Hepatitis E virus (HEV) infection

HEV white paper

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Introduction[1]

Hepatitis E virus (HEV) is a major cause of acute viral hepatitis globally. Every year, it causes an estimated:

- ~20 million infections
- ~3 million symptomatic hepatitis cases
- ~70 000 fatalities

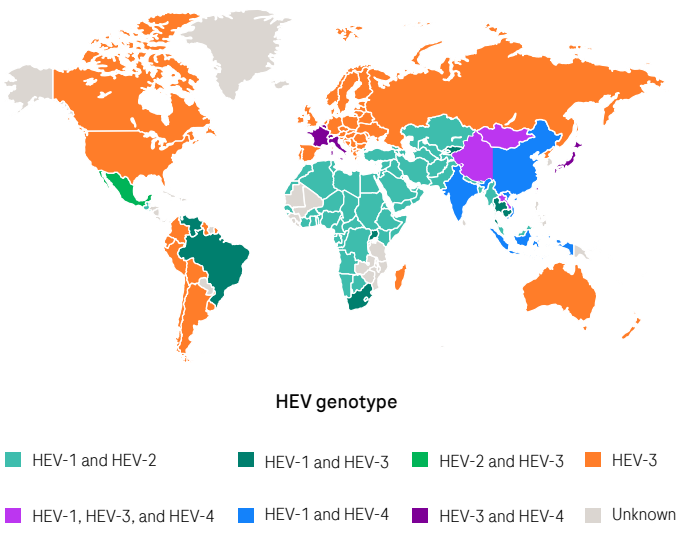
HEV virology[2,3]

HEV is a small (27-34 nm), icosahedral virus, with a **single-stranded genome** of positive-sense **RNA**, around **7.2 kb** in length, containing **3 ORFs**.

8 genotypes have been identified. **Genotypes 1-4** are responsible for **most human infections.**

Epidemiology & HEV geographical distribution

HEV is found globally, but HEV genotypes are region specific[2,3]



HEV-1 and HEV-2	HEV-3 and HEV-4
Primarily **low- and middle- income countries** in Asia and Africa and in Mexico in the 1980 outbreak.	Primarily in **developed regions**. HEV-3 is found worldwide, including in Europe, North America, South America, and Japan.
Disease occurs as **seasonal outbreaks** due to contaminated water supplies and can last from several days to months if the source of contamination is not identified.	HEV-4 is most prevalent in China but can also be found in Southeast Asia, Japan, and central Europe.
Acquired through **fecal–oral** route (human-to-human), usually through contamination of water supplies, although **person-to-person** transmission is also possible.	Occasional **sporadic** cases of locally acquired infection (autochthonous).
	Zoonotic transmission (from pigs, wild boar, deer, rabbits, mongoose, domestic dogs, and cats) to humans, possibly through consumption of undercooked meat.

Clinical features: Course of HEV acute infection

HEV infection is generally self-limited in healthy immunocompetent individuals[1-4]

Incubation	Symptomatic phase	Convalescent phase
The incubation period ranges from 2 to 10 weeks, with an average time of 5 to 6 weeks.	The majority of infections are asymptomatic, but 5–30% of individuals have symptoms indistinguishable from those of other acute forms of hepatitis, lasting from 1 to 6 weeks.	In immunocompetent patients with acute hepatitis E, the infection usually resolves spontaneously.
Most recipients excrete the virus until 3–4 weeks after infection.	The most common symptoms are malaise, fever, body aches, nausea, vomiting, jaundice, pale stools, and dark urine.	Immunocompromised patients who are infected with HEV-3 or HEV-4 might develop a chronic infection. No chronic cases of HEV-1 or HEV-2 have been reported to date.

