Hepatitis E Virus (HEV) Infection Among Immunocompromised Individuals: A Brief Narrative Review

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Abstract: Hepatitis E virus (HEV) is a single-stranded positive-sense RNA virus that belongs to Hepeviridae family. HEV is the most common cause of acute viral hepatitis worldwide. According to the World Health Organization (WHO), there are estimated 20 million HEV infections worldwide every year, leading to estimated 3.3 million symptomatic cases of HEV infection. The WHO estimates that HEV infection caused approximately 44,000 deaths in 2015, which represents 3.3% of mortality rates due to viral hepatitis. In low-income (LI) and lower-middle-income (LMI) countries, HEV is a waterborne infection induced by HEV genotype (gt) 1 and HEV gt 2 that cause large outbreaks and affect young individuals with a high mortality rate in pregnant women from South Asian countries and patients with liver diseases. HEV gt 3, HEV gt 4, and HEV gt 7 are responsible for sporadic infections with zoonotic transmission mainly through the consumption of raw or undercooked meat from different animals. Acute HEV infection is relatively asymptomatic or mild clinical form, in rare cases the disease can be moderate/severe clinical forms and result in fulminant hepatitis or acute liver failure (ALF). Furthermore, HEV infection is associated with extrahepatic manifestations, including renal and neurological clinical signs and symptoms. Pregnant women, infants, older people, immunocompromised individuals, patients with comorbidities, and workers who come into close contact with HEV-infected animals are recognized as major risk groups for severe clinical form of HEV infection and fatal outcome. Chronic HEV infection can occur in immunocompromised individuals with the possibility of progression to cirrhosis.

Keywords: acute and chronic infection, cancer, cirrhosis, hepatitis E virus, HEV, HIV, solid organ transplants

Introduction

The hepatitis E virus (HEV) is the fifth known viral hepatitis (after A, B, C, and D) and the most common cause of acute viral hepatitis worldwide. It attracts the attention of the health community during an epidemic of the so-called non-A, non-B hepatitis in Kashmir, India, in 1978. HEV was discovered by immune electron microscopy in 1983 by Balayan et al, who were investigating an outbreak of unexplained hepatitis among Soviet (Russian) soldiers situated in Afghanistan. The genome of the virus was sequenced in 1991. In the same year, a diagnostic test for its detection was developed.

Nowadays about twenty million HEV infections occur annually worldwide, resulting in approximately 3.3 million symptomatic cases with more than 70 thousand associated deaths and 3000 stillbirths mainly in Asia and Africa. One-third of the world’s population has been exposed to HEV.

The incubation period of HEV is 2 to 6 weeks. The main sites of HEV replication are the liver as well as extrahepatic organs, including the small intestine, colon, spleen, stomach, kidney, and placenta. In general, acute HEV infection is a relatively asymptomatic or mild clinical form presenting with elevated liver enzymes (alanine aminotransferase, ALT, and aspartate aminotransferase, AST), fatigue, dark urine, abdominal pain, jaundice, malaise, nausea/vomiting, muscle...
pain, and pale stools.⁴,¹¹ Acute icteric hepatitis is noted in around 5–30% of patients infected by HEV.⁹ These clinical signs usually last 1–6 weeks and are frequently similar to those observed in other liver diseases.⁴ In low-income (LI) countries and lower middle-income (LMI) countries, the virus affects especially badly pregnant women (especially those in the second or third trimester) and neonates; case fatality rates (CFR) of 20–30%.⁹,¹² It is not clear why pregnant women are at greater risk as no suitable animal model exists, but it is thought to be related to changes in hormone levels during pregnancy and their effect on the immune system.⁹

Although HEV infection is usually a self-limited illness, a chronic presentation could be observed in immunocompromised persons such as solid organ and stem cell transplant recipients, people living with HIV, patients with cancer and rheumatic diseases.¹,⁵

Additionally, HEV infection is associated with extrahepatic manifestations, including mainly renal and neurological symptoms and complications.¹⁰,¹³ Pregnant women, infants, adults/elderly, male sex, immunocompromised individuals, patients with comorbidities (such as hypertension, diabetes mellitus, cardiovascular diseases, malignant diseases, chronic liver diseases, immunodeficiency disorders, etc.) as well as workers who have close contact with HEV-infected animals have been recognized as major risk groups for severe clinical form, chronic infection, or fatal outcome.⁴,⁵,¹⁴ Serological and nucleic acid tests for HEV detection have been developed for both epidemiologic and diagnostic purposes.⁴

The present review summarizes the current knowledge of HEV infection and its presentation among solid organ transplant recipients, people living with HIV, cancer patients, persons with inflammatory bowel diseases, rheumatic disease patients, and individuals with chronic liver disease. All steps of manuscript preparation – from the collection of scientific information in the accessible databases before the critical analysis to the final design of the manuscript – were carried out according to the SANRA Guidelines (Scale for the Assessment of Narrative Review Articles).¹⁵

### Etiology of HEV

HEV is a small virus with a spherical shape, icosahedral symmetry, and a single-stranded, positive-sense RNA genome. Its diameter is 27–30 nm as determined by immunoelectron microscopy, 32–34 nm after sucrose density gradient centrifugation, and 38.5–42 nm when analyzed by freezing electron microscopy.²,¹⁶

Today, HEV is a part of the *Hepeviridae* family.²,³ The current classification divided the *Hepeviridae* family into two subfamilies: *Orthohepevirinae* (contains all mammalian and avian HEV isolates) and *Parahepevirinae* (includes fish HEVs) based on the analysis of the existing sequence information.²,¹⁷ More information about them is summarized in Table 1.

