Viral Hepatitis

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Introduction to Viral Hepatitis

- **Definition:** Inflammation of the liver caused by viral infection
- **Global health burden:** Affects millions annually
- **Primary causes:** Five major hepatotropic viruses (A-E)
- **Spectrum of disease:** From asymptomatic to fulminant hepatic failure
- **Long-term concerns:** Chronic infection, cirrhosis, and hepatocellular carcinoma

Classification of Hepatitis Viruses

Virus	Family	Genome	Transmission
HAV	Picornaviridae	ssRNA (+)	Fecal-oral
HBV	Hepadnaviridae	Partially dsDNA	Parenteral, sexual, vertical
HCV	Flaviviridae	ssRNA (+)	Primarily parenteral
HDV	Deltavirus	Circular ssRNA (-)	Requires HBV co-infection
HEV	Hepeviridae	ssRNA (+)	Fecal-oral, zoonotic

Global Epidemiology

- **HAV:** Endemic in developing countries; decreased incidence in developed nations due to improved sanitation
- **HBV:** 296 million chronic carriers worldwide; hyperendemic in Asia and Africa
- **HCV:** 58 million chronically infected globally; highest prevalence in Egypt, Pakistan, and specific regions
- **HDV:** 15-20 million co-infected with HBV; endemic in Mediterranean basin, Middle East, and parts of South America
- **HEV:** Endemic in South Asia, Middle East, Africa; emerging zoonotic reservoirs in developed countries

HAV - Introduction

- **Structure:** Non-enveloped, icosahedral, 27-32 nm diameter
- **Family:** *Picornaviridae*
- **Genome:** Single-stranded, positive-sense RNA
- **Epidemiology:** ~100 million infections annually worldwide
  - Higher prevalence in Africa, Asia, and Latin America
  - Endemic in areas with poor sanitation and limited clean water

HAV: Transmission

- Primary transmission:
  - Fecal-oral route
  - Contaminated food (especially undercooked shellfish)
  - Contaminated water supplies
  - Person-to-person contact in settings with suboptimal hygiene

HAV: Risk Factors

- High-risk groups:
  - International travelers to endemic regions
  - Men who have sex with men (MSM)
  - Military personnel deployed to endemic areas
  - People who use recreational drugs
  - Children and workers in daycare centers
  - Homeless populations

HAV: Pathogenesis

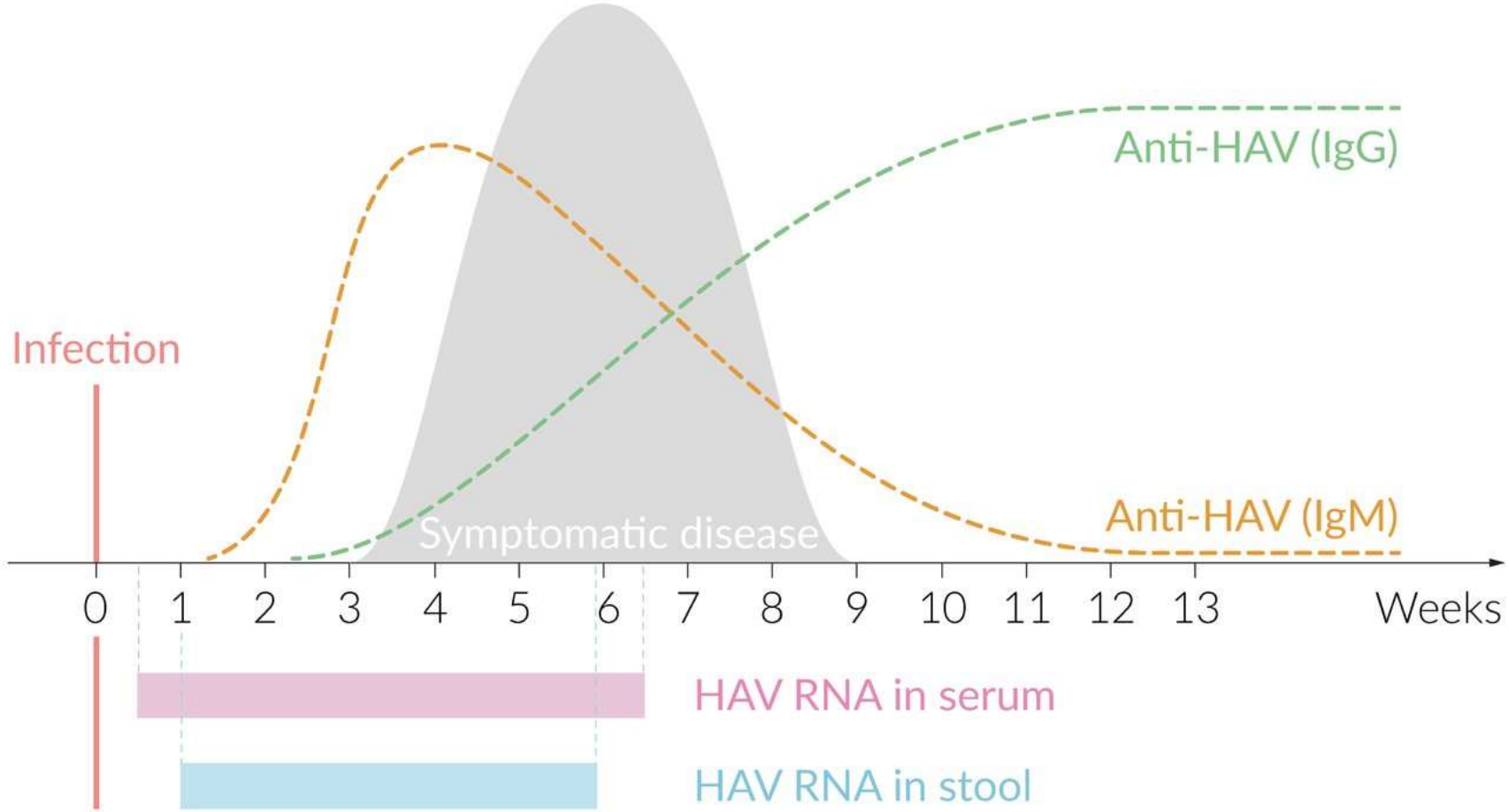
- Virus ingested → crosses intestinal epithelium
- Reaches liver via portal circulation
- Replicates in hepatocytes
- **No direct cytopathic effect**
- Liver injury is primarily **immune-mediated**:
  - Cytotoxic T-cell response against infected hepatocytes
- Virions excreted in bile and shed in feces
- Peak infectivity: Before symptom onset (important for transmission dynamics)