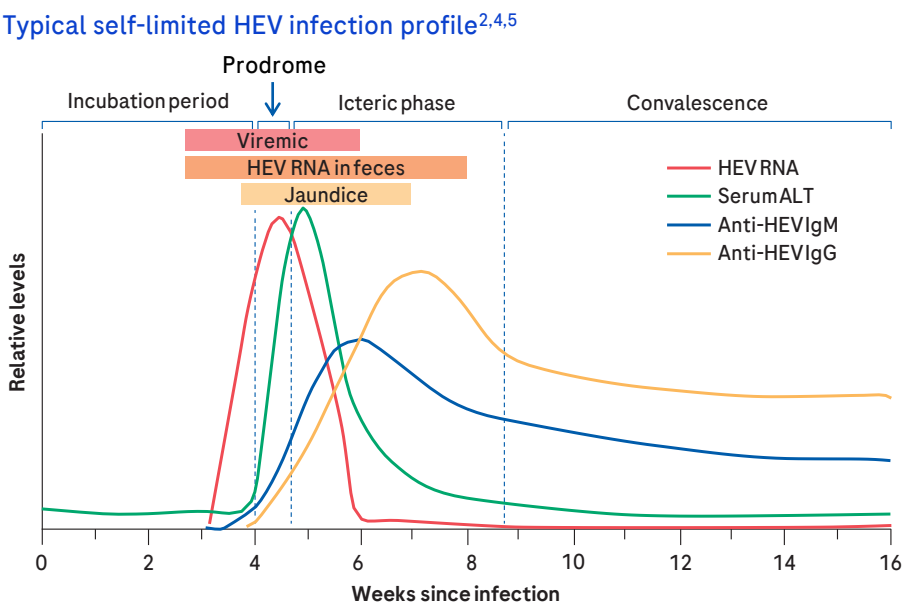
In rare cases, HEV-infected individuals develop acute liver failure, a life-threatening condition.[2,4,6,7]

The presence of pre-existing chronic liver diseases increases the risk of liver failure, with mortality of up to 67% in such patients who also have acute HEV infection.[4,5]

HEV-1 infection in pregnant women, particularly in the 3rd trimester, is associated with high maternal and fetal morbidity and mortality.[6-8]

Immune response: HEV diagnostic markers profile

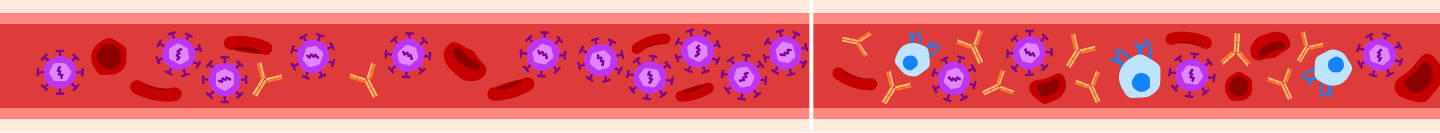
Typical self-limited HEV infection profile[2,4,5]



- HEV RNA and capsid antigen become detectable in blood and stool ~2 weeks after viral contact and persist for ~4 weeks and ~6 weeks in blood and stool, respectively.
- Anti-HEV IgM is detectable in blood from the 4th week after viral exposure and lasts a maximum of 6–9 months.
- Anti-HEV IgG appears shortly after IgM and persists for several years in blood.
- ALT levels, an indicator of liver damage, generally increase 4 weeks after initial viral exposure.

In immunocompromised patients who develop **chronic HEV infection, HEV RNA** persists in blood, stool, and body fluids for **> 3 months.** These patients likely have **low or undetectable** levels of **anti-HEV antibodies.**

In immunocompetent hosts, HEV infection induces **broad cytotoxic T-cell response**, which likely supports long-lived disease immunity and protection.