#### Table 1 Classification of Hepeviruses

<table>
<thead>
<tr>
<th>Genus</th>
<th>Genotypes</th>
<th>Infects (Main Reservoirs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subfamily Orthohepevirinae</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avihepevirus</td>
<td>At least 5 genotypes</td>
<td>Poultry as well as duck, egret, owl, sparrow, buzzard</td>
</tr>
<tr>
<td>Chirohepevirus</td>
<td></td>
<td>Bat species, no evidence for transmission to humans</td>
</tr>
<tr>
<td>Pastiohepevirus</td>
<td>HEV gt 1</td>
<td>Humans; primates</td>
</tr>
<tr>
<td></td>
<td>HEV gt 2</td>
<td>Humans; primates</td>
</tr>
<tr>
<td></td>
<td>HEV gt 3</td>
<td>Zoontic (wild and domestic mammals; humans)</td>
</tr>
<tr>
<td></td>
<td>HEV gt 4</td>
<td>Zoontic (wild and domestic mammals; humans)</td>
</tr>
<tr>
<td></td>
<td>HEV gt 5</td>
<td>Wild boars</td>
</tr>
<tr>
<td></td>
<td>HEV gt 6</td>
<td>Wild boars</td>
</tr>
<tr>
<td></td>
<td>HEV gt 7</td>
<td>Dromedary camels; humans</td>
</tr>
<tr>
<td></td>
<td>HEV gt 8</td>
<td>Bactrian camels</td>
</tr>
<tr>
<td>Rocahepevirus</td>
<td>HEV-C1</td>
<td>Isolated from the mammalian orders Rodentia and Soricomorpha; documented cases of human infections</td>
</tr>
<tr>
<td></td>
<td>HEV-C2</td>
<td>From the other mammalian Carnivore</td>
</tr>
<tr>
<td><strong>Subfamily Parahepevirinae</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piscihepevirus</td>
<td></td>
<td>Fish: Rainbow trout, Atlantic salmon, European eel</td>
</tr>
</tbody>
</table>

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The Orthohepevirinae subfamily contains four genera: Avihepevirus, Chirohepevirus, Paslahepevirus, and Rocahepevirus. Members of Avihepevirus genus infect chickens and other avian species. As the virus spreads through the fecal-oral route, a vertical transmission is also assumed. Among leghorn hens, broiler breeders, and dual-purpose hens, the HEV infection was related to increased mortality, reduced egg production, abdominal bleeding, splenomegaly, enlarged not fatty livers, and pale combs and wattles. Coinfections with avian HEV and other pathogens (eg, avian leukemia virus subgroup J and Marek’s disease virus) have been reported. Avian HEVs share an antigenic and genetic resemblance to human and swine HEV strains. The possibility of an avian HEV transmission to humans should be taken into consideration.

Members of Chirohepevirus genus are isolated from bats. So far, there is no evidence of human infection with these viruses. There is great attention on these members of the Hepeviridae family because of the likely association of bats (order Chiroptera) with the emergence of new human pathogenic viruses, including Ebola disease virus, Severe Acute Respiratory Syndrome Coronavirus 1 (SARS-CoV-1), and SARS-CoV-2.

Paslahepevirus genus includes eight genotypes. They infect humans (HEV gt 1 – HEV gt 4, HEV gt 7), pigs (HEV gt 3 and HEV gt 4), wild boar (HEV gt 3 – HEV gt 6), mongoose (HEV gt 3), deer (HEV gt 3), yak (HEV gt 4), camels (HEV gt 7 and HEV gt 8), and other animal species. HEV gt 3 and HEV gt 4 are restricted to higher primates and adapted specifically to humans.

Members of Rocahepevirus genus have been isolated from rodents, insectivore and carnivore species. The ability of C1 genotype viruses to infect humans has been reported.

Parahepevirinae subfamily includes only one genus – Piscihepevirus, the only representative of which is Piscihepevirus A (also known by its historic name of Cutthroat Trout Virus – CTV). In 1988, in California CTV was first found in obviously healthy cutthroat trout (Oncorhynchus clarkii) and since then has been established in several different species of trout and Atlantic salmon (Salmo salar) in New Brunswick, Canada, and North America. Two genotypes (CTV-1 and CTV-2) Canadian CTV isolates have been described. Infected Atlantic salmon (Salmo salar) and chinook salmon (Oncorhynchus tshawytscha) served as hosts and potential reservoirs of CTV-2. Both genotypes CTV-1 and CTV-2 have not been linked with any disease in the fish and do not seem to affect people.

Epidemiology and Animal Reservoirs

Two distinct epidemiological patterns of HEV infection have been described. HEV gt 1 and HEV gt 2 are prevalent in LI/LMI countries and can result in huge outbreaks originating from contaminated water. Acute hepatitis in pregnant women and infants exists and could be fatal. In contrast, HEV gt 3 and HEV gt 4 are zoonotic, and the transmission of these genotypes to humans occurs mainly through the consumption of raw or undercooked meat from infected animals.

