



**Consensus Document of the Diagnosis, management, and prevention of  
infection with the hepatitis E virus: Study Group for Viral Hepatitis  
(GEHEP) of the Spanish Society of Infectious Diseases and Clinical  
Microbiology (SEIMC)**

[www.seimc.org](http://www.seimc.org)

**FEBRUARY 2018**

## **Editorial Committee:**

### **Coordinator:**

Antonio Rivero Juárez

*Queen Sofía University Hospital of Cordoba. Maimonides Biomedical Research Institute of Cordoba (Instituto Maimonides de Investigación Biomédica de Córdoba – IMIBIC). Cordoba, Spain.*

### **Editors:**

Luis E. Morano Amado

*Álvaro Cunqueiro University Hospital. South Galicia Health Research Institute. Vigo, Spain.*

Antonio Aguilera

*University of Santiago Hospital Complex (Complejo Hospitalario Universitario Santiago – CHUS) & University of Santiago. Santiago de Compostela, Spain.*

Nicolás Merchante

*Virgin of Valme University Hospital. Institute of Biomedicine of Seville (Instituto de Biomedicina de Sevilla – IBIS). Seville, Spain.*

Miguel García Deltoro

*University General Hospital Consortium of Valencia. Valencia, Spain.*

José Antonio Oteo

*San Pedro University Hospital. Logroño, Spain. Centre for Biomedical Research of La Rioja (Centro de investigación Biomédica de La Rioja – CIBIR).*

### **Reviewers:**

Francisco Téllez

*Puerto Real University Hospital. Cádiz, Spain.*

Juan Macías

*Virgin of Valme University Hospital. Institute of Biomedicine of Seville (Instituto de Biomedicina de Sevilla – IBIS). Seville, Spain.*

Ana Avellón

*National Centre of Microbiology. Carlos III Health Institute. Madrid, Spain.*

- Federico García *San Cecilio University Hospital, Bio-health Research Institute (Instituto de Investigación Biosanitaria – IBS). Granada, Spain.*
- Juan Antonio Pineda *Virgin of Valme University Hospital. Institute of Biomedicine of Seville (Instituto de Biomedicina de Sevilla – IBIS). Seville, Spain.*
- Antonio Rivero *Queen Sofía University Hospital of Cordoba. Maimonides Biomedical Research Institute of Cordoba.*
- Rafael Granados *Dr Negrin University Hospital of Gran Canaria. Las Palmas de Gran Canaria, Spain.*
- María Teresa Pérez Gracia *Institute of Biomedical Sciences, School of Health Sciences, CEU (Centro de Estudios Universitarios – Centre for University Studies) Cardenal Herrera University. Valencia, Spain.*
- Christian Gortazar *Cynegetic Resources Research Institute (Instituto de Investigación en Recursos Cinegéticos – IREC), High Council for Scientific Research (Consejo Superior de Investigaciones Científicas – CSIC), University of Castile-La Mancha (Universidad de Castilla-La Mancha – UCLM). Ciudad Real, Spain.*
- David Rodríguez Lázaro *School of Sciences. University of Burgos (Universidad de Burgos). Burgos, Spain.*

## Table of contents

### 1. Introduction

1.1. Justification, objectives, and scope	6
1.2. Methodology	7
1.3. Abbreviations	8

### 2. Who should be screened for the hepatitis E virus?

2.1. Acute hepatitis	9
2.2. Chronic hepatitis	11
2.3. Contacts or cohabitants of a patient with HEV infection	12
2.4. Solid organ donors and blood donors	13
2.5. Patient with extrahepatic manifestations	15
2.6. Patient with suspected drug-induced hepatitis	17

### 3. How is hepatitis E virus infection diagnosed?

3.1. Dynamics of HEV serological and virological markers in acute and chronic hepatitis E	18
3.2. Diagnostic methods for HEV infection	20
3.2.1. Direct diagnostic methods	20
3.2.1.1. Detection of HEV-Ag	20
3.2.1.2. Detection of HEV-RNA	21
3.2.2. Indirect diagnostic methods	22
3.2.2.1. Detection of Anti-HEV-IgM antibodies	22
3.2.2.2. Detection of Anti-HEV-IgG antibodies	23
3.2.2.3. Detection of Anti-HEV-IgA antibodies	24

3.3. Diagnostic criteria for HEV infection	24
--	----

#### **4. Who to treat and how to treat hepatitis E virus infection?**

4.1. Acute hepatitis	29
4.2. Chronic hepatitis	30
4.2.1. Reduction of immunosuppression	30
4.2.2. Antiviral treatment	31
4.3. Extrahepatic manifestations	37

#### **5. How should we follow-up on a patient diagnosed with hepatitis E virus infection?**

5.1. Acute hepatitis	38
5.2. Chronic hepatitis	41
5.3. Infection with extrahepatic manifestations	42

#### **6. What measures should be recommended for preventing infection with the hepatitis E virus?**

6.1. General measures in the general population and in the immunosuppressed population	45
6.2. Other populations and contacts	47
6.3. Vaccines	48

<b>7. References</b>	<b>53</b>
----------------------	-----------

<b>8. Declaration of conflict of interests</b>	<b>69</b>
--	-----------

# 1. INTRODUCTION

## 1.1. Justification, objectives, and scope

Hepatitis E virus (HEV) infection is one of the main causes of acute hepatitis in both developed and developing countries. This infectious disease has a high prevalence and incidence in Europe [1]. HEV infection has a greater clinical impact in vulnerable populations, such as immunosuppressed patients, pregnant women, and patients with underlying liver disease. Thus, the *World Health Organisation* (WHO) ranks it as one of the leading causes of death due to acute hepatitis of viral origin worldwide [2]. However, national and international recommendations for the screening, diagnosis, and treatment of HEV have not been developed, which makes it difficult to manage patients. This, combined with the fact that HEV infection is not a notifiable disease in most countries, allows us to speculate that its incidence and clinical impact may be higher than expected. The *European Food Safety Authority* (EFSA) has indicated that HEV infection is a major public health problem in Europe because the infection is transmitted efficiently by the consumption of contaminated animal foods, and there are no protocols or specific plans for prevention in animal production or in food production chains [3]. Finally, there are no recommendations for the screening of this disease in blood, tissue, or organ donors, which may cause this route to be an important source of disease transmission [4].