HAV: Clinical Presentation

- **Incubation period:** 2-6 weeks (average 4 weeks)
- **Age-dependent severity:**
  - Children <6 years: Often asymptomatic
  - Older children and adults: Symptomatic disease
- **Typical symptoms:**
  - Prodrome: Fever, malaise, anorexia
  - Gastrointestinal: Nausea, vomiting, RUQ pain
  - Hepatic: Jaundice, dark urine, pale (clay-colored) stools
  - Physical exam: Hepatomegaly common

HAV: Laboratory Findings

- **Liver enzymes:**
  - ALT/AST often >10× upper limit of normal
  - Typically higher than in other viral hepatitis
- **Bilirubin:** Elevated (both direct and indirect)
- **Alkaline phosphatase:** Moderately elevated
- **Serological markers:**
  - Anti-HAV IgM: Acute infection (appears early, persists 3-6 months)
  - Anti-HAV IgG: Past infection or immunity (lifelong) → Due to prior HAV infection and/or vaccination
- **Viral detection:** HAV RNA in serum/stool (rarely used clinically)



The presence of anti-HAV IgM antibodies or HAV RNA confirms active hepatitis A. Detection of anti-HAV IgG antibodies in the absence of anti-HAV IgM antibodies indicates immunity against HAV due to prior infection or vaccination.

Liver biopsy

- Most viral hepatitis produce a similar histopathological pattern
- Hepatocyte swelling (necrosis)
  - “Ballooning degeneration”, thought to be caused by ATP depletion and disruption of cytoskeleton
  - Hyperplasia may also occur due to regeneration of tissue (active cell replication) lost to viral damage
- Monocyte infiltration
  - Occurs due to viral infection and hepatocyte necrosis
- Councilman bodies
  - Apoptotic bodies form round pink (eosinophilic) bodies known as Councilman bodies

HAV: Disease Course & Complications

- **Typical course:** Self-limited, complete recovery in 3-6 weeks
- **Rare complications:**
  - Fulminant hepatic failure (<1%, higher risk in older adults and those with underlying liver disease)
  - Cholestatic hepatitis (prolonged jaundice, pruritus for weeks to months)
  - Relapsing hepatitis (symptom return after initial improvement in ~10% of patients)
- **Key characteristic:** Never progresses to chronic infection (100% clearance)

Treatment

- Hepatitis A is generally self-limited.
- Offer supportive care.
  - Recommend rest as needed.
  - Consider symptomatic treatment, e.g., antiemetics.
- Recommend alcohol avoidance.
- Use medications that are metabolized by the liver with caution (e.g., acetaminophen).

