Hepatitis

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"Hepatitis Viruses" – Introduction

Definition

- Hepatitis = inflammation of the liver caused by multiple agents.

- Five "true" hepatitis viruses (main site of infection = liver):

    - HAV – Hepatitis A virus
    - HBV – Hepatitis B virus
    - HCV – Hepatitis C virus
    - HDV – Hepatitis D (Delta) virus
    - HEV – Hepatitis E virus

👉 Other viruses (e.g., EBV, CMV, Yellow fever virus) can infect liver but are not exclusively hepatotropic, so not in this main group.

Key Shared Features

- Belong to different families → DNA vs RNA, enveloped vs non-enveloped.

- Tropism (the ability of a virus to infect specific cell types for hepatocytes = due to surface proteins that bind specific hepatocyte receptors.

- Non-cytotoxic directly:

    - Hepatocyte death = mediated by cytotoxic T cells.
    - Mechanism: viral antigens on hepatocyte surface + MHC I → $CD8^+$ T cell attack.

Exam Points

- Only DNA virus in the group = HBV.

- Only defective virus = HDV (requires HBV → uses HBsAg for its envelope).

- DNA polymerase inside virion = unique to HBV.

- Non-enveloped viruses = HAV & HEV (important for transmission: fecal-oral, stable in environment).

- Immune-mediated hepatocyte injury = common to all.

❖ Glossary of Hepatitis Viruses and Their Serologic Markers

HAV

- Hepatitis A virus
- A picornavirus (nonenveloped RNA virus)

IgM HAV Ab

- IgM antibody to HAV
- Best test to detect acute hepatitis A

HBV

- Hepatitis B virus
- A hepadnavirus (enveloped, partially double-stranded DNA virus)
- Also known as the Dane particle

HBsAg

- Surface antigen of HBV
- Found on both infectious virions and noninfectious

particles in blood

- Positive during acute disease
- Persistence indicates carrier state

HBsAb

- Antibody to HBsAg
- Provides immunity to HBV

HBcAg

- Core antigen of HBV

HBcAb

- Antibody to HBcAg
- Positive during window phase
- IgM HBcAb → indicates recent disease

HBeAg

- "e antigen" in HBV core
- Important indicator of high transmissibility

HBeAb

- Antibody to e antigen
- Indicates low transmissibility

Non-A, non-B

- Term used for hepatitis viruses that are neither HAV nor HBV

HCV

- Hepatitis C virus
- A flavivirus (enveloped RNA virus)
- One of the non-A, non-B viruses

HDV

- Hepatitis D virus

- Small RNA virus with HBsAg envelope
- Defective virus: replicates only in HBV-infected cells

HEV

- Hepatitis E virus
- A hepevirus (nonenveloped RNA virus)
- One of the non-A, non-B viruses

❖ Important Properties of Hepatitis Viruses

HAV (Hepatitis A virus)

- Genome: ssRNA
- Replication: No defective replication
- DNA polymerase in virion: No
- HBsAg in envelope: No
- Virus family: Picornavirus

HBV (Hepatitis B virus)

- Genome: dsDNA (interrupted, circular)
- Replication: Not defective
- DNA polymerase in virion: Yes
- HBsAg in envelope: Yes
- Virus family: Hepadnavirus

HCV (Hepatitis C virus)

- Genome: ssRNA
- Replication: No defective replication
- DNA polymerase in virion: No
- HBsAg in envelope: No
- Virus family: Flavivirus

HDV (Hepatitis D virus)

- Genome: ssRNA (circular, negative-stranded)
- Replication: Defective virus – requires HBV for replication
- DNA polymerase in virion: No
- HBsAg in envelope: Yes
- Virus family: Deltavirus

HEV (Hepatitis E virus)

- Genome: ssRNA
- Replication: No defective replication
- DNA polymerase in virion: No
- HBsAg in envelope: No
- Virus family: Calicivirus

❖ Summary of Clinical Features of Hepatitis Viruses

Hepatitis A virus (HAV)

- Mode of transmission: Fecal-oral
- Chronic carriers: No
- Diagnosis: IgM HAV antibody
- Vaccine available: Yes
- Immune globulins useful: Yes

Hepatitis B virus (HBV)

- Mode of transmission: Blood, sexual contact, perinatal (at birth)
- Chronic carriers: Yes
- Diagnosis: HBsAg, HBsAb, IgM HBcAb
- Vaccine available: Yes
- Immune globulins useful: Yes

Hepatitis C virus (HCV)

- Mode of transmission: Blood, sexual contact (sexual spread possible but less well documented)
- Chronic carriers: Yes
- Diagnosis: HCV antibody
- Vaccine available: No
- Immune globulins useful: No

Hepatitis D virus (HDV)

- Mode of transmission: Blood, sexual contact (likely but not well documented)
- Chronic carriers: Yes
- Diagnosis: Antibody to delta antigen
- Vaccine available: No (but HBV vaccine indirectly protects by preventing HBV coinfection)
- Immune globulins useful: No

Hepatitis E virus (HEV)

- Mode of transmission: Fecal-oral
- Chronic carriers: No
- Diagnosis: None
- Vaccine available: No
- Immune globulins useful: No

⚡ High-yield exam pearl:

- HAV & HEV → fecal-oral, no chronic carriers.
- HBV, HCV, HDV → blood/sexual/perinatal, chronic carriers common.
- Only HAV & HBV have vaccines, and both also have useful immune globulins.

