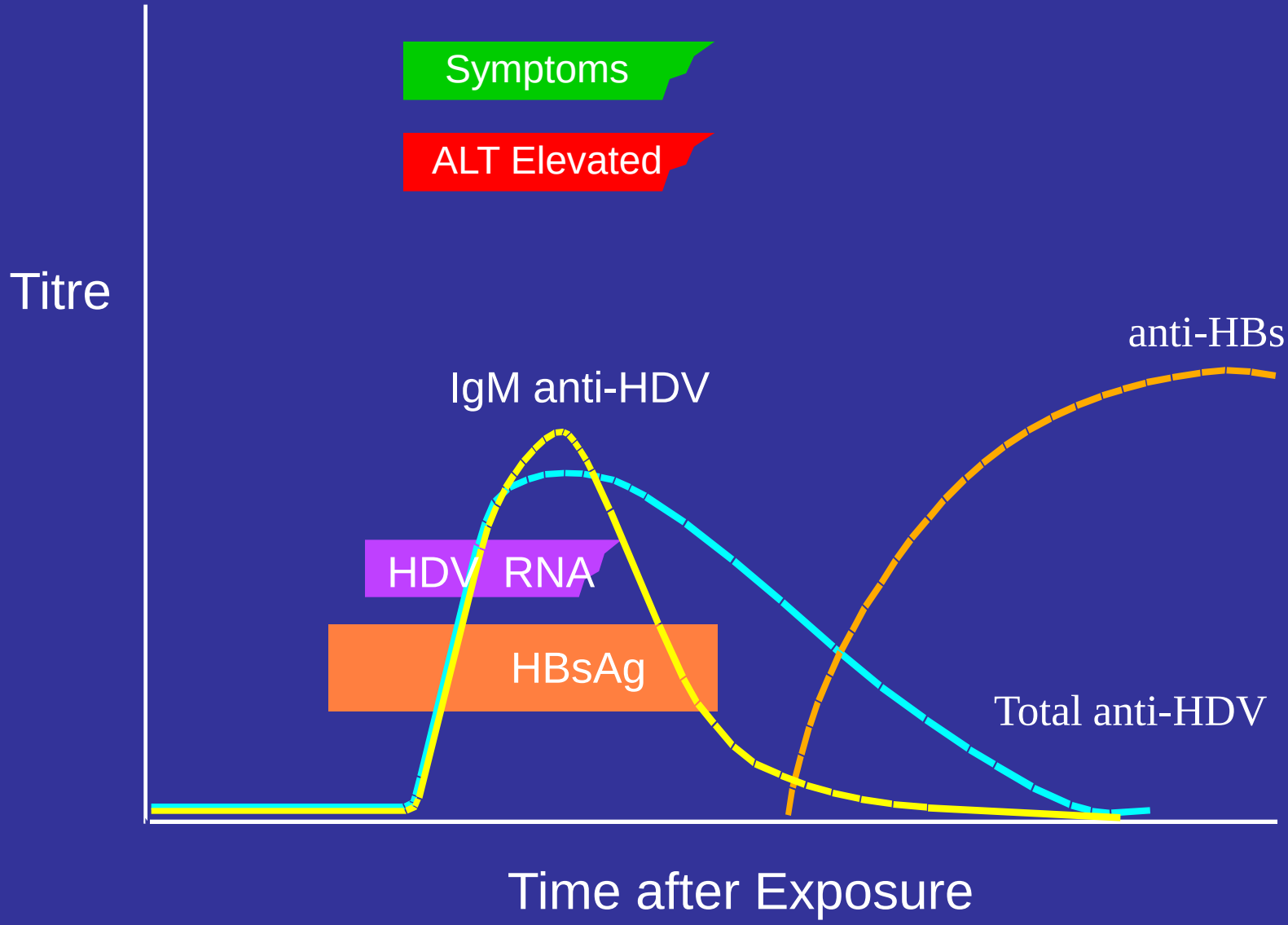
- Coinfection
  - severe acute disease.
  - low risk of chronic infection.
- Superinfection
  - usually develop chronic HDV infection.
  - high risk of severe chronic liver disease.
  - may present as an acute hepatitis.