Infections by HEV gt 3 and HEV gt 4 have become the most common cause of acute viral hepatitis in several upper middle-income (UMI) countries and high-income (HI) countries. The situation in China is a good example. In that country HEV gt 1 was previously the most common genotype but was subsequently overtaken by HEV gt 4 as a result of improved sanitary and hygienic conditions.

Several routes for transmission of HEV infection are known (Figure 1). One of them is through contamination with human feces water (refers to HEV gt 1 and HEV gt 2) and occurs in poor sanitary conditions (mainly in LI/LMI countries). The presence of HEV in water supply systems with safe sanitary practices has also been demonstrated even in UMI/HI countries.

HEV gt 3 and HEV gt 4 are spread zoonotically (mainly through infected meat, but also through contact), and the sources are infected animals, mainly domestic pigs and wild boars, sika deer in Japan, but also rabbits, sheep, cattle, dogs, camels. Inactivation of the virus in meat can be achieved at a temperature of 70.0°C for 30 min and by heating to 100.0°C in milk. Domestic pigs are considered for the main reservoir of zoonotic HEV gt 3 and HEV gt 4 in UMI/HI countries. HEV is endemic in domestic swine farms worldwide and can infect pigs of all ages. Consequently, pig liver and pig liver containing products have been identified as the source of many of the foodborne HEV outbreaks in Europe. Fruits and vegetables that are washed with contaminated water can be a putative source of HEV. Bivalve mollusks (shellfish) such as mussels and oysters who are filter feeders can concentrate HEV particles and are also recognized as a potential source of transmission.
HEV infection can also occur through direct contact with infected animals. High seroprevalence rates were observed among swine workers, veterinarians, farmers, people working at a slaughterhouse and hunters. Considering these data and the routes of transmission, it could be suggested that individuals who are exposed to contact with infected animal reservoirs are at an increased risk of obtaining the virus than the general population. New HEV strains have continuously been discovered in a wide range of hosts. So the number of animal reservoirs is expanding.

HEV can be transmitted by blood transfusion. Blood or blood products are frequently required for different clinical conditions. HEV infection that occurs by blood transfusion could be more severe or lead to chronic hepatitis and cirrhosis. Individuals at risk are pregnant women, people with liver diseases, transplanted organs and tissues, HIV infections, and leukemias. Screening for HEV RNA among blood donors is currently recognized as the only effective method of preventing transfusion-transmitted HEV infection.

The ability of HEV to be transmitted vertically to the fetus and infant from an infected mother deserves special attention. Cases of maternal death, abortions, birth of premature babies and cases of neonatal death due to liver failure have been described. Fortunately, in some cases, the pregnancy ended with a normal birth. A relationship has been found between fetal and maternal disease severity and outcome. Although all viral liver pathogens can harm the mother and the child, the greatest risk for the woman and subsequently for the fetus is observed in case of acute infection with hepatitis A virus (HAV) or HEV during the period of pregnancy. While HAV infection is self-limiting during pregnancy, HEV has a higher prevalence and is related to significant morbidity and very high maternal mortality (approximately 20%). Therefore, HEV infection in pregnancy in endemic areas requires special attention.

**HEV in Solid Organ Transplant (SOT) Recipients**

In clinical practice, differences in HEV infection between groups of healthy donors and immunocompromised individuals are noted. One explanation could be the longer durations of HEV viremia and the less effective HEV clearance in immunocompromised patients.

Chronic HEV infection in SOT recipients was defined as HEV replication (viremia) – HEV ribonucleic acid detectable in plasma, for more than 3 months after the onset of infection. Furthermore, spontaneous clearance of HEV infection
in transplant recipients could occur 3 months after the first detection of HEV viremia. However, it was reported that some healthy individuals were HEV positive for more than 6 months. In 2008, Kamar et al reported chronic HEV infection in SOT. They presented patients after a kidney or liver transplantation with acute HEV infection, persistent elevation of liver enzymes, liver fibrosis, and histological activity on follow-up. A chronic HEV gt 7 post-transplantation infection has been recorded in patients who had eaten camel-derived food products. 

About 20–50% up to 66% of SOT recipients developed chronic HEV infection. The infection could be asymptomatic, but sometimes fatigue, diarrhea, arthralgia, and liver enzyme abnormality could be found.

It is known that HEV gt 3 and gt 4 have been associated with chronic infection, whereas HEV gt 1 and gt 2 have not been documented to cause chronic HEV infection. HEV prevalence in non-endemic areas was 1–2% after liver transplantation. Histopathological findings in chronic infection were fibrotic damage, nodules, fibrous septa, and cirrhosis. Almost 10% of people with chronic presentation could develop cirrhosis within 2–5 years.

Liver inflammation after HEV clearance has been observed. Chronic HEV may induce post-transplant hepatitis, cirrhosis, liver failure, and even retransplantation, which may cause relapse of HEV infection in the newly transplanted liver.

