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## Significance of hepatitis E virus infection in HIV-infected patients: a challenging issue

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## ABSTRACT

Hepatitis E virus (HEV) is a small, single-stranded, non-enveloped RNA virus and belongs to the genus *Hepevirus* in the Hepeviridae family. Currently, the HEV infection is the most frequent cause of acute hepatitis in the world. In recent years, some studies have been demonstrated that immunosuppressed cases, such organ transplant recipients, cases with HIV infection and patients with hematological malignancies are at risk of HEV infection. But it is not clear whether HEV infection is a major concern in HIV infected patients or not? The answer has considerable significance, because HIV and HEV infection are now both highly endemic in many parts of the world. The purpose of this review is to provide data on the prevalence of HEV infection in HIV infected patients for determination of the significance of HEV/HIV co-infection.

## 1. Introduction

Hepatitis E virus (HEV) is a small (with a size of 27-34 nm), single-stranded, non-enveloped RNA virus and belongs to the genus *Hepevirus* in the Hepeviridae family[1]. Currently, the HEV infection is the most frequent cause of acute hepatitis in the world. It is a significant international public health concern and it is estimated that 2.3 billion people, representing one third of the world's population, are at risk of HEV infection[2].

HEV is considered as a typically self-limiting viral infection which is endemic in the developing countries[3]. In developing countries, this disease is transmitted through the water and causes serious epidemic outbreaks[4]. In developed countries, the circulation of the virus in both human and animal sewage has been confirmed; however, the incidence rate is low compared to developing countries[5]. So, HEV infection is considered non-endemic in developed countries with seroprevalence rate of 1% to 20%[2], and it is endemic in regions with poor sanitation and hygiene, such as parts of Asia, Africa and Mediterranean, where HEV prevalence can

be as high as 80%-100%[6,7]. In endemic areas, young adults are most often infected, while in developed countries, the elderly and individuals with underlying diseases are infected with HEV[8]. The rate of detectable anti-HEV antibody in adults is about 10%-100% in developing countries and 1%-20% in non-endemic areas[8,9].

## 2. Transmission routes of HEV

The main transmission route of HEV in developing countries is the fecal-oral route. It is responsible for most of the epidemic outbreaks, especially due to consumption of water contaminated with fecal matter. Outbreaks have usually occurred during the rainy season when flooding can contaminate drinking water supplies. The fecal-oral route is responsible for the transmission of genotypes 1 and 2 of HEV[2,5].

The other transmission routes of HEV are zoonotic transmission and ingestion of certain foods. These routes are considered the major causes of HEV infection in developed countries and mainly responsible for transmission of HEV genotypes 3 and 4[5,10].

Other transmission routes, which are less frequent, are vertical, direct contact and the parenteral transmission[11-13]. HEV can also be transmitted parenterally by blood transfusion[14,15]. Other modes of HEV transmission such as dialysis remain controversial[16].

Several studies have been demonstrated that immunosuppressed cases, such organ transplant recipients[17], cases with HIV infection[18] and patients with hematological malignancies and lymphoma[19,20], are at risk of HEV infection.

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### 3. Molecular epidemiology of HEV infection

HEV belongs to the genus *Hepevirus* of the family Hepeviridae. It is a non-enveloped, positive-sense, single-stranded RNA virus and contains a 7.2-kb-long genome, which is capped and polyadenylated[21].

The viral RNA genome contains three open reading frames (ORF1-3) and a short non coding region at the 5' and 3' ends. ORF1 is located at the 5' end of the genome and extends between nucleotides 28 and 5107. It encodes a polyprotein with 1693 aminoacids that undergoes post-translational cleavage into multiple nonstructural proteins requiring for virus replication and processing of viral proteins, including RNA helicase, methyltransferase, protease and RNA-dependent RNA polymerase[7,9,22,23]. ORF2 and ORF3 are at the end of the 3' terminus, and ORF2 overlaps with ORF3[7,9,23]. ORF2 extends from nucleotide 5147 to 7127 and encodes the viral capsid that is responsible for virion assembly, interaction with target cells and immunogenicity[24-27] and the ORF3 encodes a small protein of 114 aminoacids which involved in virion morphogenesis, pathogenesis and release[7,9,23].