Treatment and prevention[7,9]

In immunocompetent individuals, **most HEV infections**, symptomatic or not, are **cleared by the immune system.** However, **antiviral therapy for HEV infection may be indicated** for some acutely infected patients, and in chronically infected patients. Such as:

- **Ribavirin:** usage has achieved sustained viral response/clearance; but contraindicated in pregnant women
- **Pegylated interferon-α therapy:** used to treat chronic HEV infection

There are various ways to prevent HEV infection, including:

- Good personal hygiene
- Clean public water supplies
- Proper disposal of human excreta
- General food safety measures

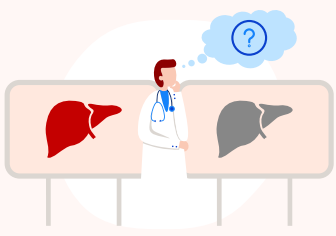
An effective vaccine against HEV infection (HEV 239/ Hecolin®) is approved for use in China and Pakistan, and is undergoing clinical studies for use in Nepal, Bangladesh and the USA.

Note: No HEV-specific antivirals have been tested in large randomized clinical trials or approved for clinical use

Diagnostic markers[2,5,10]

Clinical manifestations and liver function abnormalities associated with **HEV infection** are **often indistinguishable** from those caused by other hepatitis viruses, DILI, or autoimmune disease. **Therefore, accurate diagnosis of HEV infection relies heavily on diagnostic testing.**

Tests for HEV are based on the detection and/or quantitation of **host antibody responses**, **viral RNA**, or **viral antigen.**



Antibody tests

- Current immunoassays that detect antibodies against HEV use recombinant ORF2 and/or ORF3 proteins from HEV-1 and HEV-3 strains as antigens.
- Antibodies in patients infected with other HEV genotypes cross-react with HEV-1 epitopes.
- The presence of anti-HEV IgM in serum is a marker of acute infection but must be combined with anti-HEV (rising titers) or HEV RNA for diagnosis.
- The presence of anti-HEV IgG alone is a marker of past HEV infection.
- Current anti-HEV tests have lower detection limits of 0.25–2.5 WHO U/mL.[11]
- The diagnostic performance of IgM and IgG assays varies considerably and must be evaluated carefully.
- In immunosuppressed patients with chronic hepatitis E, anti-HEV antibodies are often undetectable.[12]

RNA tests

- HEV RNA detection and quantification in blood, feces, or other bodily fluids is the **gold standard for detecting active HEV infection** (acute or chronic).
- Most RT-PCR assays for the detection of HEV RNA target a conserved region of the HEV genome, usually located in ORF3.[13]

Antigen tests

- HEV capsid antigen tests are based on a sandwich enzyme immunoassay.
- The presence of HEV antigen in blood, feces, or other bodily fluids may be an indicator of active HEV infection.
- Capsid protein levels in blood correlate poorly with RNA concentration, probably because capsid is produced in multiple isoforms, only some of which are assembled into virions.

Use cases for HEV testing[14,15]

HEV tests have three key applications that are important to consider:

1 Individual patient diagnosis and monitoring

EASL recommends that all people with symptoms of acute hepatitis should be tested for HEV. Diagnosis of HEV infection in immunocompetent individuals should consist of serological tests for anti-HEV antibodies, in some cases supplemented by NAT. **Result interpretation is shown in the table.** Anti-HEV antibody development may be delayed or undetectable in immuno-compromised patients (e.g., transplant recipients), placing increased reliance on NAT results.

2 Screening of blood and organ donors

To reduce the risk of transfusion-associated transmission of HEV, the ECDC recommends that blood donor services screen blood donors for HEV RNA. HEV testing of organ donors is recommended in international guidelines.