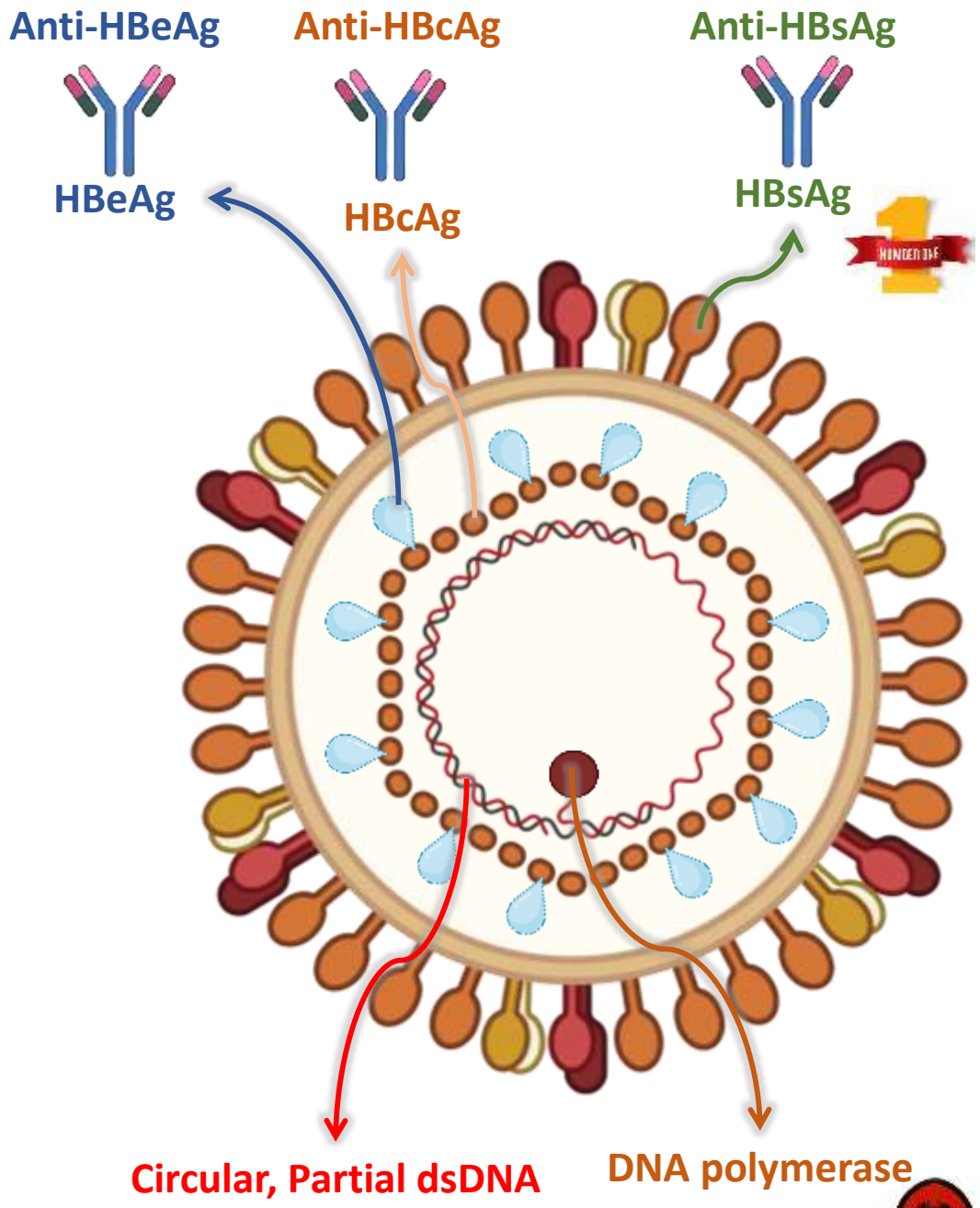
Prevention

- **Hepatitis A preexposure prophylaxis**
  - Advise all travelers to follow primary preventive measures such as food and water safety.
  - Hepatitis A vaccine (killed vaccine)

- **Hepatitis A postexposure prophylaxis**
  - Active immunization
  - Passive immunization with immune globulin
  - Both active and passive immunization

Hepatitis B

- **Family:** Hepadnaviridae
- **Structure:** Enveloped, 42 nm diameter
- **Genome:** Partially double-stranded DNA with reverse transcriptase activity
- **Viral components:**
  - **HBsAg** (surface antigen): Found on viral envelope
  - **HBcAg** (core antigen): Forms nucleocapsid
  - **HBeAg**: Secretory protein, marker of viral replication
  - Viral polymerase (with reverse transcriptase activity)
- **Transmission:** Blood, sexual contact, vertical (mother to child)



Hepatitis B - Transmission Routes

- **Sexual:**
  - Unprotected intercourse (heterosexual and men who have sex with men (MSM))
- **Parenteral:**
  - Blood transfusions (now rare in screened blood supplies)
  - Needle sharing among people who inject drugs
  - Contaminated medical/dental equipment
  - Occupational exposure (healthcare workers)
- **Vertical/perinatal:**
  - Mother-to-child transmission
  - Highest risk during delivery