Therefore, the Study Group for Viral Hepatitis (*Grupo de Estudio de Hepatitis Víricas – GEHEP*) of the Spanish Society of Infectious Diseases and Clinical Microbiology (*Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica – SEIMC*) considered it very important to prepare a

Consensus Document to help in decision making about the diagnosis, clinical-therapeutic management, and prevention of HEV infection.

## **1.2. Methodology**

The panel of experts for the preparation of this document is composed of HEV infection experts in the areas of clinical management, diagnostic microbiology, food technology, and veterinary medicine. The members of the Consensus Document panel have agreed to participate voluntarily and issue a declaration of conflicts of interest. These experts have been distributed into 5 work teams composed of an editor and 2 reviewers who oversaw the reviewing of the most relevant data and evidence from scientific publications (PubMed; languages: Spanish and English) and communications at more recent congresses (through November 12, 2017) on each of the aspects identified as key to the preparation of the document. The text prepared by each editor was assessed by the reviewers, whose comments and assertions were added to the final document that was prepared for the Panel's discussion. Once all the chapters were completed, the document was discussed by the Panel at an in-person meeting held on November 17, 2017. After the incorporation of the approved and agreed modifications in said meeting, the document was remitted to the members of the Panel for final approval. Later, the document was made available for public comment for 15 days on the webpages of the GEHEP and the SEIMC. The comments were assessed by the drafting committee and, if appropriate, sent for consideration by the Panel. Lastly, the final document was developed.

The recommendations in these guides are based on scientific evidence. The strength of the recommendation and grading of the evidence that supports it are based on a modification of the criteria of the *Infectious Diseases Society of America* [5]. According to these criteria, each recommendation must always be offered (A), in general (B), or optionally (C), and must be based on data obtained from one or more randomised clinical trials with clinical or laboratory results (I), one or more nonrandomised trials or observational cohort studies (II), or the opinion of experts (III).

### 1.3. Abbreviations

Ribonucleic acid (RNA); Alanine aminotransferase (ALT); Antigen (Ag); British Transplantation Society (BTS); European Food Safety Authority (EFSA); Acute liver failure (ALF); Global Advisory Committee on Vaccine Safety (GACVS); Study Group for Viral Hepatitis (*Grupo para el Estudio de las Hepatitis Viricas – GEHEP*); Immunoglobulin A (IgA); Immunoglobulin G (IgG); Immunoglobulin M (IgM); Cerebrospinal fluid (CSF); Milligrams per day (mg/d); Nucleic acid testing (NAT); Open reading frame (ORF); World Health Organisation (WHO); Sustained viral response (SVR); Reverse transcription nested polymerase chain reaction (RT-nPCR); Reverse transcription polymerase chain reaction (RT-PCR); Ribavirin (RBV); Guillain-Barré syndrome (GBS); Central nervous system (CNS); Peripheral nervous system (PNS); Spanish Society of Infectious Diseases and Clinical Microbiology (*Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica – SEIMC*); International units per litre (IU/L); Hepatitis A virus (HAV); Hepatitis B virus (HBV); Hepatitis C virus (HCV); Hepatitis E virus (HEV); Human immunodeficiency virus (HIV).



## **2. WHO SHOULD BE SCREENED FOR THE HEPATITIS E VIRUS?**

### **2.1. Acute hepatitis**

In recent years, the number of HEV infections in Europe has increased from 514 in 2005 to 5,617 in 2015 [1]. At the time of the drafting of this Consensus Document, only 2 countries in Europe systematically determine the presence of HEV in cases of acute hepatitis: Scotland, where laboratories determine whether the ALT exceeds 100 U/L, and Ireland, where it is performed whenever the determination of the hepatitis A virus (HAV) is requested [1]. In the rest of the European countries, HEV determination is only made after a specific request.

In 2 recent studies conducted in Spain and in the Netherlands, HEV was one of the main causes of acute hepatitis of viral origin, accounting for 57.1% and 33.5%, respectively [6, 7]. In most cases, contact with HEV produces an asymptomatic infection, mainly in women and young people, followed by spontaneous clearance of the virus [8].

HEV infection during pregnancy (particularly during the third trimester) is associated with a worse prognosis compared to other viral hepatitis infection scenarios [9-11]. Maternal mortality exceeds 30%, as demonstrated in different outbreaks [12]. Mortality due to HEV infection during pregnancy is usually restricted to infections caused by genotypes 1 and 2, but it has been reported cases produced by other genotypes [13, 14].