➢ Hepatitis A Virus (HAV)

Disease

- HAV → Acute viral hepatitis A
- No chronic carrier state (very important exam point).

Important Properties

- Family: Picornavirus (Enterovirus group; aka *Enterovirus 72*).
- Genome: ssRNA (+ sense), linear.
- Capsid: Non-enveloped, icosahedral.
- Replication site: Cytoplasm.
- Serotypes: Only one (→ lifelong immunity after infection).
- No antigenic relation to HBV or other hepatitis viruses.

Replication Cycle

- Similar to other enteroviruses (e.g., poliovirus).

- Key steps: Attachment → Entry → RNA translation → Polyprotein cleavage → Genome replication → Assembly → Release (no envelope).

Transmission & Epidemiology

- Route: Fecal-oral (contaminated food/water).
- Reservoir: Humans only.
- Fecal shedding: Virus appears 2 weeks before symptoms → quarantine ineffective.
- High-risk groups:
    - Children (commonest group).
    - Institutions: summer camps, boarding schools.
- Common-source outbreaks: Contaminated water & raw seafood (e.g., oysters).
- Blood transmission: Rare (low viremia + no chronic infection).
- Epidemiology fact: 50–75% adults in USA show

evidence of past HAV infection (IgG).

Pathogenesis & Immunity

- Replication site: Likely in GI tract → spreads via blood → liver.
- Hepatocyte injury: Not direct; likely $CD8^+$ cytotoxic T-cell attack on infected hepatocytes.
- Cytopathic effect in vitro: None.
- Resolution: Virus cleared completely, damage repaired, no chronic infection.
- Histopathology: HAV hepatitis cannot be distinguished from other hepatitis viruses.

Immune Response

- IgM anti-HAV: Appears at jaundice onset → diagnostic marker of acute infection.
- IgG anti-HAV: Appears 1-3 weeks later → provides lifelong immunity.

Exam Points

- Non-enveloped → resistant to acid, detergents, drying (important for fecal-oral spread).
- No chronic infection, no carrier state, no cirrhosis, no hepatocellular carcinoma → contrasts sharply with HBV & HCV.
- IgM = diagnosis, IgG = past infection/protection.
- One serotype only → basis for effective vaccines.

Hepatitis A Virus (HAV) – Clinical, Diagnosis, Treatment & Prevention

Clinical Findings

- Symptoms (same as other hepatitis viruses):
  - Fever, anorexia, nausea, vomiting.
  - Jaundice.
  - Dark urine, pale stools, ↑ serum transaminases.
- Course:

    - Usually resolves spontaneously in 2–4 weeks.
    - Incubation period: short (3–4 weeks) → *contrast with HBV: 10–12 weeks.*

- Asymptomatic infections: Very common → detected only by IgG anti-HAV.

- No chronic infection → no cirrhosis, no hepatocellular carcinoma (major difference from HBV/HCV).

Laboratory Diagnosis

- IgM anti-HAV:

    - Appears at onset of symptoms (jaundice).
    - Key marker of acute HAV infection.

- IgG anti-HAV:

    - Appears later, persists for life.
    - Indicates past infection or immunity.

- Fourfold rise in IgG titers → can be used for diagnosis (but rarely needed).

- Virus isolation in cell culture: possible but not routine

in clinical labs.

Treatment

- No specific antiviral therapy needed.
- Supportive care only → disease is self-limiting.

Prevention

Active Immunization (Vaccine)

- Inactivated HAV vaccine:
  - Virus grown in human cell culture → inactivated with formalin.
  - Doses: 2 doses (initial + booster after 6–12 months).
  - Provides long-lasting protection → no further boosters required.
- Indications:
  - Travelers to endemic areas (developing countries).
  - Children (2–18 years).
  - Men who have sex with men (MSM).

- Twinrix: Combination vaccine (HAV + HBV).

Passive Immunization

- Immune serum globulin (ISG):
    - Given before infection or within 14 days post-exposure.
    - Provides immediate short-term protection.

- Often combined with vaccine = passive-active immunization (ISG for immediate protection + vaccine for long-term).

Other Preventive Measures

- Good hygiene: proper sewage disposal, handwashing after bowel movements, avoiding raw/contaminated food.

- Vaccine effective post-exposure prophylaxis if given within 2 weeks.

Exam Points

- HAV = Acute, Self-limiting, No Chronicity.

- IgM = Acute marker, IgG = Immunity.
- Incubation shorter (3–4 weeks) than HBV (10–12 weeks).
- Twinrix vaccine = dual protection against HAV + HBV.
- Passive–active immunization concept is important for rapid + long-term protection.