HEV isolates are classified into five major genotypes which belong to one serotype[28]. Each genotype is classified into several subgenotypes. Genotypes 1, 2, 3 and 4 are classified into five, two, ten and seven subgenotypes, respectively[21]. These subgenotypes are circulated via zoonotic transmission between human beings and animals in the same area[29].

Genotypes 1 and 2 exclusively infect humans and transmitted via contaminated water in developing countries and often associated with outbreaks and epidemics in these areas. HEV1 occurs mainly in Asia and HEV2 in Africa and Mexico[4,7,27]. Genotypes 3 and 4 infect humans, pigs and other animal species and have been responsible for sporadic cases of disease in both developing and developed countries[4,7,30]. HEV3 has a worldwide distribution. By contrast, HEV4 commonly occurs in South-East Asia, but it has recently isolated from European pigs[29,31]. Genotype 5 infects rabbits[32,33], rats[34] and wild boars[27].

### 4. Clinical presentations of HEV

HEV infection can be presented in two forms, outbreaks and sporadic. The outbreaks are mainly seen in developing countries and are due to the consumption fecally-contaminated water[35,36], especially after natural disaster or in overcrowded refugee camps[5]. HEV outbreaks are mainly caused by HEV1 in Asia and HEV2 in Africa and Mexico. HEV epidemics affect young adults specially the age range of 15-35 year old and men are clinically infected 2 to 5 times more than women in most outbreaks[4,7].

Sporadic HEV infection mainly reported in developed countries. HEV represents 1% of the acute viral hepatitis in these areas. HEV infection in developed countries was attributed to patients with history of travel to endemic areas[37,38]. However, cases without any travel history (autochthonous hepatitis) are reported with increasing frequency in these countries[39-41]. Autochthonous cases of HEV infection are due to genotype 3 or 4. This form of HEV infection has a predilection for middle aged and elderly men with male to female ratio 3:1[41].

Clinical features of HEV infection range from asymptomatic to acute hepatitis and even to acute or subacute liver failure and fulminant hepatitis[8,42]. HEV infection often follows a silent clinical course[23]. Asymptomatic infections occur more often among children than adults[43].

The incubation period of HEV infection ranges from 3 to 8 weeks, with a mean of 40 days[43]. In symptomatic cases, jaundice, fever,

anorexia, hepatomegaly, joint and muscle pain, abdominal pain, nausea and vomiting are observed[23]. Headache, loss of appetite, weight loss, bowel disturbances and purpuric skin rash are also observed in some cases[7]. These symptoms are usually self-limiting and resolve in 4 to 6 weeks[8]. Some patients, however, have a severe course including pregnant women, individuals with pre-existing chronic liver diseases and those with active alcohol abuse who are at a higher risk of HEV associated liver failure[44,45].

Chronic HEV infection (CHE) is defined as persistence of HEV-RNA in serum or stool for more than 6 months in association with increased levels of liver enzyme[5]. CHE can result progressive liver fibrosis, cirrhosis and subsequent liver failure[23,27,46], which occasionally require liver transplantation[47]. CHE mainly seen in immunocompromised patients such as HIV infected cases, patients with solid organ transplantation, patients with hematologic malignancies and lymphoma, primary immunodeficiencies and those under treatment with corticosteroids and immunosuppressive agents[48]. CHE often shows nonspecific symptoms and usually has unremarkable clinical presentation. Most of the patients are asymptomatic and few show jaundice, fatigue, abdominal pain, fever and asthenia[23,27].

Some extra-hepatic manifestations of HEV infection have been described including pancreatitis, hematological manifestations such as thrombocytopenia and hemolytic anemia[5], membranoproliferative and membranous glomerulonephritis[27] and occasional neurological complications such as Guillain-Barré syndrome, Bell's palsy, neuralgic amyotrophy, acute transverse myelitis and acute meningoencephalitis[49-52].