Hepatitis B - Outcomes of HBV Infection

- **Acute infection:**
  - Self-limited in 95% of immunocompetent adults
- **Chronic infection:** Persistence of HBsAg >6 months
  - Risk inversely related to age at infection:
    - 90% in neonates
    - 25-30% in children
    - 5-10% in adults

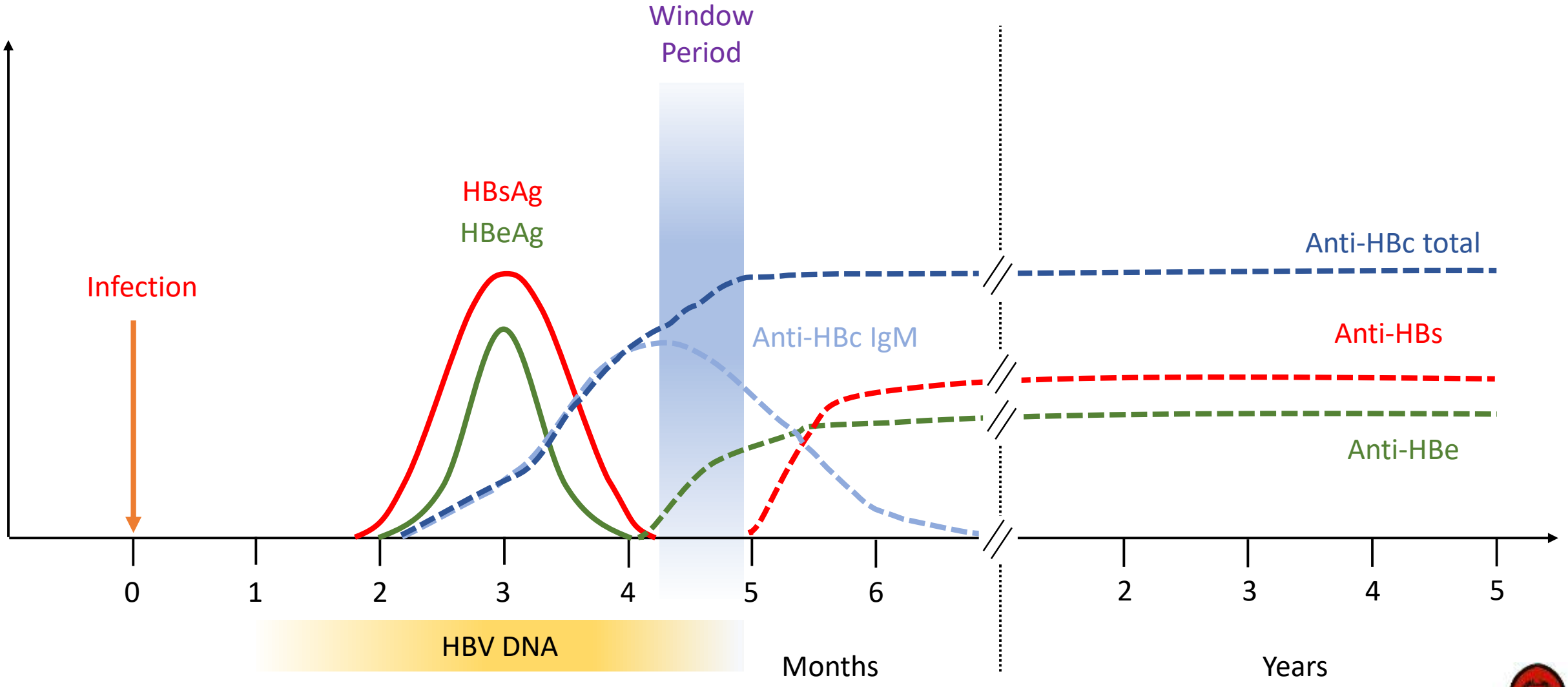
Hepatitis B - Clinical features

- Symptomatic hepatitis (~ 30% of cases)
  - Fever, skin rash, arthralgias, myalgias, fatigue
  - Nausea, anorexia
  - Jaundice, pale stool, dark coloured urine
  - Right upper quadrant pain
- May develop into fulminant hepatitis (~ 0.5% of cases)