Lung transplant recipients are less frequently infected with HEV compared to liver transplant recipients. One explanation could be the small number of lung transplantation per year. Other reasons could be ribavirin therapy for respiratory syncytial virus (RSV) or hepatitis C virus (HCV) infections, which lung recipients received.

A meta-analysis for HEV seroprevalence in 14,626 SOT people found a range of 6.0% to 29.6% depending on different diagnostic assays. In this study, HEV-RNA was positive in 1.2%. Another report found 0.66% HEV-RNA positivity in 2419 SOT recipients. A study published in 2021 presented a high HEV prevalence in SOT recipients (20.2%), whereas the highest was in a group of liver recipients (27.2%) and the lowest in lung recipients (5.6%). A significantly higher HEV prevalence was estimated in LI/LMI countries compared to UMI/HI countries (41.8% vs 18.9%).

Unlike most immunocompetent individuals who do not require specific treatment for acute HEV infection, chronic infection in immunocompromised hosts (ie, organ transplant recipients) should be treated to avoid a rapid progression to cirrhosis or even death.

The first-line therapeutic option is to reduce immunosuppressive therapy. In one-third of patients, this pattern leads to viral clearance. However, this stage increased the risk of organ rejection and graft-vs-host reaction; consequently, these patients should be followed up closely. It is documented that drugs such as cyclosporine and tacrolimus may increase HEV replication in vitro, whereas mycophenolate mofetil demonstrated an antiviral effect. This information is useful for physicians in selecting immunosuppressive therapies for transplant patients who are infected with HEV.

Ribavirin has been used off-label as a second step in the treatment of chronic HEV infection. Ribavirin is a guanosine analog that expresses an antiviral action by inducing lethal mutations and inhibiting viral RNA-dependent RNA polymerase (RdRp). The achieved sustained virological response (SVR) rate was 91%, 76%, 67%, and 63% in liver, kidney, lung, and heart transplant recipients, respectively. Six percent of patients were non-responders, and relapse has been noted in 18%. A large European retrospective multicenter study estimated that ribavirin was highly efficient for treating chronic HEV infection in SOT recipients. There are probably at least two reasons that could explain the satisfactory SVR: (i) better awareness among physicians, resulting in earlier diagnosis and initiation of treatment for chronic HEV infection; (ii) published guidelines and improved knowledge for treatment strategies (optimal timing, dosage, and duration of therapy). Some aspects of the ribavirin administration schedule (eg dose) in SOT recipients needed further optimization. Clinical guidelines recommend at least 3 months of therapy in case of chronic infection. However, the optimal duration and dose of ribavirin for treating HEV infection are still undetermined. According to the EASL guideline, HEV RNA should be assessed in the serum and the stool before treatment discontinuation. The monitoring of HEV RNA in stools could be useful to determine the optimal regimen of ribavirin therapy. Unfortunately, treatment failure may occur and the only therapeutic strategy in such cases is interferon.

Some single nucleotide variants (SNVs) as well as in-frame insertions in the hypervariable region of ORF1 and other mutations in viral polymerase (Y1320H, G1634R, and K1383N) have been connected with ribavirin failure. Ribavirin treatment failure-associated mutation Y1320H in the RNA-dependent RNA polymerase of HEV gt 3 has been found to enhance virus replication in a rabbit HEV infection model. The ability of ribavirin to induce HEV mutagenesis in
treated patients has been reported. The analysis of plasma HEV kinetic patterns in 41 SOT patients during ribavirin therapy demonstrated no association with response to therapy, with the exception of a flat-partial response. 

A second treatment attempt with ribavirin can be performed for 6 months in cases of ribavirin failure, and the data showed sustained virological response in 76% of these patients. As another therapeutic option, pegylated-interferon alpha (PEG-IFNα) could be applied to liver transplant recipients, but it is contraindicated after other SOTs, because of the increased risk of allograft rejection.

Sofosbuvir is a nucleotide analog approved by the US Food and Drug Administration (FDA) for the treatment of chronic HCV infection, which has been reported to inhibit HEV-3 replication in vitro and possess an additive effect when combined with ribavirin. However, in clinical studies, only modest antiviral activity was observed and SVR was not achieved.

HEV in HIV-Positive Individuals

According to UN AIDS data up to 2022, 39 million people are living with HIV (PLWH). The distribution is the following: 37.5 million adults and 1.5 million children <15 years old; 53% of them were women and girls, and 25 million live in sub-Saharan Africa. The number of newly diagnosed HIV infections in 2022 is 1.3 million. Despite the increased coverage of antiretroviral therapy, about 15% of HIV individuals are not included.

HIV-infected patients possess many specific immunological, epidemiological, and clinical characteristics, which could influence the pathogenesis of HEV and the outcome of the infection. Some of them will be discussed in the following lines.