➢ Hepatitis B Virus (HBV)

Disease

- Causes Hepatitis B → can be acute or chronic.
- Can lead to cirrhosis and hepatocellular carcinoma (HCC) (oncogenic virus).

Important Properties

- Family: Hepadnaviridae.
- Virion:
    - 42 nm, enveloped → *Dane particle* (complete

infectious virion).
    - Core = icosahedral nucleocapsid.
    - Genome = partially double-stranded, circular DNA.

- Enzyme inside virion: DNA polymerase (with reverse transcriptase + DNA-dependent DNA polymerase activity).

- Genes & Products:

    - S gene → HBsAg (surface antigen).
    - C gene → HBcAg (core antigen) & HBeAg (secreted antigen, marker of infectivity).
    - P gene → polymerase.
    - X gene → HBx protein (transcription activator, possible oncogene; inactivates p53 tumor suppressor).

Viral Particles in Serum (Electron Microscopy)

- Three forms in blood:

    1. Complete infectious Dane particles (42 nm).

    2. Non-infectious 22 nm spheres of HBsAg.

3. Non-infectious long filaments (22 nm wide) of HBsAg.

- Ratio = 1000:1 (non-infectious: infectious).

- Clinical importance: High excess of HBsAg particles = diagnostic marker.

Antigens

- HBsAg (surface antigen):
    - Present in blood.
    - Important for diagnosis and immunization (basis of vaccine).

- HBcAg (core antigen):
    - Found in core, not detectable in serum.
    - Antibody (anti-HBc) is important marker.

- HBeAg (secreted antigen):
    - Found in blood.
    - Indicates high transmissibility & viral replication.

Serotypes

- 1 serotype for vaccine purposes → vaccine effective worldwide.
- 4 subtypes for epidemiology: adw, adr, ayw, ayr → based on "a" determinant + (d/y, w/r).

Host Range

- Humans only (no animal reservoir).

Tropism (Liver Specificity)

- Entry via specific hepatocyte receptors.
- Transcription promoted by hepatocyte-specific transcription factors.

Replication Cycle

1. Entry → nucleocapsid transported to nucleus.
2. DNA repair → partially dsDNA → completed dsDNA.
3. mRNA synthesis by host RNA polymerase in nucleus.

4. Full-length +RNA made (pregenomic RNA).

5. In cytoplasm:

    - Viral polymerase uses RNA template → reverse transcription → -DNA strand.
    - DNA-dependent DNA synthesis fills in incomplete +DNA strand.

6. Progeny nucleocapsid acquires envelope with HBsAg → released by budding.

⚡ Key uniqueness: HBV = DNA virus that replicates via reverse transcriptase (like retroviruses, but with DNA genome instead of RNA).

Carrier State & Chronic Infection

- Chronic HBV → virus persists, patient becomes carrier.

- HBV DNA mostly exists as episomes (circular DNA) in hepatocyte nucleus.

- Small portion integrates into host genome → may contribute to oncogenesis.

Exam Points

- Dane particle = infectious virion.
- HBsAg in serum = infection or carrier state.
- HBeAg = marker of infectivity.
- HBx gene → oncogenic potential (inhibits p53).
- HBV replicates via reverse transcriptase (unique among DNA viruses).
- Chronic infection + integration → predisposes to HCC.

Hepatitis B Virus (HBV) – Transmission, Pathogenesis & Immunity

Transmission & Epidemiology

Modes of transmission (3 major routes):

1. Blood
    - Needle-stick injuries (even tiny amounts of blood).

- IV drug users at high risk.
- Blood transfusions (rare today due to screening).

2. Sexual intercourse

- Found in semen & vaginal secretions.
- Important natural transmission route.

3. Perinatal (mother → child during birth)

- NOT usually transplacental.
- NOT transmitted via breast milk.

⚡ Key comparison:

- HAV (non-enveloped) → fecal-oral, stable in environment.
- HBV (enveloped) → fragile, transmitted via intimate contact (blood/sex/perinatal).

Global prevalence:

- Worldwide distribution.
- High in Asia (75% of 300M carriers).

- Explains high incidence of HCC in Asia.
- Vaccination programs → reduced incidence of hepatoma in children.
- HBV vaccine = first vaccine proven to prevent a human cancer.

Pathogenesis

- HBV itself is non-cytopathic → damage caused by immune response.
- Steps:
    1. Virus enters blood → infects hepatocytes.
    2. Viral antigens displayed on hepatocyte surface with MHC-I.
    3. Cytotoxic T cells attack → inflammation + hepatocyte necrosis.
    4. Antigen-antibody complexes → cause extrahepatic manifestations.

Immune complex-mediated complications:

- Arthralgia, arthritis, urticaria (early).
- Glomerulonephritis, cryoglobulinemia, vasculitis (chronic infection).

Chronic Carrier State

- Definition: HBsAg persisting ≥ 6 months in blood.
- Prevalence:
  - Adults: ~5% become chronic carriers.
  - Newborns: ~90% become chronic carriers (immature immune system).
- Risk factor for hepatocellular carcinoma (HCC).
- HBV DNA persists as:
  - Mostly episomal (free circular DNA in nucleus).
  - Partially integrated into host genome.