### 5. HEV diagnosis

HEV infection elicits both IgM and IgG antibodies against HEV. Serologic diagnosis of HEV infection is the method of choice using in most laboratories. There are several commercial enzyme immunoassays (ELISA) to detect anti-HEV antibodies (IgM and IgG) in serum, although there is remarkable variability in their sensitivity and specificity. The diagnosis of acute infection is based on the presence of IgM anti-HEV which can be detected during the acute phase of the disease and can last approximately 4 or 5 months. IgG anti-HEV appear just after the raising of IgM and increase from the acute phase until convalescent phase. Therefore, positive IgM results suggest an acute infection and elevated IgG levels shows previous exposure to HEV[5,7,23].

Viral nucleic acid (HEV-RNA) can be detected in both blood and stool at the peak of the acute serological response by RT-PCR. HEV-RNA levels in both serum and stool are transient. The virus can be detected in stool one week before the onset of the clinical signs and persists during two weeks, although sometimes it has been detected until 52 days after the beginning of the clinical signs. In blood, viremia is present during the incubation period and in the early symptomatic phase and became undetectable within 21 days of the onset of symptoms[5,7,23].

As IgM and IgG anti-HEV are often negative in immunosuppressed patients, RT-PCR is strongly recommended in these cases to detect HEV-RNA in blood and stool samples[53,54].

### 6. HEV infection in HIV infected patients

The occurrence of CHE in persons undergoing immunosuppressive therapy for solid organ transplantation, increased awareness of HEV infection in immunocompromised individuals such as HIV infected patients[17]. Infections caused by hepatotropic viruses such as HEV may affect HIV positive patients, but its prevalence is variable, depending on geographic differences or different major risk groups

in the studying population[55,56]. Some studies showed that HIV infected patients may acquire HEV infection more frequently than HIV negative cases[18,56]. Although, other studies have not shown significant differences in HEV prevalence between HIV-infected and non-infected individuals[57,58].

The association between HEV and HIV infection had been reported in the 1990s based on serological studies[35,56,59-62]. In these studies a higher risk of HEV infection was reported in HIV infected men having sex with men (24%)[59], but no association was found in other groups[60,63]. Later, Fainboim *et al.*[56] reported a higher IgG anti-HEV prevalence rate in HIV infected patients than blood donors (6.6% vs 1.8%) in Argentina. A similar result was showed in Balayan *et al.* investigation in Russia[35], with IgG anti-HEV seroprevalence rate of 11.1% in HIV infected cases versus 1.7% in the general population. However, Bissuel and Gessoni *et al.* didn't find significantly difference in seroprevalence of IgG anti-HEV between subjects infected and non-infected with HIV[60,61].

Since 2009, some studies conducted in HEV/HIV co-infection in Europe and they reported prevalence rates of HEV antibodies or HEV-RNA in HIV infected cases from 0% to 11.3%[57,58,64-70]. In a recent study in Spain by Mateos-Lindemann *et al.*[71], IgG anti-HEV was found in 10.4% of HIV infected patients and significantly different to that observed in blood donors. These data were similar to Jardi *et al.* results, that reported the high prevalence of anti-HEV IgG antibodies (9%) in HIV positive patients[72]. On the other hand, other investigators found similar HEV seroprevalence in HIV infected and control groups and suggest that HIV infection is not a risk factor for HEV acquisition[68].

An investigation from US showed that HEV infection accounted for 4% of acute liver abnormalities among HIV-infected persons[73]. Overall, HEV was detected in 6% of HIV-infected patients which is similar to the HEV prevalence reported earlier in the general population of the United States[74]. On the basis of this study and data from other industrialized countries[66,68], HEV is a cause of liver abnormalities in HIV-infected persons but does not seem to be more common in this population than in the general population.

**Table 1**

Studies investigating HEV infection rate in HIV infected patients.