HEV infection is the cause of the 5% of the acute liver failure (ALF) reported in Europe [17], although the proportion of patients who develop ALF during HEV infection is small (0.5%–4%) [18-21]. The highest risk of developing ALF during the course of hepatitis caused by HEV occurs in pregnant women (usually during the third trimester of pregnancy) and patients with concomitant chronic liver disease [22-24]. In India, 52.6% of pregnant women with HEV infection develop ALF [23]. On the other hand, in a series of patients with chronic hepatitis B in China, the occurrence rate of ALF in patients with HEV superinfection was 39.7% [21]. In another series of patients with cirrhosis that originated in India, the presence of HEV-RNA was detected in 50% of the cases of liver decompensation [23]. Finally, another study conducted in India showed a 12-month mortality of up to 70% in patients with HEV genotype 1 infection and underlying chronic liver disease [24].

In developed countries, the impact in terms of HEV morbidity and mortality in patients with underlying chronic liver disease is unknown because specific screening for HEV is not routinely requested in these patients [25]. In a prospective study conducted in the United Kingdom and France, which included cirrhotic patients, the rate of decompensation was similar among patients with HEV infection and those uninfected individuals [26].

#### **RECOMMENDATIONS:**

- ***All patients with acute hepatitis should be screened for HEV infection (AII).***

- *All patients with ALF HEV infection hepatitis should be screened for HEV infection (All).*
- *HEV screening should be performed in patients with known or recently diagnosed chronic liver disease with decompensation and/or data suggestive of acute liver inflammation (All).*

## **2.2 Chronic hepatitis**

HEV is one of the possible causes of what has been called liver damage of uncertain origin; thus, HEV screening should be included in the study of these patients [27, 28]. HEV genotype 3 (and rarely genotype 4) can produce a chronic infection, which is defined as the persistence of HEV-RNA in the serum or faeces for a period of more than 3 months. Clinical manifestation of chronic HEV infection are unspecific [29]. Although it has been reported cases of chronic HEV infection in immunocompetent patients [30, 31], HEV infection chronification occurs mainly in immunocompromised patients, such as solid organ transplant recipients, HIV-infected patients with a CD4+ lymphocyte count lower than 200 cells/mL, oncology patients diagnosed of lymphoma and leukaemia treated with rituximab, and patients on therapy with anti tumoral necrosis factors drugs [32-37].

In transplant patients, HEV can become chronic in up to 2 out of 3 cases, with rapid progression of fibrosis and the development of liver cirrhosis in up to 10% of patients [34, 35]. Moreover, cases have been detected in patients with haematological diseases receiving chemotherapy [8, 25, 36]. In bone marrow transplant patients, in whom the incidence of HEV infection is low (2,4%), a chronicity rate of 62.5% has been described [37]. Therefore, as recommended in

neighbouring countries, transplant recipients with acute or chronic hepatitis, HEV should be tested [38]. It is advisable that all transplant patients should have a frozen sample of plasma or serum extracted before transplantation, which can be used for the retrospective determination of HEV in cases where it is considered necessary [38]. In Spain, exposure to HEV in patients with HIV infection is frequent and increases with age, a rural habitat, a CD4+ lymphocyte count below 500 cells/mL [39, 40]. Despite the development of chronic HEV infection has been clearly stated in HIV infected patients [25, 39, 41, 42], prospective studies have documented that it is a rare event [43].

#### **RECOMMENDATIONS:**

- *HEV screening should be included in the diagnostic of chronic hepatitis (All).*
- *In patients with unexplained liver disease HEV screening should be performed (All).*

#### **2.3. Contacts or cohabitants of a patient with HEV infection**

Person-to-person transmission (direct contact) of HEV is very inefficient, and the existing evidence is limited to cases detected during an outbreak in Uganda [46]. The inefficiency of transmission between people likely occurs because the infection and disease caused by this virus are dose-dependent and require a higher infective dose than, for example, that required for the transmission of HAV [47, 48]. However, it is recommended the screening for HEV infection in individuals where exposure to the source of infection is shared with a confirmed case of HEV infection.

## RECOMMENDATION:

- *The study of the close contacts of a case with documented HEV infection is not recommended, except in a case where they share a source of infection with the case (All).*

### 2.4. Solid organ donors and blood donors

HEV transmission through solid organ transplant is a known route of infection, and cases of HEV transmission have been reported after liver and kidney transplantation [47, 48]. The actual risk of HEV infection transmitted by transplantation is unknown. In 2016 in the United Kingdom, it was estimated that approximately 2 donor organs (deceased or alive) per year have HEV viremia at the time of donation [38]. The *British Transplantation Society* (BTS) recommends that even if the risk of transmission by a donated organ is very low, HEV screening should be performed on all donors. A positive result does not contraindicate the transplant in deceased donors but facilitates the post-transplant clinical management. In living donors in whom HEV is detected, the transplant must be deferred until the resolution of the HEV infection is confirmed, except in urgent cases [38].

HEV can be transmitted through blood transfusion. Recently, a case of HEV transmission by this route was described in Spain [49]. The transmission rate for transfusion with blood from an HEV-infected patient is estimated to be 42% and is correlated with the volume of blood transfused [50]. Transfused patients are not only subject to the risk of transmission by transfusion, but they

are also subject to the risk of acquiring HEV from food or the environment. An estimated 13 annual transfusion exposures are equivalent to the risk of infection from food [51]. The prevalence of detectable HEV-RNA in blood donations varies in different European countries from 1:2,363 in the Netherlands to 1:14,520 in Scotland [52, 53]. In Spain, three studies has been reported, two in Catalonia reporting a detectable prevalence of 1:3,333 and 1:4,720 donations [54, 55], respectively, and another study conducted in Northern and Central Spain reporting a prevalence of 1:17,500 donations [56]. Thus, HEV screening in blood donors should be recommended. Most units with HEV-RNA have negative HEV serology [50], so serological methods are not appropriate to screening HEV in this scenario.

