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Hepatology Snapshot:

Hepatitis A and E - differences and commonalities

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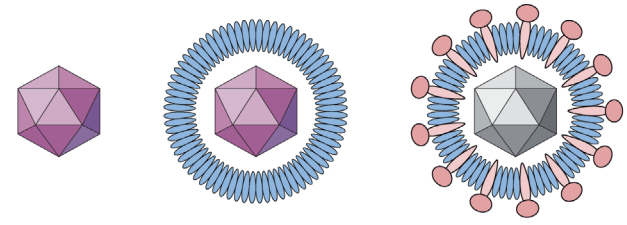
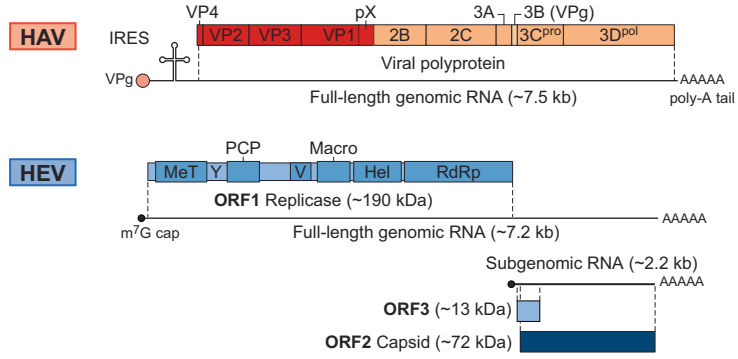
VIRUS STRUCTURE



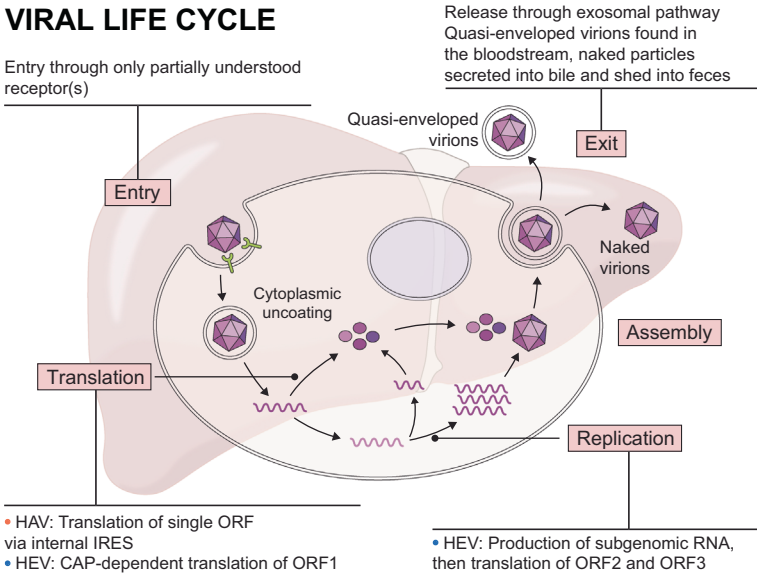
Naked virus (HAV, HEV) | Quasi-enveloped virus (eHAV, eHEV) | Conventional enveloped virus (e.g., HBV, HCV)

Adapted from Feng Z *et al*. Annu Rev Virol 2014;1:539-560 with permission.

GENOME ORGANIZATION



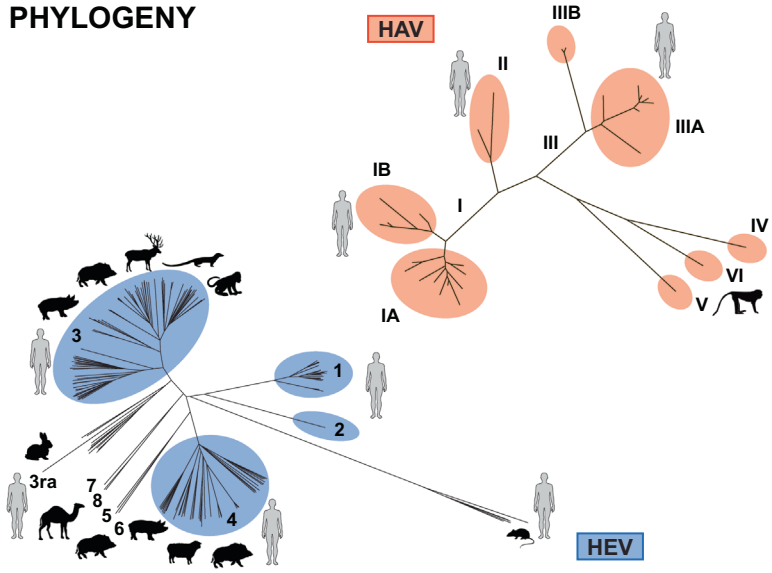
VIRAL LIFE CYCLE



- HAV: Translation of single ORF via internal IRES
- HEV: CAP-dependent translation of ORF1