Study ID	Country of study	HEV rate in HIV infected cases
Montella <i>et al.</i> , 1994 [59]	Italy	24%
Bissuel <i>et al.</i> , 1996 [60]	France	4%
Gessoni <i>et al.</i> , 1996 [61]	Italy	2.6%
Balayan <i>et al.</i> , 1997 [35]	Russia	11.1%
Fainboim <i>et al.</i> , 1999 [56]	Argentina	6.6%
Ng <i>et al.</i> , 2000 [62]	Malaysia	14.4%
Madejon <i>et al.</i> , 2009 [57]	Spain	0%
Pischke <i>et al.</i> , 2010 [64]	Germany	5%
Renou <i>et al.</i> , 2010 [65]	France	9% in South and 3% in North
Kenfak-Foguena <i>et al.</i> , 2011 [66]	Switzerland	2.6%
Sellier <i>et al.</i> , 2011 [58]	France	2.7%
Kaba <i>et al.</i> , 2011 [67]	France	Past, recent and on-going HEV infection: 3.3%, 1.6% and 0.5% respectively
Maylin <i>et al.</i> , 2012 [70]	France	2.3%
Jardi <i>et al.</i> , 2012 [72]	Spain	9%
Keane <i>et al.</i> , 2012 [68]	England	9.4%
Crum-Cianflone <i>et al.</i> , 2012 [73]	USA	6%
Caron <i>et al.</i> , 2012 [77]	Gabon ( Central Africa)	7.1% in pregnant women
Ramezani <i>et al.</i> , 2013 [79]	Iran	12%
Odaibo and Olaleye, 2013 [75]	Nigeria	12.5%
Feldt <i>et al.</i> , 2013 [76]	Ghana and Cameroon	Ghanaian (45.3%); Cameroonian (14.2%)
Jacobs <i>et al.</i> , 2014 [78]	Zambia	71%
Scotto <i>et al.</i> , 2014 [69]	Italy	2%
Mateos-Lindemann <i>et al.</i> , 2014 [71]	Spain	10.4%

In Africa, Odaibo and Olaleye[75] found a high rate (12.5%) of HEV infection in HIV positive cases attending an antiretroviral therapy clinic in Nigeria. There reported that HEV infection was not associated with low CD4 count and raised ALT. Another study among HIV positive subjects in Ghana and Cameroon, showed a high rate of anti-HEV prevalence in Ghanaian (45.3%) and Cameroonian (14.2%) adult HIV patients. However, HEV-RNA, indicating current infection, was not detected in any of the studied patients[76]. In another investigation in Gabon, IgG anti-HEV seroprevalence of 7.1% was reported in HIV-infected pregnant women[77]. Jacobs *et al.* showed that the overall HEV seroprevalence was 42% in adults in Zambia (28% in HIV negative and 71% in HIV positive adults). They suggested that HEV infection in adults is strongly associated with HIV status in Zambia[78].

In an investigation by Ramezani *et al.*[79], in Iran, the seroprevalence of HEV was moderately high (12%) in HIV infected patients, but similar to control group (10%). None of the HIV-positive subjects had recent or active infection. They found no association between HEV seropositivity and possible routes of HIV transmission, antiretroviral therapy use and HIV stage. Another survey in Malaysia showed that 14.4% of HIV infected patients had anti-HEV antibodies. IgG anti-HEV and IgM anti-HEV was detected in 10.3% and 4.1% of the subjects respectively[62]. Studies investigating HEV infection rate in HIV infected patients are summarized in Table 1.

Most of the conducted studies didn't find any association between HEV infection and low CD4 count, raised ALT, sex, age, mode of HIV transmission and infection with hepatitis B virus or hepatitis C virus[67,71,75,76,79].

## 7. Summary and conclusion

In summary, in recent years, several studies have been demonstrated HEV infection in immunocompromised patients such as recipients of organ transplant, patients with hematological malignancies and HIV infected subjects. Some investigations have suggested that HIV infected patients may acquire HEV infection more frequently than HIV negative individuals. Although, other studies have not shown significant differences between HEV prevalence in HIV infected and non-infected subjects.

HEV/HIV co-infection rates in developed countries such as US and Europe had been reported between 0% and 11.3%. Fewer studies have been conducted in this field in developing countries. In Africa this rate has been reported between 7.1% and 71% and in Asia it's between 12 and 14.4%. Most of the surveys didn't find significant association between HEV infection and low CD4 count, mode of HIV transmission and demographic characteristics.

Therefore, significance of HEV infection in HIV infected patients still remains uncertain and more studies are needed to solve the controversial data from different countries. It seems that in high endemic area such as Africa, the HEV infection in HIV positive cases should be taken seriously and it is better that HEV testing considers as a part of the management of HIV patients in these regions, but more data are needed to support this evaluation in other areas.

## Conflict of interest statement

We declare that we have no conflict of interest.

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