Hepatitis D Virus Modes of Transmission

- Percutanous exposures
  - injecting drug use
- Permucosal exposures
  - sex contact

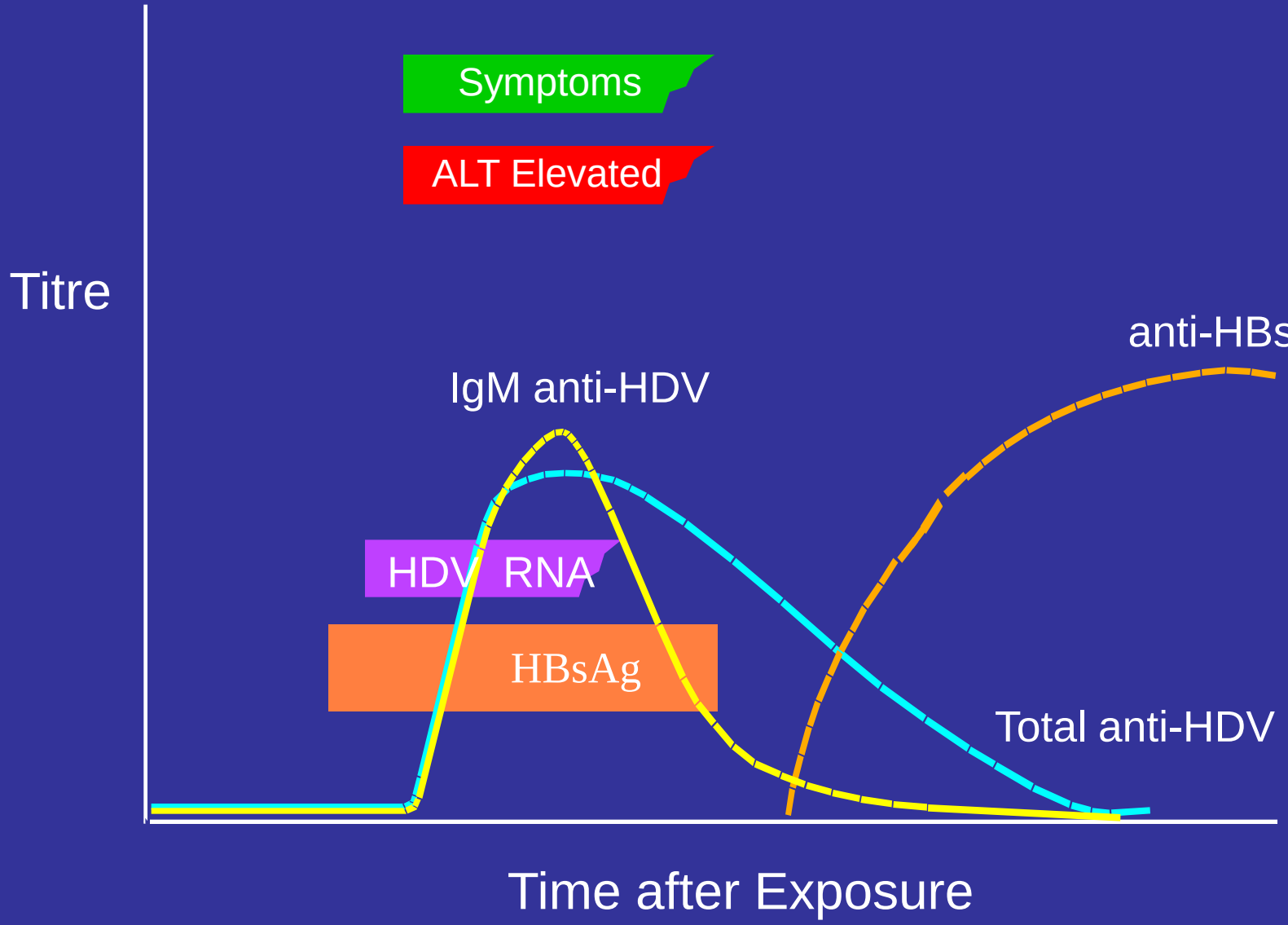
HBV - HDV Coinfection

Typical Serologic Course