- HEV: Production of subgenomic RNA, then translation of ORF2 and ORF3

PHYLOGENY



EPIDEMIOLOGY

Shedding in feces/fecal-oral transmission: Yes for both

Secondary spread:
- HAV: Yes
- HEV: Rare

Parenteral transmission: Yes for both

Propagation in cell culture: Yes for both

PREVENTION AND TREATMENT

Vaccine:
- HAV: Available worldwide
- HEV: Available only in China

Treatment:
- HAV: Supportive
- HEV: Supportive (Reduction of immune suppression if possible and ribavirin in chronic hepatitis E)

CLINICAL MANIFESTATIONS

Incubation period
- HAV: 15-50 days
- HEV: 15-60 days

Age and sex distribution:
- HAV: Any age; more severe manifestations in adults *vs.* children; similar rates in men *vs.* women
- HEV: gt 1, 2: Adolescents, young adults gt 3, 4: Middle-aged and elderly men

Asymptomatic infection: Yes, possible for both

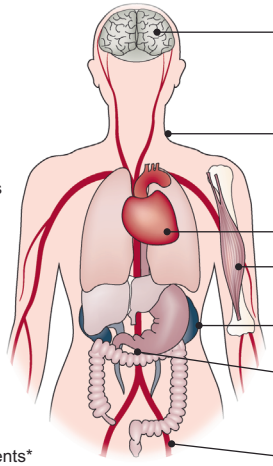
Cholestatic features: Yes

Relapsing-remitting course
- HAV: Yes
- HEV: No

Persistent infection
- HAV: No
- HEV: gt 3 in immunocompromised patients*

Acute liver failure
- HAV: Rare
- HEV: Up to 25% mortality in pregnant women infected with gt 1

EXTRAHEPATIC MANIFESTATIONS



Neurologic: Meningoencephalitis, GBS
- HAV: Mononeuritis multiplex, transverse myelitis
- HEV: Neuralgic amyotrophy, others

Rash: Rare
- HAV: In association with Henoch-Schoenlein purpura
- HEV: In association with cryoglobulinemia

Cardiac: Myocarditis for both

Rheumatologic: Arthralgia, myalgia
- HAV: Arthritis

Renal: Glomerulonephritis and others for both

Gastrointestinal: Pancreatitis (for HEV this has been described only with gt 1)

Hematologic: Hemolysis (in G6PD)
- HEV: Thrombocytopenia, monoclonal gammopathy, cryoglobulinemia

*Isolated cases of chronic hepatitis E have also been reported with gt 3ra, 4, and 7.
G6PD: Glucose-6-phosphate dehydrogenase deficiency. GBS: Guillain-Barré syndrome

Keywords: Comparison; epidemiology; extra-hepatic manifestations; hepatitis A; hepatitis E; transmission; characteristics; virology; genome; hosts; clinical patterns.

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Introduction

Hepatitis A virus (HAV) and hepatitis E virus (HEV) are the most common causes of acute hepatitis in humans worldwide.[1–7] The genomic structure of these viruses is shown in the poster. Both enterically transmitted hepatotropic viruses show a similar but not identical epidemiologic pattern, mode of transmission and clinical course. However, there are also some distinct genetic differences within the genome of the individual viruses with an impact on epidemiology and transmission. Most HAV and HEV infections are acquired through contaminated water and food. HEV genotype (gt) 1 and 2 are restricted to humans and can cause large, primarily waterborne outbreaks in resource-limited settings while gt 3 and 4 are zoonotic infections in middle- and high-income areas. Zoonotic transmission of HAV is unknown. Except for the potential for persistence of HEV gt 3 (and, to a lesser extent, gt 3ra, 4 and 7) in immune-compromised patients, both infections are usually self-limited. While hepatitis A vaccines have been licensed worldwide, an HEV vaccine is currently only manufactured in China.[8,9] Interested readers are referred to a recently published book describing the individual and common properties of HAV and HEV (Box 1).[5]

Box. 1. Viral life cycles.

The life cycles of HAV and HEV are relatively similar. The viruses enter the target cell through only partially understood (HAV) or unknown receptors (HEV), followed by uncoating and cytoplasmic release of the genomes through an uncharacterized process. The RNAs are translated into structural and non-structural proteins. In case of HAV, translation of the single open reading frame occurs via an internal ribosome entry site, with processing of the large polyprotein. In case of HEV, the genomic RNA is translated in a cap-dependent fashion, giving rise to the ORF1 protein harboring the enzymatic functions required for RNA replication (replicase). The ORF2 (capsid) and ORF3 proteins are translated from a subgenomic RNA produced during viral replication. For both viruses, newly produced virions are assembled and released through an exosomal pathway, giving rise to quasi-enveloped (or pseudo-enveloped) particles secreted into the bloodstream and non-enveloped (naked) particles secreted into bile and shed into the feces.