The transfusion of blood products contaminated with HEV acquires special relevance in patients in who the disease shows a most serious course, such immunosuppressed patients (kidney or liver transplant patients), pregnant women and patients with chronic liver disease.

Therefore, HEV screening strategies for blood donations is most effective way to prevent HEV transmission through transfusion and blood derived. necessary. The *European Pharmacopoeia* has recommended the detection of HEV in human plasma reserves and has validated the methodology necessary for the detection [57-59].

## **RECOMMENDATIONS:**

- *HEV screening should be performed on all organ donors, living or deceased (All).*
- *Studies on the prevalence of HEV infection in blood donations should be conducted across the different areas of blood bank influence to adapt HEV screening strategies to the prevalence of HEV infection in each area (All).*

## **2.5. Patient with extrahepatic manifestations**

The appearance of extrahepatic clinical manifestations has been documented in the 2–5% of cases of HEV infection ([Table 1](#)) [60]. In most HEV-infected patients with extrahepatic symptoms, hepatic manifestation may be mild or absent. Thus, in a study conducted in Europe, in 13 patients with neurological manifestations associated with HEV infection, none showed liver abnormalities [61]. In another study in which 57 cases of amyotrophic neuralgia associated with HEV infection were included, only 2 cases showed alterations in the liver [62].

**Table 1.** Extrahepatic manifestations of HEV infection

---

---

Acute pancreatitis

Haematological manifestations:

- Thrombopenia, haemolysis, aplastic anaemia, cryoglobulinemia, monoclonal gammopathy

Autoimmune phenomena:

- Membranous glomerulonephritis, Henoch-Schönlein purpura, arthralgia, skin rash

CNS neurological syndromes:

- Transverse acute myelitis
- Acute meningoencephalitis
- Aseptic meningitis
- Amyotrophic neuralgia
- Pseudotumour cerebri
- Bilateral pyramidal syndrome

PNS neurological syndromes:

- Guillain-Barré syndrome
  - Cranial nerve paralysis
  - Peripheral neuropathy
- 

**RECOMMENDATION:**

- *In patients with any of the extrahepatic clinical manifestations that have been associated with HEV infection, screening for HEV*



*infection should performed, even in the absence of liver abnormalities (BII).*

## **2.6. Patients with suspected drug-induced hepatitis**

In a series of 318 patients with suspected liver toxicity due to drugs, HEV infection was identified as the cause of acute hepatitis in 9 (3%) patients [63]. In the same way, in a study conducted in the United Kingdom, 6 of 47 cases diagnosed as drug-induced hepatitis were due to HEV infection [65]. Finally, in a study conducted in Spain, it was confirmed active HEV infection in 7% of patients with suspected drug-induced hepatotoxicity [65].

### **RECOMMENDATION:**

- *In patients with suspected drug-induced hepatitis, HEV screening should be performed (BII).*

### **3. HOW IS HEPATITIS E VIRUS INFECTION DIAGNOSED?**

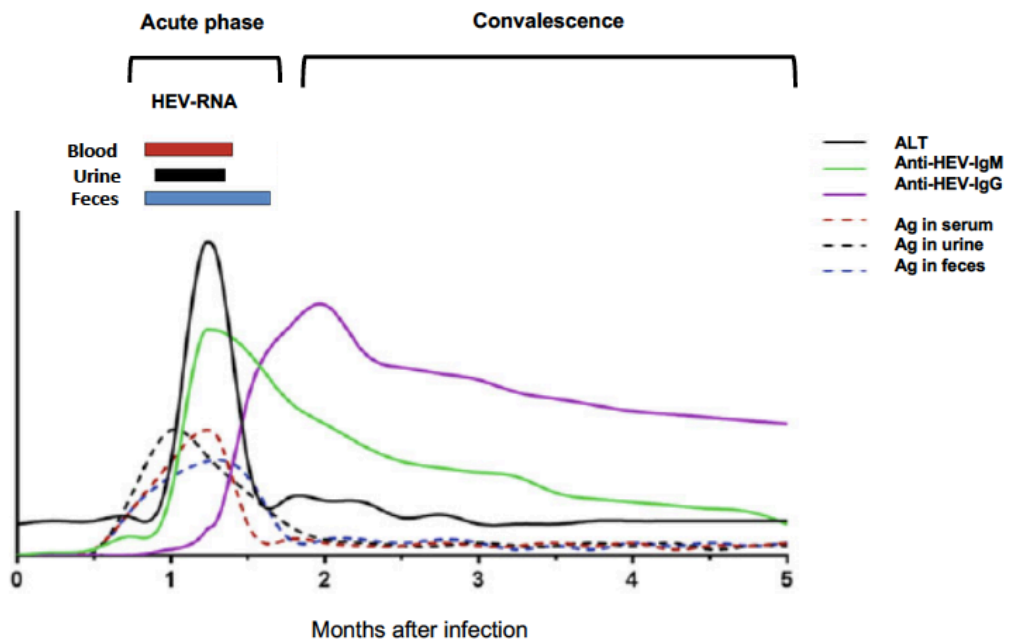
The virological markers for the diagnosis of HEV infection comprise components of the viral structure, such as nucleic acid (HEV-RNA) and the viral antigen (HEV-Ag), and products of the host immune response, such as Anti-HEV specific antibodies of classes IgA, IgG, and IgM. These virological markers are the basis not only for diagnosis but also for monitoring treatment, and they permit the characterisation of the natural history of hepatitis E in its different phases: acute, recent, resolved or past, and chronic.