HIV-positive patients are highly sensitive to infectious diseases and cancer due to the alteration of their immune status. HEV seropositivity in HIV-infected population varies among different continents. The prevalence of HEV infection is presented in Table 2. We applied a search strategy to the following scientific databases: PubMed, Scopus, and Web of Science. We used free-text terms: “Hepatitis E virus (HEV) in HIV individuals” AND “Hepatitis E virus (HEV) in AIDS patients” AND “Hepatitis E virus (HEV) in HIV/AIDS persons”. The present analysis included

<table>
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<tr>
<th>First Author</th>
<th>Year of Publication</th>
<th>Country</th>
<th>Diagnostic Method</th>
<th>Participants, n</th>
<th>HEV Positive, %</th>
<th>Reference</th>
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<td>Pawlotsky et al</td>
<td>1995</td>
<td>Central African Republic (CAR)</td>
<td>EIA IgG</td>
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<td>33.0</td>
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<td>1996</td>
<td>Greece</td>
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<td>Balayan et al</td>
<td>1997</td>
<td>Russia</td>
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<td>11.1</td>
<td>[49]</td>
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<td>Balayan et al</td>
<td>1997</td>
<td>Belarus</td>
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<td>Malaysia</td>
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<td>RT-PCR</td>
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<td>Renou et al</td>
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<td>Sellier et al</td>
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<td>Kenfak-Foguena et al</td>
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(Continued)
Table 2 (Continued).

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<th>First Author</th>
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<td>England</td>
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<td>Maylin et al</td>
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<td>France</td>
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<td>Gabon</td>
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original articles, short communications, and case series (more than 20 participants). The current analysis excluded reviews and articles with missing data for the number of investigated persons and case reports. Scientific papers for the period from January 1983 to August 2023 were studied.

Table 2 (Continued).

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<td>7.5 (IgG) 5.4 (IgM) 0.0 (RNA)</td>
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Abbreviations: EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; RT-PCR, reverse transcription polymerase chain reaction; RNA, ribonucleic acid; USA, United States of America.
There is probably no connection between HIV viremia and a higher risk for HEV infection.\(^{46}\) No significant association between HIV viral load and HEV seroprevalence in HIV-infected patients has been documented.\(^{46,91,111}\) Probably HIV infection itself is not a risk factor for HEV infection.\(^{46}\) Differences in HEV seropositivity between HIV-1- and HIV-2-infected patients have not been noted.\(^{56}\)

Both acute and chronic HEV infections have been described in PLWH, especially among MSM and in patients with severe immunodeficiency.\(^{46}\) Chronic HEV infection can persist despite a CD4+ T-cell count >200 cells/mm\(^3\).\(^{3,56}\) The rate of chronic HEV infection among PLWH is low (0.0–0.5%) and mainly for individuals receiving appropriate antiretroviral therapy.\(^{46,81}\)

Men who have sex with men are at higher risk for HIV infection, and also for pathogens transmitted by the oro-fecal route, for example HAV and HEV.\(^{116}\) In contrast to HAV, the available data do not indicate that sexual transmission is among the major routes of HEV infection in MSM.\(^{85,117}\) MSM and PWUD are not at higher risk for being HEV IgG seropositive than blood donors.\(^{85,117}\)

Over the course of evolution, HEV has developed strategies to counteract and escape the host immune response and the development of chronic HEV infection is associated with immunosuppression.\(^{46}\) Effective immune control by both CD4+ and CD8+ T cells is necessary to prevent chronic viral replication.\(^{118}\) It has been reported that HEV-specific CD8+ T cells do not function properly in immunocompromised individuals and this contributes to the establishment of chronic infection with this virus.\(^{119}\) So, the measures to improve the immune response could have a good influence on HEV clearance. In agreement with this hypothesis was a manuscript that presented a self-limiting HEV infection in people living with HIV as a result of initiation of antiretroviral therapy and decreasing HIV viral load.\(^{55}\) Serologic screening alone may be insufficient to diagnose HEV infection in HIV-infected patients with very low CD4 counts because seroconversion (IgG) may be delayed or may not occur.\(^{55}\)

While abundant information is available on therapeutic options for chronic HEV infection in liver transplant patients, data for PLWH are extremely limited.\(^{5}\) There were reports for ribavirin (RBV) monotherapy; a combination of pegylated interferon and RBV for 12 and 24 weeks of treatment; and a combination of sofosbuvir and RBV for 12 weeks.\(^{5,120–122}\)

**HEV in Patients with Neoplasm**

The research on the relationship “HEV–cancer” is important for at least three reasons. First, patients with neoplastic diseases often have a suppressed immune system due to the cancer itself or the applied therapy (cancer chemotherapy or immunosuppressive drugs because of stem cell transplantation), which makes them more susceptible to further bacterial and viral infections or reactivation of latent pathogens such as *Toxoplasma gondii*, HIV, HBV, HCV, herpes simplex virus, and so on. This may increase morbidity and cancer death rates.\(^{123–125}\) Second, oncology patients are commonly transfused with blood products, which pose a possible route of HEV transmission.\(^{126,127}\) Third, 15.4% of all cancers are caused by infectious agents of various categories, and more than 10% of them are attributed to viruses, including HBV and HCV.\(^{126,127}\)

It seems that the incidence of HEV in patients with neoplasms is similar in the general population.\(^{128}\) In the scientific literature, we can find publications that presented a case, cases, or series of cases on HEV infection and neoplastic patients. Chronic HEV infection has been registered in a person with non-Hodgkin’s lymphoma undergoing treatment.\(^{129}\) A case has been published of acute lymphoblastic leukaemia after allogeneic stem cell transplantation who developed reactivation of HEV infection.\(^{130}\) The results of a multicentre cohort study across 11 European centres were published in 2019 and showed liver morbidity and mortality related to HEV among patients with hematologic cancers.\(^{131}\)