Epidemiology

HAV and HEV infection share a relatively similar epidemiology but also have some unique differences. In resource-limited areas and regions of high endemicity, HAV infects mainly toddlers, adolescents and young adults while in developed countries, HEV infection rate increases with age, mostly affecting adults over 50. Both viruses are predominantly associated with contaminated water and food. In resource-limited areas, HAV (all gts) as well as HEV (mainly gt 1 and 2) are transmitted through the fecal-oral route and can lead to waterborne outbreaks. In middle- and high-income areas, including Europe, Japan and the USA, HEV gt 3 and 4 cause sporadic zoonotic infection while zoonotic transmission of HAV is unknown. The incidence of both infections correlates with socio-economic status, access to clean water and sanitation as well as exposure to infected food products. HEV gt 3 and 4 infection mainly occurs through the consumption of raw or undercooked pork or game meat but likely also through other routes, including transmission through transfusion of blood products. Risk groups for HAV infection in middle- and high-income regions include persons who inject drugs, men who have sex with men, homeless persons and travelers to areas of high endemicity. The demography of HEV infection is changing, as zoonotic HEV infection has emerged with 'hotspots' of infection throughout Europe. Anti-HEV(IgG) antibody seroprevalence rates vary between 5 and 20% in many developed countries and reach 86% in the South of France. Improved socio-economic and sanitary conditions as well as vaccination against HAV have led to a declining incidence in HAV infection worldwide. While HAV infection with recovery, and probably immunization too, provide life-long immunity against HAV, re-infection with HEV is possible (Box 2).

Box. 2. Clinical manifestations of HAV and HEV.

Certain clinical presentations have been linked to specific genotypes of HEV (*i.e.* fulminant hepatitis in pregnancy related to gt 1 and 2) while the clinical course of HAV infection is independent of the viral genotype. There are 6 HAV genotypes. Genotypes I-III infect humans while genotypes IV-VI infect non-human primates. HAV genotype I is the most abundant type worldwide, particularly genotype IA, which dominates in North, Central and South America, China, Japan, Thailand and Europe. HAV subtype IB is reported mainly from the Mediterranean region and South Africa. There are 8 HEV genotypes, four of which (gt 1-4) commonly affect humans. HEV gt 1 and 2 predominantly occur in natives and travelers to Asia, Africa and parts of Mexico. HEV gt 3 and 4 are zoonotic viruses. HEV gt 3 (and to a lesser extent gt 3ra, 4 and 7) infection can persist and cause chronic hepatitis in immunocompromised patients. Human infections with rabbit HEV (gt 3ra) and rat HEV (a member of species Orthohepevirus C) have been reported recently[11-13]. All human pathogenic HEV strains can cause acute-on-chronic liver failure in patients with preexisting chronic liver disease.

Summary – differences and commonalities between hepatitis A and E

While the incidence of hepatitis A is rapidly declining in developed countries, HEV infection is now recognized as an important primarily porcine zoonosis. Consequently, clinicians and virologists are encouraged to familiarize themselves with the differences and commonalities of both viruses.

Differences

- Virus taxonomy/classification
- 7.2 kb *vs.* 7.5 kb positive-strand RNA genomes; 1 *vs.* 3 open reading frames
- HEV gt 3 and 4 represent a primarily porcine zoonosis
- Relapsing hepatitis well-described for HAV but not for HEV
- High mortality of HEV genotype 1 and 2 infection in pregnancy

- Chronic hepatitis E with persistent viremia may develop in immunocompromised patients
- Antiviral therapy for chronic hepatitis E with ribavirin
- Reliable serologic diagnosis for hepatitis A but less so for hepatitis E, especially in immunocompromised patients (PCR for HEV RNA recommended, especially in the latter)
- Hepatitis A vaccine available worldwide, hepatitis E vaccine only in China
- Hepatitis E increasingly recognized in middle- and high-income areas while the incidence of hepatitis A is declining

Commonalities

- Enterically transmitted, primarily hepatotropic positive-strand RNA viruses
- Virion naked in stool and quasi-enveloped (or pseudo-enveloped) in blood
- Fecal-oral transmission (HAV as well as HEV gt 1 and 2)
- Usually self-limited acute hepatitis
- Severity of liver disease is age-dependent
- Neurologic complications and other extrahepatic manifestations
- Available vaccine

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.05.011.

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