HCC Mechanisms:

1. HBx protein → inactivates p53 tumor suppressor.

2. Chronic cell injury & regeneration → increased mutation risk.

3. Insertional mutagenesis → HBV DNA integration may activate oncogenes.

    - Almost all HCC cells have integrated HBV DNA.

e Antigen & Infectivity

- HBeAg positive carriers → high replication, highly infectious.

- HBeAg negative carriers → low replication, less infectious.

- Key marker: HBeAg presence in blood = transmissibility.

Immunity

- Natural infection → lifelong immunity.

- Protective antibody = Anti-HBs (HBsAb)
    - Neutralizes virus → blocks entry into hepatocytes.
    - Basis of vaccine protection.
- Non-protective antibody = Anti-HBc (HBcAb)
    - Core antigen is hidden inside virion → antibodies cannot neutralize.

🔥 Summary Points

- 3 major transmission routes: blood, sex, perinatal.
- Immune-mediated damage → NOT direct cytopathic effect.
- Immune complex manifestations = arthritis, rash, GN, vasculitis.
- Chronic carriers: 5% adults vs. 90% neonates.
- HBsAg ≥ 6 months = carrier.
- HBeAg = infectivity marker.

- HBx gene → oncogenic (inactivates p53).
- HBV vaccine prevents cancer (unique fact).
- Anti-HBs = protective, Anti-HBc = not protective.

Hepatitis B Virus (HBV) – Clinical Findings & Diagnosis

Clinical Findings

- Incubation period:
    - HBV: 10–12 weeks (longer than HAV: 3–4 weeks).
- Acute infection:
    - Symptoms more severe than HAV.
    - Some cases progress to fulminant, life-threatening hepatitis.
    - Many infections are asymptomatic → detected only by HBsAg antibody.
- Chronic carriers:
    - Usually asymptomatic.
    - Some → chronic active hepatitis → cirrhosis →

death.

- Extrahepatic manifestations:
    - Acute HBV: serum sickness–like illness → fever, rash, arthralgias.
    - Chronic HBV: neuropathies, glomerulonephritis, polyarteritis nodosa (PAN).
    - Autoantibodies: cryoglobulins, rheumatoid factor.

- HBV + HIV co-infection:
    - Treat HBV first → otherwise, immune reconstitution after HIV therapy worsens hepatocyte destruction by reactivated cytotoxic T cells.

Laboratory Diagnosis

Key Serologic Markers

- HBsAg (surface antigen):
    - Appears early (incubation period).
    - Persists during acute disease.
    - If >6 months → carrier state.

- HBsAb (surface antibody):
    - Protective, appears after recovery or after vaccine.
    - Not detectable during active disease or in carriers (masked by circulating HBsAg).
- HBcAb (core antibody):
    - Present in acute, chronic, and recovered infections (NOT after vaccination).
    - IgM-HBcAb → acute infection (disappears ~6 months).
    - IgG-HBcAb → past infection or chronic infection.
- HBeAg (envelope antigen):
    - Appears in incubation and acute disease.
    - Indicates active replication + high infectivity.
    - Persistent in some carriers = highly infectious.
    - HBeAb → indicates lower infectivity (but transmission still possible).
- Window phase:
    - Period when HBsAg has disappeared but HBsAb not

yet detectable.
    - Only marker = HBcAb (IgM).

- Viral DNA (PCR):

    - Confirms active viral replication.
    - Used to monitor therapy (falling viral load = effective treatment).

Serology Table

Stage	HBsAg	HBsAb	HBcAb IgM	HBcAb IgG	HbeAg	HbeAb	Notes
Acute infection	+	−	+	−	+	−	Early disease, infectious
Window period	−	−	+	−	±	±	Only IgM-HBcAb positive

Chronic infection	+	−	−	+	±	±	Carrier state (>6m), HBsAb absent
Recovered	−	+	−	+	−	±	Lifelong immunity, not infectious
Vaccinated	−	+	−	−	−	−	Only HBsAb present

Exam Points

- Carrier state = HBsAg ≥ 6 months.

- Window period → only IgM-HBcAb positive.
- HBsAb = protective antibody (seen after recovery or vaccination).
- Chronic carriers never show HBsAb (masked by excess HBsAg).
- HBeAg positivity = high infectivity; HBeAb = lower infectivity.
- HBcAb distinguishes natural infection (past or present) from vaccination.

Hepatitis B – Treatment & Prevention

Treatment

Acute HBV

- No specific antiviral therapy.
- Supportive only.

Chronic HBV

- First-line drugs (preferred):

    - Entecavir (Baraclude)
    - Tenofovir (Viread)
    - 👉 *Nucleoside analogues* → inhibit reverse transcriptase of HBV.