#### **3.1. Dynamics of serological and virological markers of HEV in acute and chronic hepatitis E**

After an incubation period of between 2 and 6 weeks, the viral RNA and HEV-Ag are detectable in the blood, urine, and faeces just before the onset of symptoms [67, 68]. HEV-RNA is usually undetectable in the blood 3 weeks later, although it can be detected in the faeces for 2 more weeks; it is generally considered a viremia of short duration. Conversely, the immune response follows a typical pattern of seroconversion with an initial and transient increase in IgM that leads to a sustained IgG response (Figure 1). Anti-HEV-IgM antibodies are detected during the acute phase of the disease and may last approximately 4 or 5 months, indicating recent exposure, whereas IgG antibodies, which become detectable soon after those of the IgM class, can last more than 10 years and usually indicate past or remote exposure. Finally, IgA antibodies can also be detected during the acute phase of HEV infection.

Conversely, chronic HEV infection has been described in immunocompromised patients with different causes. In these patients, who have elevated transaminase levels and a depleted immune response, viral RNA is usually detectable in the serum, faeces, and urine for more than 3 months [69].

Figure 1. Dynamics of serological and virological markers



### **3.2. Diagnostic methods for HEV infection**

The diagnosis of HEV infection can be made directly by detecting the viral antigen or the genomic RNA in the blood or other bodily fluids [70], or indirectly by detecting the corresponding specific antibodies against the virus (Anti-HEV-IgA, Anti-HEV-IgG, and Anti-HEV-IgM) in the serum [70, 71].

#### **3.2.1. Direct diagnostic methods**

Currently, the most commonly used methods for the direct diagnosis of HEV infection include serological assays that detect HEV-Ag and molecular assays that detect and/or quantify HEV-RNA, both of which are commercially available [67]. There are also other methods that permit the direct diagnosis of the infection, such as electronic immunomicroscopy, cell culture, and immunohistochemistry, but their use is restricted because they are technically complex, not very sensitive, or require invasive procedures to perform them [67, 72].

##### **3.2.1.1. Detection of HEV-Ag**

Recently, an indirect double-antibody immunoassay for the pORF2 protein has been marketed for the detection of HEV-Ag [73]. HEV-Ag, despite its lower sensitivity, particularly with viral loads below 1,000 copies/mL [73], correlates very well with HEV-RNA [74, 75], and its simultaneous detection with Anti-HEV-IgM antibodies is particularly useful in the diagnosis of the infection in immunosuppressed patients who do not produce antibodies. In addition, some studies have demonstrated the usefulness of detecting HEV-Ag in urine, which

could be a good marker for the diagnosis of HEV infection since it is present as a virion or as a free antigen [68].

### **3.2.1.2. Detection of HEV-RNA**

The detection of viral RNA in different biological samples [67, 76] is the reference method (*gold standard*) for the diagnosis of HEV infection. However, due to the short duration of viremia, an undetectable result in the symptomatic phase does not necessarily exclude a recent infection. Likewise, the pre-analytical conditions of the sample can dramatically influence the result obtained. The methods for the detection of HEV-RNA mainly include conventional RT-nPCR and real-time RT-PCR assays. The first RT-nPCR assays were based on the ORF1 and ORF2 regions of the viral genome, and in addition to the variability in their results [71, 77], they demand strict requirements to avoid non-specific results due to contamination [63]. For its part, real-time RT-PCR is a highly specific, sensitive, and procedurally simple technique, which also uses various probes that are aimed at targets of the conserved regions of ORF3 [71, 78], thus permitting the detection of different genotypes without requiring oligonucleotides or degenerate probes.

In addition to the diagnosis and confirmation of acute HEV infection, the detection and quantification of HEV-RNA are particularly useful for diagnosing infection in immunosuppressed patients, with or without chronic infection, and for monitoring the efficacy of antiviral treatment in the former. Conversely, the use of antibody detection alone is insufficient for characterising patients with hepatitis E who present extrahepatic manifestations. In these cases, the detection of HEV-

RNA in different clinical samples is important for establishing the degree of causality of the clinical syndrome with HEV infection [61] and for the subsequent viral characterisation at the genotype and subtype level by sequencing and phylogenetic analysis of the product amplified by RT-nPCR of the ORF2 region.

### **3.2.2. Indirect diagnostic methods**

HEV infection can also be diagnosed using indirect methods by detecting specific antibodies (IgA, IgG, and IgM) in the patient's serum. Typically, the initial screening diagnosis is usually made indirectly because of the speed and availability of serological techniques. Enzyme immunoassays that have been commercialised for the detection of antibodies are based on synthetic peptides or recombinant antigens of the ORF2 and ORF3 regions from HEV genotype 1, which can detect the presence of IgG and IgM antibodies induced by the 4 main genotypes, since they constitute a single serotype [67, 71]. The different sensitivities of the various techniques and their successive versions have been shown in several comparisons [79].

#### **3.2.2.1. Detection of Anti-HEV-IgM antibodies**

The different immunoassays marketed for the detection of Anti-HEV-IgM antibodies generally vary in their sensitivity and specificity within acceptable ranges, regardless of the format used [67]. The introduction of antibody-capture assays for their detection has improved the specificity problems exhibited by the first indirect immunoassays. The future use of conformational and neutralisation epitopes will likely be decisive in the improvement of the newly available reagents [67]. Conversely, immunochromatographic assays for the detection of Anti-HEV-

IgM are also sold in rapid assay format, which have the advantage of being easy to use and providing results in a few minutes; they are ideal for laboratories with limited resources [80]. The presence of Anti-HEV-IgM antibodies is an indicator of acute infection, with an important implication in the clinical diagnosis, but when its reactivity is isolated, the possibility of a false positive should be considered, and in this case, confirmed with immunoblotting and/or performing a new determination to demonstrate the seroconversion to Anti-HEV-IgG.