Hepatitis B - Diagnosis

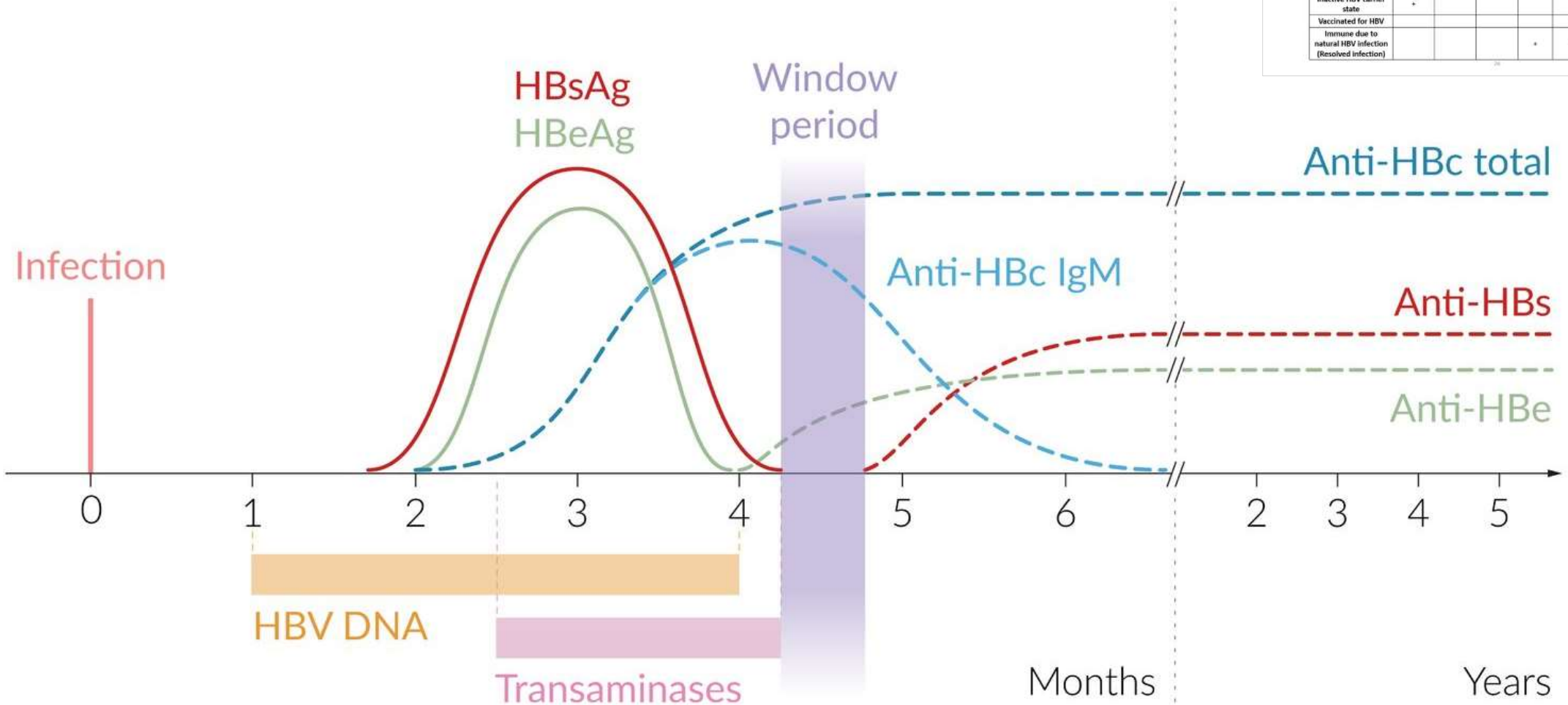
- Liver chemistries:
  - ALT and AST
    - AST:ALT ratio < 1 in acute infection
    - AST:ALT ratio > 1 in chronic hepatitis may be a sign of cirrhosis.
  - Laboratory diagnostics for cirrhosis
    - ↓ Albumin, ↑ INR
    - ↑ Bilirubin
    - ↓ Platelets
- HBV serology

Hepatitis B


Window
Period
HBsAg
HBeAg
Infection
Anti-HBc total
Anti-HBc IgM
Anti-HBs
Anti-HBe
0
1
2
3
4
5
6
2
3
4
5
HBV DNA
Months
Years

Hepatitis B - Serology interpretation

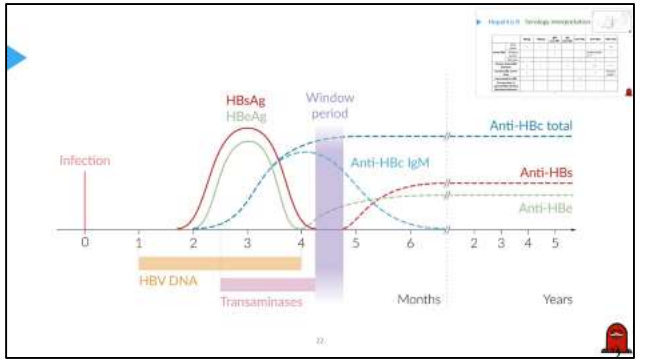
		HBsAg	HBeAg	IgM anti-HBc	IgG anti-HBc	Anti-HBs	Anti-HBe	HBV DNA
Acute HBV	*Early phase*	+	+	+				+++
	Window period			+			Undetectable or ↑	+
	Recovery				+	+	+	
Chronic active HBV infection		+	+		+		+/-	++
Inactive HBV carrier state		+					+	Normal/ mildly +
Vaccinated for HBV						+		
Immune due to natural HBV infection (Resolved infection)					+	+		