A case series of women with underlying gynecological cancers who developed HEV infection has been reported.\(^{132}\) A study (950 cancer patients and 950 control volunteers) from Shandong province, Eastern China revealed a higher seroprevalence of IgG and IgM antibodies in cancer patients.\(^{133}\) The highest incidence of HEV infection has been found in leukemia patients (32.3%), followed by liver cancer patients (31.1%), the lowest HEV seropositivity was noted in individuals with gastric cancer (18.9%).\(^{133}\) The highest seroprevalence in a group of leukemia patients can be attributed to severe immune dysfunctions observed in acute and chronic leukemia.\(^{134,135}\) Also, the treatment of acute lymphoblastic leukemia often included stem cell transplantation, radiation therapy, and application of immunosuppressive drugs or blood transfusions – so there were predispositions for immune disturbances, on one hand, and transfusion-transmitted ability, on the other hand.\(^{126,127}\)
Nevertheless, the influence of HEV infection on cancer development (in particular liver carcinogenesis) has been poorly studied for a variety of reasons:

- Chronic HEV infection mainly presents in immunocompromised individuals, and the overall number of cases is low.\(^5\),\(^{136}\)
- The onset of liver cirrhosis occurs relatively soon after chronic HEV infection, whereas the development of HCC takes longer – at least 8 years.\(^{28}\),\(^{137}\) Other hepatotropic oncoviruses such as HBV or HCV usually lead to HCC 20–30 years after the initial infection.\(^{28}\),\(^{137}\)
- An extremely limited number of clinical cases of HEV-related HCC has been reported. Atsama et al described the association between anti-HEV IgG prevalence and HCC in a study performed in Cameroon.\(^{138}\) HEV positivity has been detected in 31.1% of liver cancer patients.\(^{133}\) A case of HCC complicating chronic HEV infection has been reported in 2018 by French researchers.\(^{137}\) The possibility of cancer cells being more sensitive to HEV infection is discussable.\(^{139}\)
- Globally, HEV infection is not routinely tested.\(^1\),\(^5\)
- Basically, cancer develops in a small fraction of people infected with the respective oncovirus.\(^5\),\(^{10}\)
- Studies on biology and oncogenic potential of HEV are limited because of the difficulties to propagate at conventional cell lines and the available appropriate experimental systems (cell cultures and animal models).\(^{139},^{140}\)

**HEV Among Individuals with Inflammatory Bowel Disease (IBD)**

Inflammatory bowel disease (IBD) is characterized by repetitive episodes of inflammation of the gastrointestinal tract caused by an abnormal immune response to gut microflora.\(^{141},^{142}\) Two main diseases are ulcerative colitis and Crohn’s disease.\(^{141},^{142}\) There were a few articles on HEV and IBD. Senosiain et al presented 87 patients with IBD from Madrid, Spain. The estimated prevalence of anti-HEV IgG antibodies was 1.3%, HEV IgM – 2.7%, HEV RNA – 0.0%, chronic HEV infection – 0.0%.\(^{143}\) In 2019, German scientists performed a study on HEV among 328 patients with Crohn’s disease and 150 patients with ulcerative colitis.\(^{144}\) They reported HEV IgG seropositivity of 17.4% in Crohn’s disease individuals, 24.7% in ulcerative colitis patients, and no positive results for HEV by RT-PCR.\(^{144}\) Grigas et al presented 203 patients with inflammatory bowel disease (Crohn’s disease – 47 persons and 156 with ulcerative colitis).\(^{145}\) These Lithuanian scientists announced higher levels of anti-HEV IgG and IgM antibodies among Crohn’s disease patients – 12.8% (95% CI: 3.2–22.3) and 8.5% (95% CI: 0.5–16.5), versus lower level of anti-HEV IgG and IgM antibodies in ulcerative colitis individuals – 12.2% (95% CI: 7.1–17.3) and 5.8% (95% CI: 2.1–9.4).\(^{145}\) Furthermore, Grigas et al reported 22-year-old woman with ulcerative colitis and HEV gt 3i (GenBank accession number: MT585816), which was genetically closer to wild boar and domestic pig isolates from Lithuania.\(^{145}\) In retrospective, multicenter, observational research of 327 patients with Crohn’s disease and 161 ulcerative colitis individuals from 16 French general hospitals was presented.\(^{146}\) These French authors established a HEV IgG seroprevalence rate of 14.2% among all patients, and HEV IgM was detected in 0.9%, and HEV RNA was undetectable in all participants.\(^{146}\) At this stage of knowledge, the number of studies on HEV infection among IBD individuals with IBD is small and are not enough to draw up conclusions and recommendations for this specific patient group.