- Other agents (less common now):

    - Pegylated interferon-α (Peginterferon alfa-2a, Pegasys)
    - Lamivudine (Epivir-HBV)
    - Adefovir (Hepsera)
    - Telbivudine (Tyzeka)
    - Tenofovir + emtricitabine (Emtriva) combination.

Key points

- These drugs:

    - ↓ Hepatic inflammation.
    - ↓ Viral load.
    - Improve long-term outcomes.

- NOT curative – virus replication resumes once therapy is stopped.

- Coinfection with HIV:
    - Start HBV treatment before HAART.
    - Reason: treating HIV first may trigger immune reconstitution syndrome (IRIS) → cytotoxic T-cell damage worsens HBV.

Prevention

1. Vaccine

- Recombinant HBsAg produced in yeast (e.g., Recombivax).
- Highly effective (~95% seroconversion in healthy adults).
- Indicated for:
    - Healthcare workers, medical/dental students.
    - Patients needing frequent transfusions or on dialysis.
    - IV drug abusers.
    - Individuals with multiple STDs.
    - Long-term travelers to endemic areas.
    - All newborns and adolescents (per U.S. guidelines).

- Regimen: 3 doses.
    - No boosters routinely recommended.
    - Exception: high-risk patients (e.g., dialysis) with falling antibody titers → booster may be considered.
- Impact:
    - Dramatically reduced hepatocellular carcinoma in children → first vaccine to prevent a human cancer.
    - Twinrix = combined HBV + HAV vaccine.

2. Hepatitis B Immune Globulin (HBIG)

- High titer of HBsAb → provides immediate passive immunity.
- Indications:
    - Accidental needle-stick with HBsAg-positive blood.
    - Newborns of HBsAg-positive mothers.
    - Used together with vaccine = passive-active immunization (short + long-term protection).

3. Practical Scenarios

- Needle-stick from HBsAg-positive patient:
    - Give HBV vaccine + HBIG (at separate sites).
- Neonate of HBsAg-positive mother:
    - Give HBV vaccine + HBIG immediately after birth.
    - Very effective in preventing transmission.
- Cesarean section:
    - No proven benefit in preventing HBV → not recommended.
- Breastfeeding:
    - Safe if neonate is immunized.

4. Other Preventive Measures

- Screen all blood donations for HBsAg.
- Exclude donors with any history of hepatitis.
- Screen high-risk groups to detect carriers → treat &

reduce spread.

- Pre-exposure prophylaxis for HIV (Truvada: tenofovir + emtricitabine) → also protects against HBV.

Serologic Test Results in HBV Infection Stages:

1. Acute Disease

- HBsAg: Positive (surface antigen present → active viral replication)
- HBsAb (anti-HBs): Negative (antibody not yet formed)
- HBcAb (anti-HBc): Positive (IgM anti-HBc is the first antibody to appear)

2. Window Phase

- HBsAg: Negative (surface antigen has disappeared)
- HBsAb: Negative (not yet detectable)
- HBcAb: Positive (IgM anti-HBc remains the *only marker* during window phase → diagnostic clue)

3. Complete Recovery

- HBsAg: Negative (virus cleared)
- HBsAb: Positive (protective immunity against reinfection)
- HBcAb: Positive (IgG anti-HBc persists for life, marker of past infection)

4. Chronic Carrier State

- HBsAg: Positive (persistent infection)
- HBsAb: Negative (never developed immunity)
- HBcAb: Positive (IgG anti-HBc present, but virus not cleared)

👉 The key diagnostic point:

- Window period marker = IgM anti-HBc
- Recovery = HBsAb + HBcAb (IgG)
- Chronic carrier = HBsAg persists >6 months, with

HBcAb but no HBsAb

🔥 Exam Pearls

- Chronic HBV drugs suppress but do not cure infection.
- First-line: entecavir, tenofovir.
- IRIS risk if HIV treated first → treat HBV first.
- HBV vaccine prevents hepatocellular carcinoma → first anti-cancer vaccine.
- Needle-stick & neonates: HBV vaccine + HBIG (passive-active immunization).
- Vaccine = recombinant HBsAg, not whole virus.
- Immunized person: HBsAb (+), HBcAb (–).

➢ Hepatitis C Virus (HCV)

Disease

- Causes hepatitis C.

- Major cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC).

Important Properties

- Family: *Flavivirus*
- Genome: ssRNA, + polarity, enveloped.
- No virion polymerase.
- Genotypes: ≥6 (with many subtypes).
    - Genotype 1 → ~75% of U.S. infections.
- Hypervariable region in envelope glycoprotein →
    - Caused by high mutation rate.
    - Viral RNA polymerase lacks proofreading.
    - → Results in *quasispecies* (multiple subspecies in one patient).

🔑 Clinical correlation:

- High genetic variability = immune evasion + resistance to vaccines.

- Explains difficulty in making an effective vaccine.

Chronicity & Carcinogenesis

    - 50% infections → chronic infection (much higher than HBV).

- Chronic HCV infection predisposes strongly to HCC.

- Mechanism: HCV protease inactivates signaling proteins needed for interferon induction → weak antiviral response.