### **3.2.2.2. Detection of Anti-HEV-IgG antibodies**

Immunoassays that detect Anti-HEV-IgG vary considerably in their performance [81] and show large differences in the data provided concerning the epidemiology [67, 71, 82] and the pathology of HEV infection, making it difficult to analyse and compare them. This variability, which must be considered when interpreting the observed data of the HEV seroprevalence in the literature, can be attributed to different factors that affect the characteristics of the assays, such as the heterogeneity of the viral genome, the diverse antigenic structure of the proteins, and their ability to induce antibodies [83]; the different types of antibodies present in the different phases of the infection; and the prevalence of the genotypes and the risk of infection in the geographical region considered, which determines their choice [67].

Conversely, avidity assays, which determine the low affinity of these antibodies, have been developed but are not yet marketed. These assays are usually used only as an auxiliary method for the diagnosis of recent infection because of their low specificity. Anti-HEV-IgG antibodies are used as indicators

of past infection in epidemiological studies. However, an increase of more than 4-fold over the baseline level of antibodies can also be used as a diagnostic criterion for recent HEV infection [67].

### **3.2.2.3. Detection of Anti-HEV-IgA antibodies**

Anti-HEV-IgA antibodies can also be used as a marker of acute or recent infection, particularly in oral fluid samples [84], although their persistence and diagnostic significance should still be confirmed with clinical and epidemiological studies [67].

### **3.3. Diagnostic criteria for HEV infection**

The principal markers of acute HEV infection are HEV-RNA, HEV-Ag, Anti-HEV-IgM, and -IgA; increasing titres or low affinity of Anti-HEV-IgG antibodies are also indicative of acute HEV infection. However, these markers appear at different times, persist for different periods, and differ in their meaning in the clinical diagnosis. Therefore, regardless of whether the high titres or low affinity of Anti-HEV-IgG-specific antibodies can be considered suggestive of acute HEV infection, their mere presence should not be considered a diagnostic criterion. Consequently, any diagnostic algorithm of HEV infection ([Table 3](#)) should be based mainly on the presence of Anti-HEV-IgM-specific antibodies and/or the presence of HEV-Ag and HEV-RNA infectivity markers.

The possible patterns that define acute infection are:

In immunocompetent individuals:



- Anti-HEV-IgM+, Anti-HEV-IgG+, HEV-RNA+/HEV-Ag+
- Anti-HEV-IgM+, HEV-RNA+/HEV-Ag+
- Anti-HEV-IgM+, Anti-HEV-IgG+
- Anti-HEV-IgM+ isolated with seroconversion to Anti-HEV-IgG in follow-up sample
- Anti-HEV-IgG+, HEV-RNA+/HEV-Ag+
- HEV-RNA+/HEV-Ag+ isolated with the appearance of Anti-HEV-IgM or seroconversion to Anti-HEV-IgG in follow-up samples

In immunocompromised individuals, in addition to the above:

- HEV-RNA+/HEV-Ag+ isolated

The diagnosis of chronic HEV infection is usually based almost exclusively on the presence of HEV-RNA in the blood or other body fluids for more than 3 months, whereas that of resolved infection is characterised by the isolated presence of Anti-HEV-IgG antibodies.

Table 3. Diagnostic algorithm for HEV infection

<b>Anti-HEV-IgM*<sup>1</sup></b>	<b>Positive</b>			<b>Negative</b>			
<b>HEV-RNA and/or HEV-Ag**</b>	<b>Positive</b>	<b>Negative</b>		<b>Positive</b>		<b>Negative</b>	
<b>Anti-HEV-IgG*</b>		<b>Positive</b>	<b>Negative</b>	<b>Positive</b>	<b>Negative</b>	<b>Positive</b>	<b>Negative</b>
<b>Interpretation</b>	Acute infection  Chronic infection (RNA+ >3 months)	Recent infection	Cross-reactivity <sup>1</sup>	Acute infection  Possible reinfection	Window period  Chronic infection (RNA+ >3 months)	Past infection	Absence of infection
<p>* Serum and/or plasma                  ** Serum, plasma, CSF, faeces, urine, etc.  <sup>1</sup> Anti-HEV-IgM reactivity should be confirmed with immunoblotting and a subsequent seroconversion study</p>							

In recent years, significant progress has been made in the development of serological and molecular assays for diagnosing infection produced by HEV. However, these assays, particularly those that detect antibodies, are still improvable. Although significant advances have been made to improve their sensitivity and specificity, there are still numerous deficiencies and challenges in terms of concordance, validation, and standardisation of their results in anti-HEV-IgG antibody assays, and in the positive predictive value of results from some assays for Anti-HEV-IgM antibodies [85]. For this reason, the development of more reliable and standardised diagnostic tests should be amongst the main priorities in hepatitis E research. Meanwhile, the use of the HEV serological reagents (code 95/584) and molecular standards (code 6329/10) of the WHO, which are intended for the quantification and standardisation of the respective assays, can help minimise the current deficiencies [86, 87]. Finally, in the diagnosis of HEV infection, the different virological markers are usually complementary and should not be substituted for one another because of the different situation of immune and infective dynamics present in each patient. Therefore, the final diagnostic criteria should always be established based on the results of a combination of markers, together with the clinical manifestations present.