**HEV Among Rheumatic Diseases Patients**

Rheumatic diseases include different autoimmune and autoinflammatory illnesses that are characterised by musculoskeletal disorders and systemic presentations.\(^{147},^{148}\) Furthermore, the adaptive and innate immunity can support to the inflammatory processes that take part in the pathogenesis of these debilitating diseases.\(^{147},^{148}\) There are still few studies on HEV infection in individuals with rheumatic diseases. Bauer et al did a retrospective multicenter questionnaire-based survey (initiated by the Society of Rheumatology in France) among nearly 2400 French physicians.\(^{149}\) For the period of 44 months (between January 2010 and August 2013) the surveyed physicians announced 23 clinical cases of HEV infection among patients with rheumatic diseases (axial spondyloarthritis, n = 5; other types of arthritides, n = 3; psoriatic arthritis, n = 4; and rheumatoid arthritis, n = 11).\(^{149}\) All 23 patients had an acute infection, and the diagnosis was made by positive results from the RT-PCR test (n = 14) and ELISA HEV IgM test (n = 9). Due to the initial phase of investigations on HEV infection in rheumatic patients, it is hard to make in-depth conclusions and recommendations.
HEV Among Individuals with Chronic Liver Disease

Chronic hepatitis B virus (HBV) is an immune-related chronic liver disease.150 Essentially, HBV does not directly damage the liver but through abnormal immune response.151 In chronic HBV infection, the virus continues to replicate and the host immune response is insufficient.152 The most common obstacles to eliminate HBV are the following: dysfunction of T cells; persistent presence of HBV cccDNA (covalently closed circular DNA); insufficient response of B cells; and integration of HBV DNA in hepatocytes.153 In 2007, Bayram et al reported 13.7% (26/190) anti-HEV IgG positive results among Turkish adult patients with chronic HBV.154 Chinese authors presented a study including 188 persons with chronic HBV, 136 with HEV superinfection and 52 with HAV superinfection.155 Most of the individuals in the group “chronic HBV + HEV” had complications (94.9%), hepatic failure (39.7%), and high mortality (33.8%).155 In 2019, McGivern et al announced 28.5%/1.7% anti-HEV IgG/IgM seroprevalence in 600 adult persons with chronic HBV living in the USA and Canada.156 Chinese scientists found 1.27% (10/790) anti-HEV-IgG positive results in patients with chronic HBV versus 4.21% (22/522) in persons with HBV-related cirrhosis (OR = 3.04; p < 0.05).157 In 2019, Kilonzo et al established 35.9% anti-HEV IgG seroprevalence among chronic HBV patients.158 American authors reported 19.86% HEV IgG seroprevalence in US adults with chronic HBV.159

Immune cell detection of HCV activates signaling pathways that produce interferons and trigger the innate immune response against this virus, ie preventing HCV spread and replication.160 Furthermore, cells in the innate immune system (including dendritic cells, Kupffer cells, and natural killer cells) interact with infected hepatocytes and present viral antigens to B and T cells where their effector responses contribute to HCV infection outcome.161 Despite all these immune mechanisms, HCV can evade the host immune response and establish chronic infection. Turkish authors reported 54.0% (94/174) anti-HEV IgG positive results in adult persons with chronic HCV.154 In 2017, Mellgren et al found 30.0% anti-HEV IgG prevalence among 204 Swedish patients with chronic HCV infection.162 Chinese scientists announced 3.23% anti-HEV-IgG positive results in individuals with chronic HCV versus 10.81% in persons with HCV-related cirrhosis.157 In 2019, Bricks et al noted 13.2% anti-HEV seroprevalence among chronic HCV patients with cirrhosis and 8.0% in chronic HCV persons without cirrhosis (OR = 1.74; p = 0.04).163 Brazilian authors found 12.0% (22/181) anti-HEV IgG seropositivity in individuals with chronic HCV.164 In 2021, Wong et al reported 8.66% HEV IgG seroprevalence among adults with chronic HCV.159 Korean scientists presented 33.3% anti-HEV IgG positivity prevalence in 502 patients with chronic HCV.165

Cirrhosis is a dynamic chronic liver disease. Furthermore, cirrhosis and acute-on-chronic liver failure (ACLF) are associated with severe systemic inflammation, respectively, with oxidative stress, increased inflammatory cytokines, and some markers of activated macrophages and neutrophils in the liver and in the blood.166 In liver cirrhosis, an immune deficiency or “immune paralysis” is often observed – cirrhosis-associated immune dysfunction (CAID) syndrome.167 The intensity of CAID syndrome correlates with the severity of acute/chronic liver failure and bacterial translocation.168 Kumar Acharya et al reported that HEV infection among 107 Indian patients with cirrhosis is associated with rapid decompensation and death.169 Spanish authors reported 17.5% anti-HEV IgG positive results in persons with chronic liver disease and cirrhosis versus 32.1% in individuals with liver transplant and cirrhosis.67 In 2019, Fantilli et al found 25.0% HEV seroprevalence among 140 Argentinian patients with cirrhosis.170 Chinese scientists noted 1.41% anti-HEV-IgG positive results in persons with chronic alcoholic hepatitis versus 9.40% in individuals with alcoholic cirrhosis.157 American researchers recorded 6.58% HEV IgG seroprevalence among adults with alcoholic liver disease.159 In 2022, Korean authors reported that acute HEV infection mortality rate was higher among individuals with cirrhosis, and especially high in those with ACLF.171