Replicative Cycle (Summary)

- Cannot be grown in routine cell culture, but parallels other flaviviruses.

- Genome RNA → translated into polyprotein → cleaved by virion protease into functional proteins.

    - Protease = drug target.

- NS5A protein works with viral RNA polymerase → genome replication.

    - NS5A = drug target.

- Replication enhanced by miR-122 (liver-specific microRNA) → boosts HCV mRNA synthesis.

    - Antisense drug miravirsen blocks miR-122 → ↓ viral RNA levels.

🔑 Exam point: Direct-acting antivirals (DAAs) often target protease and NS5A.

Transmission & Epidemiology

- Reservoir: Humans.

- Main transmission: Blood.

    - Injection drug use → almost all new infections.
    - Mother → child at birth.
    - Needle-stick (lower risk vs HBV).
    - Blood transfusion (rare now due to screening).
    - Sexual transmission: uncommon.
    - Not transmitted via placenta or breastfeeding.

- Most prevalent blood-borne pathogen in U.S.

- ~4 million chronically infected (1–2% of U.S. population).
- Worldwide: ~180 million infected.

- Screening:
  - High-risk groups (IV drug use, transfusion before 1992, etc.).
  - Born 1945–1965 → high prevalence; CDC recommends screening.

- Other notes:
  - No insect vector (unlike yellow fever virus, another flavivirus).
  - Unique: rare transmission via commercial immune globulin (only infectious disease documented this way).

🔥 Exam Points

- HCV → *RNA virus, Flavivirus family, enveloped, +ssRNA.*

- Genetic diversity → quasispecies → immune escape + vaccine difficulty.

- >50% → chronicity (vs HBV lower).
- Chronic HCV → cirrhosis + HCC (major risk factor).
- Protease & NSSA = key drug targets.
- miR-122 enhances replication → target for experimental drug miravirsen.
- Transmission: IVDU > vertical at birth > transfusion (rare now).
- Sexual, transplacental, breastfeeding → rare/uncommon.
- Most common blood-borne infection in U.S.

Hepatitis C Virus (HCV) – Pathogenesis, Immunity & Clinical Findings

Pathogenesis

- Target cells: Hepatocytes.
- Direct cytopathic effect? ✗ No evidence.

- Mechanism of liver injury:
    - Mainly immune-mediated → destruction of hepatocytes by cytotoxic T cells (CD8+).
- Hepatocellular carcinoma (HCC):
    - HCV predisposes strongly to HCC.
    - BUT:
        - No viral oncogene identified.
        - No viral genome integration into host DNA.
    - Mechanism → Indirect:
        - Chronic liver damage + regeneration cycles → ↑ mutations → HCC.
    - Alcoholism greatly accelerates risk of HCC.
    - Cirrhosis of *any origin* also ↑ HCC risk (so mechanism = indirect injury, not direct viral oncogenesis).

Immunity

- Antibodies produced, but → 75% remain chronically infected.
    - (Compare: HBV → chronic carriage ~10%).

- Chronic consequences:
    - ~10% → Chronic active hepatitis & cirrhosis.
- Immunity after clearance:
    - Uncertain if reinfection can occur.
    - Lifelong immunity is not established.

Clinical Findings

- Incubation period: ~8 weeks (longer than HAV, shorter than HBV).
- Acute HCV:
    - Often asymptomatic.
    - If symptomatic → usually mild.
        - Malaise, nausea, RUQ pain.
        - Classic hepatitis features: fever, anorexia, vomiting, jaundice, dark urine, pale feces, ↑ transaminases.
- Chronic HCV:

    - Much more common than in HBV.
    - Leads to chronic hepatitis, cirrhosis, and HCC.
    - Cirrhosis due to HCV = #1 indication for liver transplantation.

- Extrahepatic manifestations (immune-mediated):

    - Autoimmune phenomena:
        - Vasculitis
        - Arthralgias
        - Purpura
        - Membranoproliferative glomerulonephritis
    - Essential mixed cryoglobulinemia (EMC):
        - HCV is the main cause.
        - Cryoglobulins = immune complexes (HCV Ag + Ab).
        - Precipitate in cold → dissolve on warming.

🔥 Exam Points

- HCV liver damage = immune attack (CD8+), not viral cytotoxicity.

- Strong link with HCC → via chronic injury, not oncogene integration.

- Alcohol accelerates HCC risk.
- Chronicity rate = ~75% (higher than HBV).
- Cirrhosis from HCV = leading cause of liver transplantation.
- Extrahepatic disease: vasculitis, glomerulonephritis, cryoglobulinemia (classic exam favorite!).

Hepatitis C Virus (HCV) – Laboratory Diagnosis, Treatment, and Prevention

Laboratory Diagnosis

- Screening test: ELISA for anti-HCV antibodies
    - Uses recombinant proteins from stable HCV antigens (not variable envelope proteins).
    - Does not distinguish IgM vs IgG, or acute vs chronic vs resolved infection.
- Confirmatory test: PCR for HCV RNA (viral load)
    - Detects active infection.
    - Used to monitor drug therapy success.