#### **RECOMMENDATIONS:**

- *The diagnosis of acute HEV infection in immunocompetent individuals is based on the presence of Anti-HEV-IgM and/or HEV-RNA (AII).*

- *In laboratories that do not have adequate technology for molecular diagnosis, despite its lower sensitivity, it's recommended the detection of HEV-Ag as alternative, as a direct method for the diagnosis of HEV infection (AIII).*
- *Although it lacks diagnostic utility, the characterisation of HEV at the genotype and subtype levels through direct or new generation sequencing and subsequent phylogenetic analysis may be important for studies of the molecular epidemiology of HEV infection (All).*
- *Quality control systems based on WHO standards should be established, and reagents available for this purpose for the standardisation of the different results obtained in molecular and serological techniques should be determined (BII).*

## **4. WHO TO TREAT AND HOW TO TREAT HEPATITIS E VIRUS INFECTION?**

The treatment of HEV infection varies depending on the immunological situation of the patient and the clinical presentation of the infection (acute vs chronic). If indicated, the treatment objective is to eradicate HEV, which is determined by the achievement of a sustained viral response (SVR), defined as the absence of HEV-RNA at 12 weeks after the end of treatment. For this, the absence of HEV-RNA in both the serum and the faeces should be confirmed.

### **4.1. Acute hepatitis**

In most cases, acute hepatitis due to HEV only requires symptomatic treatment since it is usually mild and self-limiting in immunocompetent patients. In rare cases of fulminant hepatic failure secondary to acute HEV infection, liver transplantation may be necessary.

There is little information on the role of antiviral treatment in patients with acute hepatitis E. Given the high mortality associated with acute hepatitis E in patients with underlying advanced liver disease, treatment with ribavirin (RBV) has been attempted in some centres, but the accumulated experience is limited to a very small number of cases [26]. Similarly, some retrospective case series of acute hepatitis E in patients with immunosuppression have suggested a possible beneficial role for RBV [88-92]. Thus, in a European study [88], 21 patients with acute hepatitis E of genotype 3 or 4 were treated with RBV (dose 600–1200 mg/d) for a median of 26 days. In 6 of the patients, the

immunosuppressive treatment was also suspended. All patients cleared the virus at 6 weeks (median time 29 days). In a series of 12 cases of acute hepatitis E in patients with haematological malignancy treated with RBV (dose 600–1000 mg/d, median time 3 months), all patients showed viral clearance [86]. However, the absence of a control group in these studies prevents the determination of whether the viral clearance is due to the use of RBV or whether it occurred spontaneously.

#### **Recommendation:**

- *Antiviral treatment for acute hepatitis E should be considered in patients with liver cirrhosis or immunosuppression from any cause (BII). If treatment is indicated, this will consist of RBV adjusted for weight (1000 mg if < 75 kg or 1200 mg if > 75 kg) for 3 months (AII).*

## **4.2. Chronic hepatitis**

### **4.2.1. Reduction of immunosuppression**

Chronic hepatitis E occurs almost exclusively in the context of transplantation or in immunosuppressed patients due to another cause. The first step in the treatment of chronic hepatitis E is the reduction or withdrawal of immunosuppressive treatment in situations where possible. Thus, in a retrospective series of 85 patients with chronic hepatitis E and previous solid organ transplantation, this measure achieved viral eradication in approximately one-third of the patients [34, 88]. However, in most patients, it is not possible to reduce the immunosuppressive treatment, such as in those with a high risk of rejection of the transplanted organ. Regardless of whether it is possible to reduce

the immunosuppressive treatment, beginning with antiviral treatment should be considered. Similarly, in patients who are immunosuppressed for non-pharmacological reasons, such as HIV-infected individuals, antiviral treatment should be considered simultaneously.

#### **4.2.2. Antiviral treatment**

Although no randomised clinical trial has evaluated the use of RBV in the treatment of chronic hepatitis E, several case series have provided data suggesting its usefulness in this scenario [93-97]. Thus, in a large retrospective series of 59 patients who received solid organ transplants and who had chronic hepatitis E treated with RBV (median dose 600 mg/d, average duration 3 months), 78% achieved SVR [93]. Overall, there were no significant differences in cure rates between those treated for more than 3 months compared to those treated for less than 3 months. However, the SVR rate was 50% in the 18 patients who were HEV-RNA-positive at week 4 and who were treated for 12 weeks, whereas it was 83% in the 6 patients who were HEV-RNA-positive at week 4 and who were treated for a duration longer than 12 weeks.

Based on these results, the recommended treatment regimen for a first episode of chronic hepatitis E is RBV adjusted for weight (1000 mg if < 75 kg or 1200 mg if > 75 kg) for 12 weeks. Similar to the use of RBV in other indications, the patient should be monitored for the appearance of adverse effects, particularly haematological effects, during the treatment. If haemoglobin falls below 10 g/dL, the dose of RBV should be reduced by 200 mg each week until the haemoglobin level is again above this threshold. In case of a decline in

haemoglobin below 8.5 g/dL, the RBV should be suspended and restarted 1 week later at a dose of 600 mg/d.