Non-alcoholic fatty liver disease (NAFLD) has been recently re-named as “metabolic dysfunction-associated fatty liver disease” (MAFLD).172 MAFLD is the main cause of chronic liver disease worldwide. MAFLD can range from steatosis to non-alcoholic steatohepatitis (NASH), cirrhosis, and hepatocarcinoma.173 Furthermore, MAFLD is an independent risk factor for diabetes mellitus (type 2), different cardiovascular diseases, and high mortality rate.174 In 2019, Yang et al reported 0.0% anti-HEV-IgG positive results among Chinese patients with chronic NASH versus 25.0% in persons with NASH-related cirrhosis.157 American authors announced 8.81% HEV IgG seroprevalence among individuals with NAFLD.159
Schistosomiasis is a neglected tropical disease, impacting approximately 250 million infected persons in more than 70 countries.\textsuperscript{175} This infection is caused by trematode blood flukes of \textit{Schistosoma} genus.\textsuperscript{176} The main clinically important \textit{Schistosoma} species are as follows: \textit{S. haematobium}, \textit{S. japonicum}, and \textit{S. mansoni}.\textsuperscript{177} Other species of the genus \textit{Schistosoma} have regional and local importance – \textit{S. guineensis}, \textit{S. intercalatum}, and \textit{S. mekongi}.\textsuperscript{178} The main lesions in \textit{Schistosoma} spp. are due to the eggs laid by the female worms.\textsuperscript{175} A large proportion of eggs are trapped in the liver of the definitive host.\textsuperscript{176} In the liver, they secrete different components including proteolytic enzymes that elicit eosinophilic inflammatory immune responses.\textsuperscript{175} Furthermore, \textit{S. japonicum} and \textit{S. mansoni} can cause the formation of granulomas, which are progressively replaced by fibrotic deposits eventually resulting in advanced or intestinal hepatosplenic schistosomiasis.\textsuperscript{176} Abdel Rahman et al reported 31.0\% HEV IgM positive results among 100 Egyptian individuals with \textit{S. mansoni} infection.\textsuperscript{179} Brazilian authors found 10.0\% HEV seropositivity in 30 patients with schistosomiasis.\textsuperscript{180} Passos-Castilho et al presented 18.8\% anti-HEV IgG positive results among 80 patients with \textit{S. mansoni}.\textsuperscript{181} In 2023, Brazilian scientists announced 3.08\% anti-HEV IgG positive results in 227 individuals with chronic liver disease (alcohol-related liver disease – 17 individuals; HBV – 50; HCV – 33; mixed disease – 62; NAFLD – 49; and schistosomiasis – 16).\textsuperscript{182}

A brief review of the scientific literature showed that HEV infection can occur and may be more frequent among individuals with underlying chronic liver disease. HEV-related complications and mortality could be observed more often in this population. This is important for daily clinical practice because HEV could lead to a severe clinical form in individuals with underlying chronic liver disease. In this regard, it is recommended to consider HEV infection in case of patients with chronic liver disease.

**Prevention of HEV Infection**

Prevention against HEV infection is focused on several basic recommendations. First, it is known from the scientific literature that HEV gt 1 and HEV gt 2 are transmitted by ingesting contaminated water.\textsuperscript{1,5} Consequently, access to safe water sources and safe water supplies is needed. Second, HEV gt 3, HEV gt 4, and HEV gt 7 are transmitted by eating raw or undercooked meat, meat products, fish, seafood, and meat from different animals (domestic pigs, wild boars, deer, rabbits, camels, etc.).\textsuperscript{1,5} In this regard, it is highly recommended that meat, meat products, fish, and seafood undergo heat treatment at 70.0°C for a minimum of 2 min.\textsuperscript{5} Third, another important preventive measure is HEV vaccination, which is mainly done in China.\textsuperscript{183} Currently, the development of several vaccines against HEV is proceeding at different stages.\textsuperscript{4} Fourth, special protective equipment for persons coming into close direct contact with animal reservoirs (veterinarians, hunters, workers in pig farms, etc.) is also recommended. Fifth, proper washing and cleaning of stem vegetables and fruits before their use. Sixth, maintaining good personal hand hygiene. Seventh, the risk of transfusion-transmitted HEV is low. However, it is recommended to conduct HEV blood screening as well as other routine tests for some infectious pathogens. In conclusion, the implementation of all these measures could reduce the risk of HEV transmission and consequently HEV infection, which could be more severe in immunocompromised persons compared to immunocompetent individuals.

**Conclusion**

In the past two decades, the incidence of HEV infection has increased worldwide. Moreover, HEV is a serious challenge for immunocompromised individuals. In recent years, the number of transplant recipients has increased, HIV infection continues to be a serious problem for developing countries, and cases of neoplasms are frequent in all continents. These conditions lead to an increase in the population of individuals with compromised immune status. Also, there is a group of people with disorders in the immune system (inflammatory bowel diseases, rheumatic diseases, chronic liver diseases, etc.). All these facts indicate the increment of the importance of HEV infection among immunocompromised individuals. So, public health institutions and organizations should take preventive measures against the spread of HEV in different countries. This is a health problem that cannot be overlooked by public health specialists. Physicians in different medical specialties should be involved in the surveillance and management of HEV.
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Author Contributions
All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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References
Alexandrova et al


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