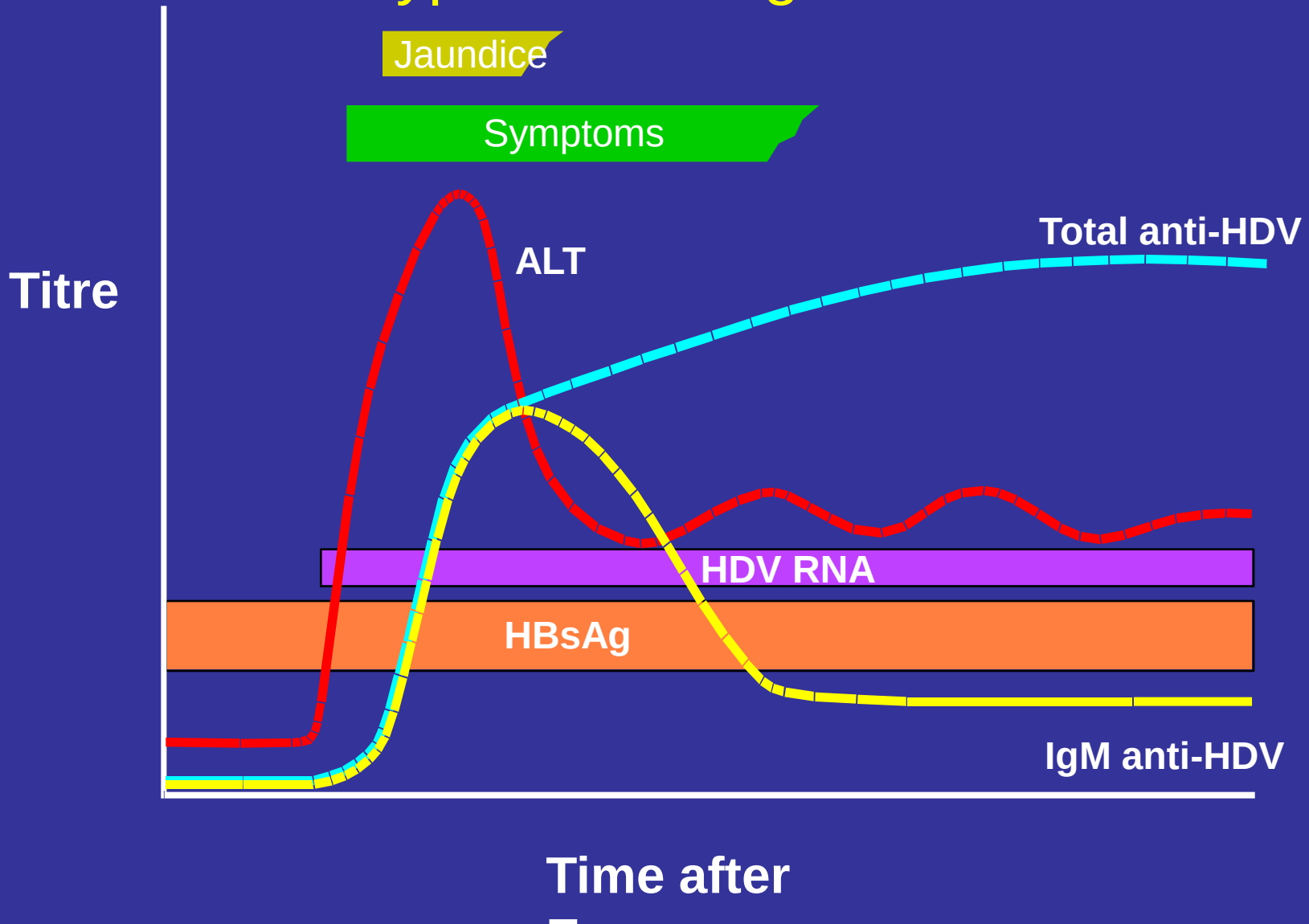
HBV - HDV Coinfection

Typical Serologic Course



HBV - HDV Superinfection

Typical Serologic Course



Hepatitis D - Prevention

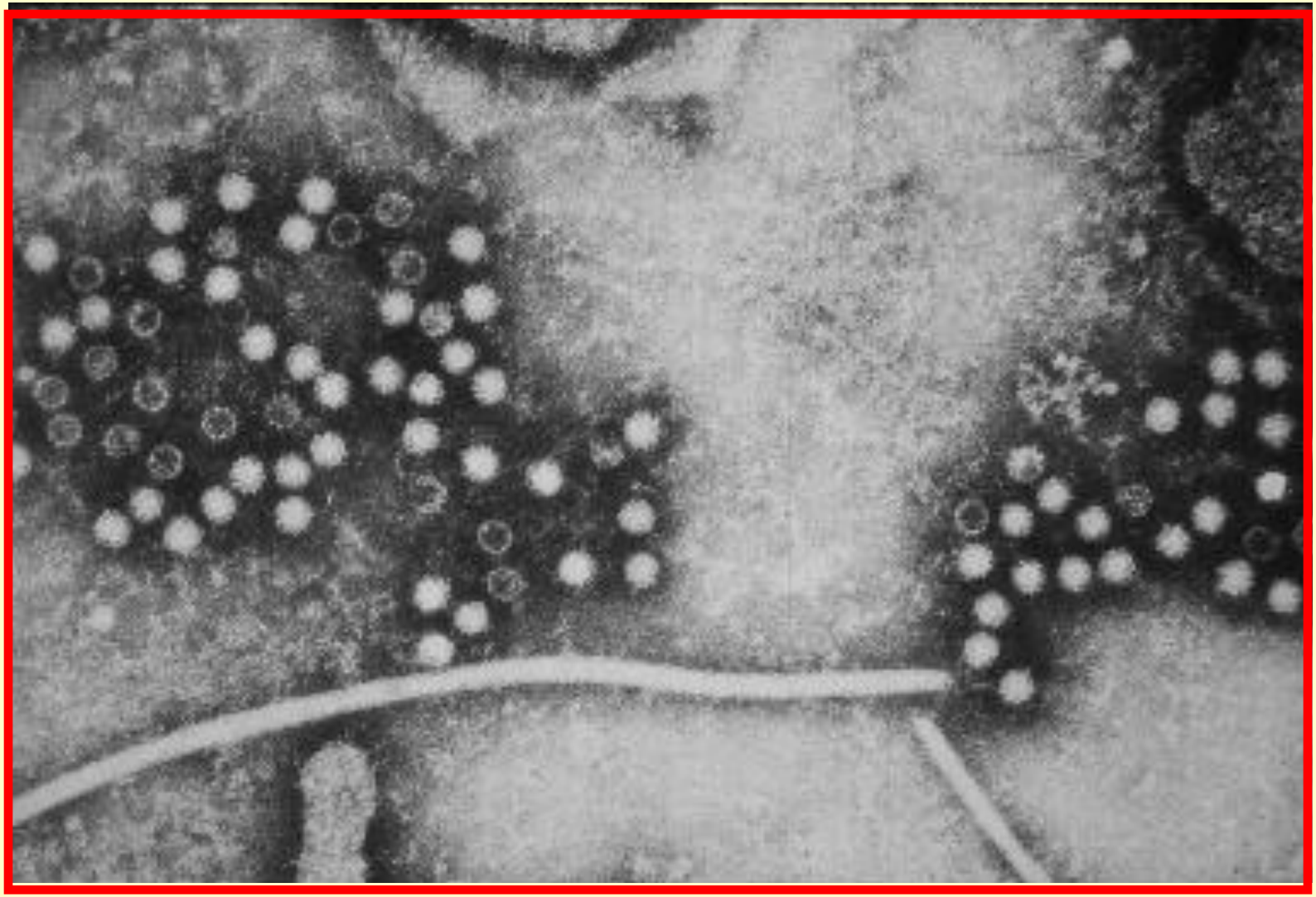
- HBV-HDV Coinfection

  Pre or postexposure prophylaxis to prevent HBV infection.

- HBV-HDV Superinfection

  Education to reduce risk behaviors among persons with chronic HBV infection.