HBV Serological Markers

Importance of hepatitis B serological markers	
HBsAg	• Hepatitis B virus surface glycoproteins • Detectable during acute infection • Persistence >6 months = **chronic infection**
HBeAg	• Hepatitis B virus polypeptide • Detectable during acute infection • Indicates ↑ **viral replication** & infectivity
Anti-HBc IgM	• Detectable during **acute** infection • Present during **window phase** (between HBsAg & anti-HBs)
Anti-HBs	• Seen with cleared infection or vaccination • Confers long-term **immunity**
Anti-HBe	• Develops in cleared infection & later in chronic infection • Indicates ↓ **viral replication** & infectivity
Anti-HBc IgG	• Present in both acute & chronic infection • **Not present** after vaccination

Hepatitis B - Serology interpretation



		HBsAg	HBeAg	IgM anti-HBc	IgG anti-HBc	Anti-HBs	Anti-HBe	HBV DNA
Acute HBV	*Early phase*	+	+	+				+++
	Window period			+			Undetectable or ↑	+
	Recovery				+	+	+	
Chronic active HBV infection		+	+		+		+/−	++
Inactive HBV carrier state		+					+	Normal/ mildly +
Vaccinated for HBV						+		
Immune due to natural HBV infection (Resolved infection)					+	+		

Hepatitis B - Prevention

- **Hepatitis B Immunoglobulin (HBIG)** → Used to provide immediate, passive protection
  - Accidental exposure in non vaccinated individuals
- **Vaccine (Recombinant HBsAg):**
  - Check response by measuring anti HBsAg antibodies (>10 mIU/ml is protective)
  - Part of the Jordanian national immunization program (three IM doses at 2, 3, 4 months)
- Both the vaccine and HBIG should be administered to newborns whose mothers test positive for HBsAg, ideally within 12 hours of birth.

Hepatitis C

- RNA virus of the Hepacivirus genus and Flaviviridae family, (+) ssRNA genome, enveloped icosahedral capsid
- 8 genotypes
- Spread via infected blood and sexual contact.
- 6-8 week incubation period.
- Clinical infections are generally less severe than HBV.
- HCV has a higher incidence of chronic liver disease than HBV.
- 170 million cases globally
- Has viral RNA–dependent RNA polymerase → Without proofreading mechanism