- Chronic HCV infection criteria:
    - Elevated transaminases (e.g., ALT)
    - Positive ELISA antibody
    - Detectable HCV RNA $\geq$ 6 months
- Note: Virus isolation from patients is not done.

Laboratory Test Results in Different Stages of HCV Infection

1. Acute HCV Infection

- Antibody to HCV: Becomes positive after 6–24 weeks; negative early in infection
- Viral load (HCV RNA in serum): Detectable within 1–2 weeks (earliest marker of infection)
- ALT (alanine aminotransferase): Elevated

2. Chronic HCV Infection

- Antibody to HCV: Positive
- Viral load (HCV RNA): Detectable (persistence of RNA confirms chronicity)

- ALT: Typically elevated but fluctuates, sometimes near normal

3. Recovered from HCV Infection

- Antibody to HCV: Positive (remains as marker of past infection)
- Viral load (HCV RNA): Undetectable (virus cleared)
- ALT: May be normal, but can fluctuate (some residual liver injury possible)

⚡ High-yield points for exams:

- Earliest marker of acute HCV = HCV RNA (1–2 weeks)
- Antibody to HCV appears late (6–24 weeks)
- Chronic infection confirmed when HCV RNA persists >6 months
- Recovered patients → HCV Ab positive, RNA negative

Treatment

- Acute HCV: Peginterferon alfa → reduces progression

to chronic infection.

- Chronic HCV:
    - Oral drug combinations (Table 41-6):
        - RNA polymerase inhibitors (e.g., Sofosbuvir, Dasabuvir)
        - NSSA inhibitors (e.g., Ledipasvir, Velpatasvir, Ombitasvir, etc.)
        - Protease inhibitors (e.g., Simeprevir, Grazoprevir, Glecaprevir, etc.)
    - Superior to old regimens (pegylated interferon alfa ± ribavirin).
    - Effective against different genotypes of HCV.
    - Offer potential for a "cure."

- Important adverse effect: Reactivation of HBV during HCV treatment (mechanism unknown).

Oral Drugs for Chronic HCV Infection

1. RNA Polymerase Inhibitors

- Sofosbuvir
    - Nucleoside (uridine) analogue

- Mechanism: Inhibits genome RNA synthesis (chain-terminating drug)

- Dasabuvir

  - Non-nucleoside inhibitor
  - Mechanism: Inhibits genome RNA synthesis

2. NSSA Inhibitors

- Ledipasvir, Ombitasvir, Daclatasvir, Elbasvir, Velpatasvir, Pibrentasvir

- Mechanism: Block NSSA protein, a cofactor required for RNA polymerase activity → inhibits genome RNA synthesis

3. Protease Inhibitors

- Boceprevir, Simeprevir, Telaprevir, Paritaprevir, Grazoprevir, Glecaprevir

- Mechanism: Inhibit cleavage of HCV precursor polypeptide → block production of functional structural and nonstructural viral proteins

⚡ Exam High-Yield:

- Sofosbuvir = chain terminator
- NSSA inhibitors = block viral replication complex
- Protease inhibitors = prevent processing of viral polyprotein

Prevention

- No vaccine; no hyperimmune globulin.
- Pooled immune serum globulin not useful for post-exposure prophylaxis.
- Needle-stick injury: no effective prophylaxis; only monitoring.
- Blood donor screening (since 1994): virtually eliminated transfusion-related HCV.
- Screening recommended: All individuals born between 1945-1965 (high prevalence).
- Patient advice:

- Avoid alcohol → reduces risk of cirrhosis and hepatocellular carcinoma.
- Monitor cirrhotic patients with AFP + liver ultrasound for carcinoma detection.

- Liver transplant: possible, but reinfection of graft is typical.

- HCV + HIV coinfection:

  - HAART can worsen hepatitis (IRIS).
  - Prefer treat HCV before starting HAART.

⚡ Exam Tip:

- ELISA (screen), PCR (confirm + monitor)

- 6 months RNA + ALT elevation = chronic infection

- No vaccine / immune globulin for HCV (vs HAV, HBV).

Drug Combinations Effective for Treatment of Chronic HCV Infection (Not Important for Micro Exam)

Genotype 1

- Sovaldi + Olysio
    - Sofosbuvir → RNA polymerase inhibitor
    - Simeprevir → Protease inhibitor
- Viekira Pak
    - Dasabuvir → RNA polymerase inhibitor
    - Ombitasvir → NSSA inhibitor
    - Paritaprevir → Protease inhibitor
    - Ritonavir → Booster of protease inhibitor

Genotype 1 or 3

- Sovaldi + Daklinza
    - Sofosbuvir → RNA polymerase inhibitor
    - Daclatasvir → NSSA inhibitor

Genotype 1 or 4

- Zepatier
    - Elbasvir → NSSA inhibitor
    - Grazoprevir → Protease inhibitor

Genotype 1, 4, 5, or 6

- Harvoni
    - Sofosbuvir → RNA polymerase inhibitor
    - Ledipasvir → NSSA inhibitor

Genotype 4

- Technivie
    - Ombitasvir → NSSA inhibitor
    - Paritaprevir → Protease inhibitor
    - Ritonavir → Booster of protease inhibitor

All 6 Genotypes

- Epclusa
    - Sofosbuvir → RNA polymerase inhibitor
    - Velpatasvir → NSSA inhibitor
- Mavyret
    - Pibrentasvir → NSSA inhibitor
    - Glecaprevir → Protease inhibitor

➢ Hepatitis D Virus (HDV / Delta Virus)

Disease

- Causes Hepatitis D (Delta hepatitis).
- Occurs only in HBV-infected individuals (requires HBsAg).