Hepatitis E Virus



Hepatitis E Virus

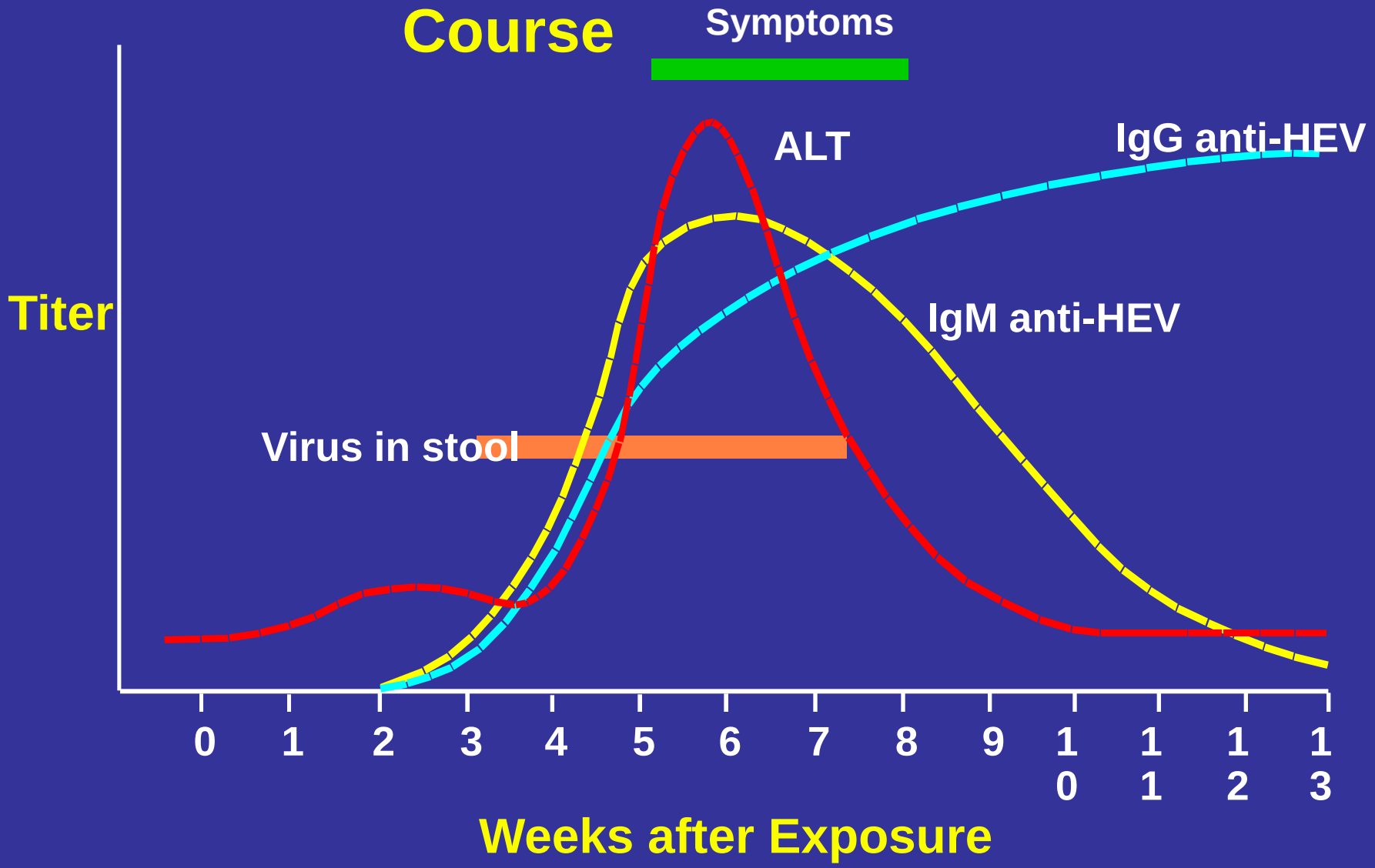
- Calicivirus-like viruses
- unenveloped RNA virus, 32-34nm in diameter
- +ve stranded RNA genome, 7.6 kb in size.
- very labile and sensitive
- Can only be cultured recently

Hepatitis E - Clinical Features

- Incubation period: Average 40 days
Range 15-60 days
- Case-fatality rate: Overall, 1%-3%
Pregnant women, 15%-25%
- Illness severity: Increased with age
- Chronic sequelae: None identified

Hepatitis E Virus Infection

Typical Serologic Course



Hepatitis E - Epidemiologic Features

- Most outbreaks associated with faecally contaminated drinking water.
- Several other large epidemics have occurred since in the Indian subcontinent and the USSR, China, Africa and Mexico.
- In the United States and other nonendemic areas, where outbreaks of hepatitis E have not been documented to occur, a low prevalence of anti-HEV (<2%) has been found in healthy populations. The source of infection for these persons is unknown.
- Minimal person-to-person transmission.

Prevention and Control Measures for Travelers to HEV-Endemic Regions

- Avoid drinking water (and beverages with ice) of unknown purity, uncooked shellfish, and uncooked fruit/vegetables not peeled or prepared by traveler.
- IG prepared from donors in Western countries does not prevent infection.
- Unknown efficacy of IG prepared from donors in endemic areas.
- Vaccine?