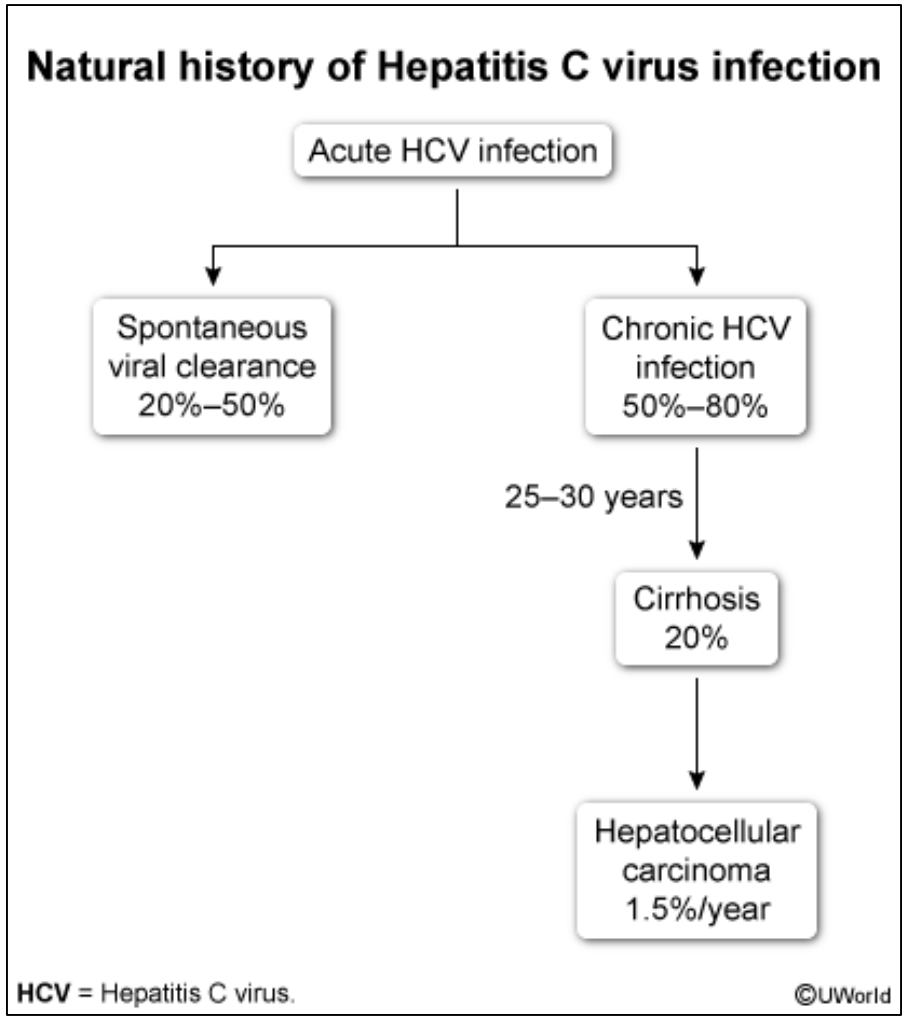
Transmission

- Parenteral
  - Needle sharing among individuals who use injection drugs
  - Needlestick injury (e.g., health care workers)
  - Blood transfusion
  - Dialysis
- Organ transplantation
- Sexual: rare (in contrast to HBV and HIV)
- Perinatal (vertical)

Symptoms of Hepatitis C

- Majority of people (70-80%) do not experience symptoms
- If present, symptoms may include:
  - Icterus and jaundice
  - Fatigue
  - Arthralgias, myalgias
  - Abdominal pain
  - Fever
  - Nausea, vomiting, diarrhea
  - Very rare: severe disease with acute liver failure

Hepatitis C


Natural history of Hepatitis C virus infection
Acute HCV infection
Spontaneous viral clearance 20%–50%
Chronic HCV infection 50%–80%
25–30 years
Cirrhosis 20%
Hepatocellular carcinoma 1.5%/year
HCV = Hepatitis C virus.
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Risk factors for HCV infection

- Injection drug use (An estimated 70–90% of all persons who regularly inject drugs are HCV-positive.)
- Hepatitis B virus or HIV positivity
- Individuals born between 1945 and 1965
- Individuals who received a blood transfusion or organ transplant before 1992

Diagnosis

- Anti-HCV antibodies (EIA/ELISA immunoassay): initial test for immunocompetent individuals who are HCV naïve
- HCV RNA (qualitative PCR)
  - Gold standard confirmatory test for active HCV infection
  - If anti-HCV antibody test is positive
  - Alternatively, as the initial test in patients with the following
    - Prior HCV infection
    - Immunocompromise
- Remember: Anti-HCV antibodies **THEN** confirm by PCR
- NOTE: A positive antibody test in someone with prior infection doesn't distinguish between past resolved infection and current active infection. Only RNA testing can determine if there is active viral replication (indicating reinfection or relapse)