Important Properties

- Defective virus → cannot replicate independently.
- Helper virus = HBV (provides HBsAg as envelope protein).
- Genome:
    - ssRNA, negative polarity, circular, covalently closed.
    - Very small genome → encodes only delta antigen (core protein).

- Replication:
    - No viral polymerase → uses host RNA polymerase.
    - RNA genome is a ribozyme (self-cleaves & ligates).
    - Replicates in the nucleus.
- Serotype: Only one (because HBsAg has only one serotype).
- Reservoir: None known outside humans.

Transmission & Epidemiology

- Same as HBV: blood, sexual, perinatal.
- In U.S. → mostly IV drug users (needle sharing).
- Worldwide distribution overlaps with HBV.

Pathogenesis & Immunity

- Mechanism similar to HBV: cytotoxic T-cell damage to infected hepatocytes.
- Some evidence that delta antigen itself is cytopathic.

- Immunity:
    - IgG anti-delta antigen not long-lasting.
    - Unclear if durable long-term immunity exists.

Clinical Findings

- Requires HBV infection → occurs as:
    1. Coinfection = HBV + HDV simultaneously.
        - More severe acute hepatitis than HBV alone.
        - BUT chronic hepatitis incidence ≈ HBV alone.
    2. Superinfection = HDV infects a chronic HBV carrier.
        - Much more severe disease.
        - High risk of: fulminant hepatitis, chronic hepatitis, liver failure.

Laboratory Diagnosis

- Detection of delta antigen in serum – OR –
- IgM antibody to delta antigen.

Treatment

- Peginterferon alfa: may mitigate chronic hepatitis effects.
- No specific anti-HDV therapy.
- No cure for chronic HDV.

Prevention

- No HDV vaccine.
- BUT: HBV vaccination indirectly prevents HDV (since HDV cannot replicate without HBV).

🔥 Exam Pearls

- HDV = defective virus → requires HBV (HBsAg) as helper.
- Coinfection = acute, severe, but not more chronic.
- Superinfection = severe, fulminant, ↑ risk of chronicity & failure.

- HDV genome = ribozyme (unique self-cleaving RNA property).

- Prevention = HBV vaccine (indirect).

➢ Hepatitis E Virus (HEV)

Properties

- Nonenveloped, ssRNA virus.

- Family: Hepevirus.

- Transmission: Fecal-oral (contaminated water, poor sanitation).

Epidemiology

- Major cause of waterborne epidemics in Asia, Africa, India, Mexico.

- Rare in the U.S.

- More common than HAV in many developing countries.

Clinical Features

- Similar to HAV (self-limiting acute hepatitis).
- Key difference: High mortality in pregnant women (up to 20–25%).
- In immunocompromised patients → can cause chronic infection, chronic hepatitis, cirrhosis.
- No link to hepatocellular carcinoma.

Diagnosis

- IgM antibody to HEV.
- PCR for HEV RNA also available.

Treatment

- No specific antiviral for acute infection in immunocompetent.
- In immunocompromised → ribavirin may clear infection.

Prevention

- No vaccine available (unlike HAV).
- Improved sanitation & clean water.

🔥 Exam Pearls

- Fecal-oral → waterborne epidemics.
- Pregnancy = high mortality risk (esp. 3rd trimester).
- Can be chronic in immunocompromised, but not oncogenic.

➢ Hepatitis G Virus (HGV / GB virus C / Pegivirus H)

Properties

- Flavivirus family (like HCV).
- Transmission: blood & sexual intercourse.

Epidemiology

- Found in:
    - 2% of U.S. blood donors.

    - 15% of those with HCV.
    - 35% of those with HIV.

- Carried in millions worldwide.

Clinical Features

- Unlike HCV:

    - No clear role in acute hepatitis, chronic active hepatitis, or hepatocellular carcinoma.

- Can cause chronic infection lasting decades.

- 60–70% clear infection → develop antibodies.

Special Note: Interaction with HIV

- HIV + HGV coinfection = better prognosis.

- Lower mortality, lower HIV viral loads.

- Hypothesis: HGV interferes with HIV replication.

Diagnosis

- Detection of viral RNA or antibodies.

Treatment & Prevention

- No specific antiviral therapy.
- No vaccine.

Exam Pearls

- HGV not clearly pathogenic for liver (unlike HCV).
- Chronic infection possible.
- May protect against HIV progression.