3 Seroprevalence studies

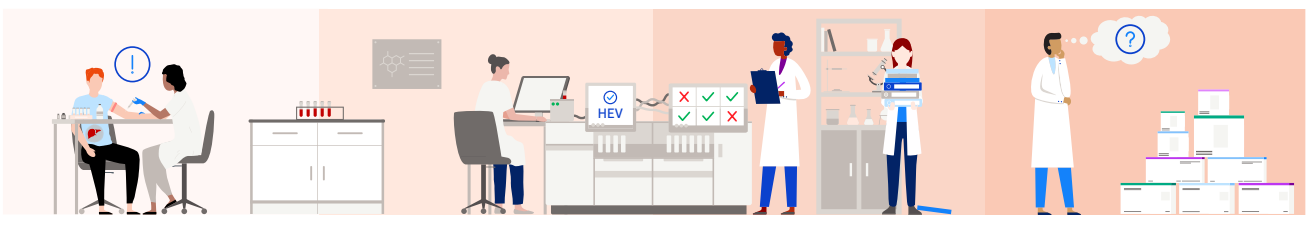
These are key to our understanding of the epidemiology and infection prevention strategies for HEV. Seroprevalence surveys are based on the detection of anti-HEV IgG in serum or plasma.

Laboratory test interpretation				
RNA	IgM	IgG	Infection phase	Virus replication
–	–	–	Not infected or incubation period	None or undetected
+	–	–	Acute (early)	✓
+	+	–	Acute (mid)	✓
+	+	+	Acute (late)	✓
–	+	+	Early recovery phase	✗
–	–	+	Late recovery phase	✗
+ (≥3 months)	–/+	–/+	Chronic	✓

There are several unmet needs in HEV diagnostics, including:

- Low and variable assay sensitivity
- Comparability of results between different tests

Summary



HEV diagnosis uses serological tests for anti-HEV antibodies, NAT for HEV RNA, or both. In immunocompromised patients, detection of viral RNA is needed to diagnose HEV infection.

Screening of blood donations by testing for HEV RNA limits risk of HEV transmission via transfusion. HEV RNA testing of organ donors is also recommended.

Seroprevalence surveys provide a better understanding of HEV epidemiology and prevention strategies based on detection of anti-HEV IgG in serum.

It's important to remember that sensitivity variations can give different results from the same samples, whilst low sensitivity can lead to misdiagnosis.

ALT, alanine transaminase; DILI, drug-induced liver injury; EASL, European Association for the Study of the Liver; ECDC, European Centre for Disease Prevention and Control; HEV, hepatitis E virus; IgG, immunoglobulin G; IgM, immunoglobulin M; U, units; NAT, nucleic acid test; ORF, open reading frame; RNA, ribonucleic acid; RT-PCR, reverse transcription polymerase chain reaction; WHO, World Health Organization.

Sources: 1. World Health Organization. Hepatitis E: Fact sheet [Internet; updated 2023 Jul 23; cited 2023 Oct 19]. Available from: http://www.who.int/mediacentre/factsheets/fs280/en/; 2. Kamar et al. Nat Rev Dis Primers. 2017; 3:17086; 3. Pallerla et al. Pathogens. 2020; 9:856; 4. Aggarwal et al. Cold Spring Harb Perspect Med. 2019; 9:a032136. 5. Al-Sadeq et al. J Med Microbiol. 2018; 67:466-80; 6. Yadav et al. Pathogens 2021;10:1180; 7. Aslan et al. World J Gastroenterol 2020;26: 5543-5560; 8. Wu et al. Virol J 2020;17:73; 9. Goel A, Aggarwal R. Clin N Am. 2020;49:315-330; 10. Kar P, Karna RA. Curr Treat Options Infect Dis 2020;12:310–320; 11. Chevaliez S, Pawlotsky JM. Hepatitis Viruses. In: Cohen J, Powderly WG, Opal SM, editors. Infectious Diseases 2. 4th ed: Elsevier; 2017. pp. 1417-25; 12. Anastasiou OE, et al. Pathogens. 2020;9:137; 13. Thodou et al. J Clin Virol. 2020; 129:104525; 14. European Association for the Study of the Liver. J Hepatol. 2018;68:1256-1271; 15. European Centre for Disease Prevention and Control. [Internet; updated 2019 Sep 9; cited 2023 Oct 19].Available from: https://www.ecdc.europa.eu/en/publications-data/options-national-testing-and-surveillance-hepatitis-e-virus-eueea-operational.