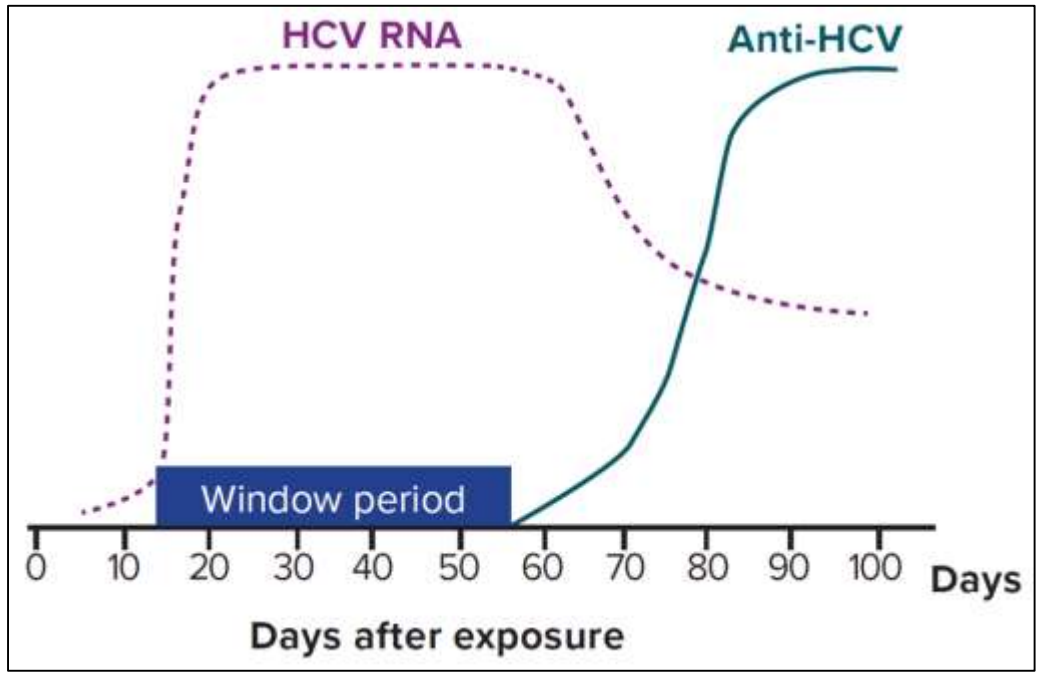
Interpretation of hepatitis C tests

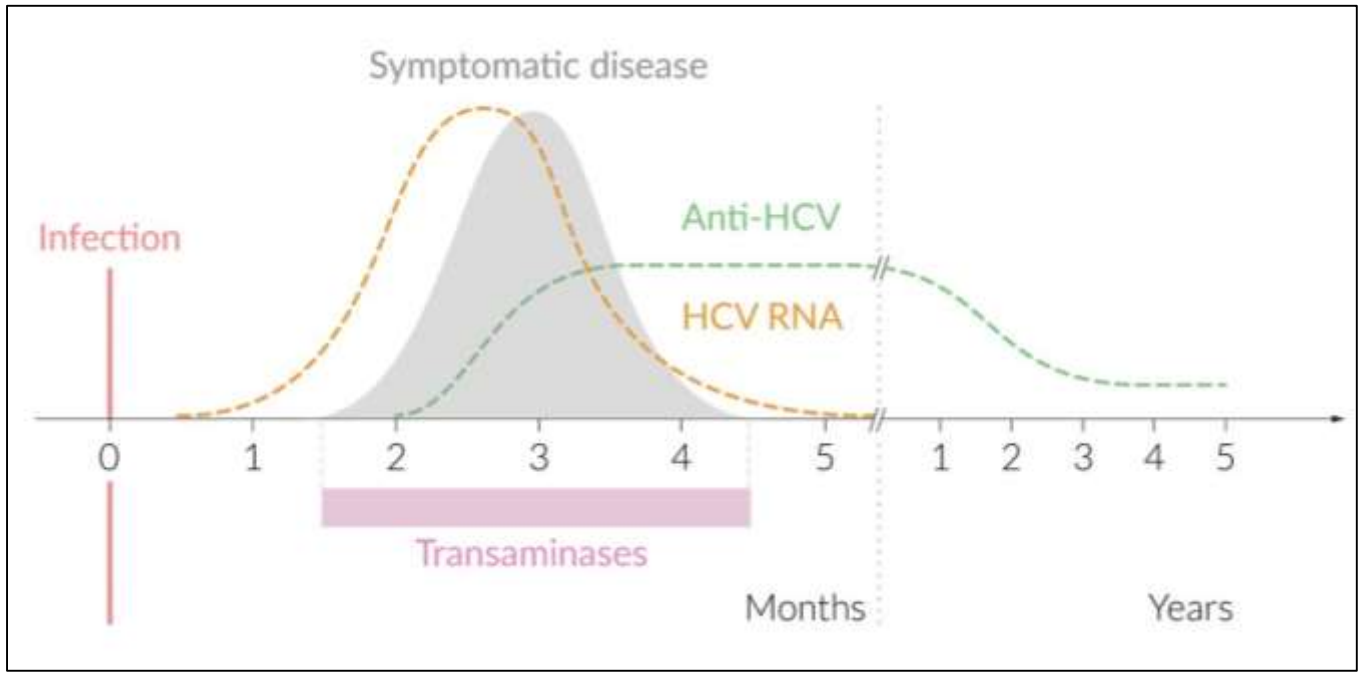
Interpretation of hepatitis C tests			
		Anti-HCV antibodies	
		Negative	**Positive**
HCV RNA	**Negative**	• No infection	• Resolved infection • Or false-positive antibody test

	Positive	• Active infection
		  • Within the window period
		  • Or patient is immunocompromised
			• Active infection (acute or chronic)

- Anti-HCV antibodies may take **as long as 6 weeks** after HCV exposure to be detectable on tests.
- HCV RNA may take as long **as 2–3 weeks** after viral exposure to be detectable on tests.

HCV serology





Treatment

- **Direct-acting antivirals (DAAs)**
  - Antivirals target and inhibit HCV-encoded proteins that are essential for the HCV replication cycle.
- **Interferon PLUS ribavirin**
  - Was the preferred treatment before the development of DAAs
  - Associated with severe adverse effects (e.g., arthralgias, thrombocytopenia, leukopenia, depression, anemia) and teratogenicity
  - Contraindicated in patients with decompensated cirrhosis (high risk of worsening cirrhosis decompensation)
- **No vaccine until 2025**
  - The lack of proofreading by the viral RNA polymerase leads to enormous genetic diversity, creating a major challenge for the host immune response

Hepatitis D virus

- It needs HBV to replicate (provide the envelop)
- Route of transmission:
  - As HBV
- conditions:
  - Co- infection with HBC
  - Super infection of HBV chronically infected patients (High risk of liver failure)
- Diagnosis: serology

Hepatitis E

- Normal case-fatality rate is 1-2%
  - But 10- 20% in pregnant women
- Symptoms
  - Asymptomatic
  - Similar to HAV, but milder
  - Increased risk of acute liver failure in pregnant individuals
- Not associated with hepatocellular carcinoma
- Diagnosis:
  - Exclude other types
  - Seroconversion + Molecular RT-PCR
- Rx: supportive

Thank You