Although 1 study has suggested that a decrease in viral load greater than 0.5 log/mL in the first week of treatment with RBV could predict the achievement of SVR [98], there is not enough evidence yet to establish treatment recommendations based on the early viral response. However, as mentioned, an undetectable viral load at week 4 can anticipate the need for a longer duration of treatment, so it is recommended to make a first determination of the serum HEV-RNA at week 4 and, if this value is positive, to prolong the treatment to 24 weeks. In patients who are HEV-RNA-negative at 4 weeks of treatment, the presence of HEV-RNA in the serum and faeces should be re-evaluated at 12 weeks, and the therapy can be suspended if both determinations are negative, given that in the presence of a response, prolonging the treatment beyond 12 weeks does not seem to increase the chances of a response [93]. If any of the samples are positive, treatment should be considered for another 12 weeks since in the presence of persistent HEV-RNA in the first weeks of treatment, prolonging the treatment for a period longer than 12 weeks could increase the chances of a response [93]. If the treatment is continued for a further 12 weeks, the determination of HEV-RNA in the serum and faeces should be repeated after that period. If the HEV-RNA persists, even if it is exclusively in the faeces, the absence of a response to treatment should be assumed, since the persistence of HEV-RNA in the faeces, even when absent in the serum, is associated with HEV recurrence following the interruption of the RBV [99]. Once the 12 or 24 weeks of treatment with RBV is completed, the absence of HEV-RNA in the serum and



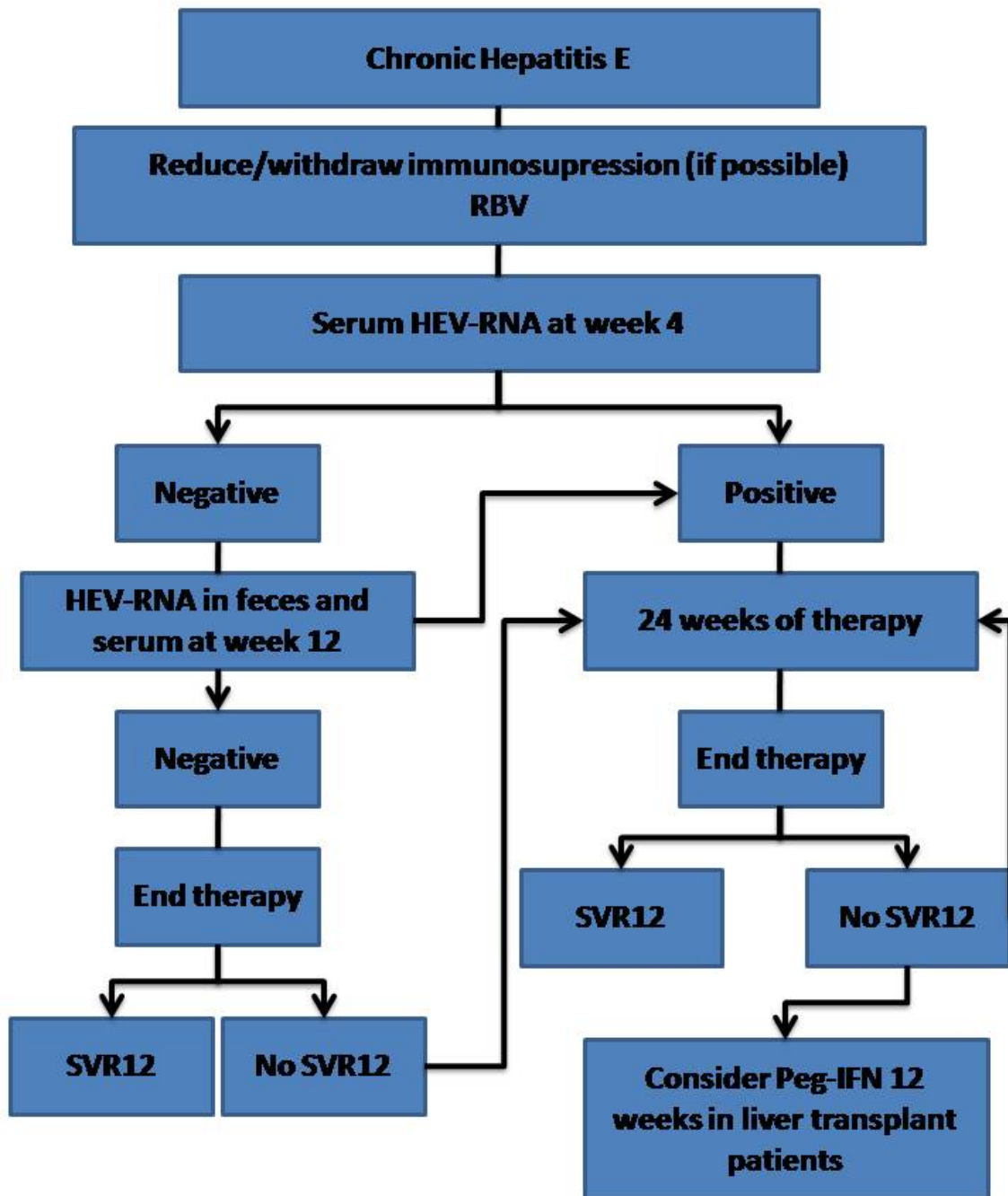
faeces should be confirmed at 12 weeks following the end of the treatment to determine whether SVR has been achieved. If HEV-RNA recurs after the completion of the treatment, retreatment with RBV should be considered for 24 weeks if the initial episode was treated for 12 weeks. Thus, in the aforementioned study [93], 4 of the 6 patients who experienced a recurrence and were retreated with a longer cycle of RBV achieved SVR.

Clinical and virological follow-up should be continued in those patients who do not achieve SVR. Currently, there is no treatment alternative to RBV for the management of chronic hepatitis E. The achievement of SVR has been reported after the use of pegylated interferon in 3 patients who were liver transplant recipients [100], so this option could be assessed in case of the failure of RBV in the scenario of the liver transplant patient, although its use poses a potential risk of acute rejection. Outside of liver transplantation, there are no data to recommend its use. A recent study has shown that Sofosbuvir can inhibit HEV replication *in vitro* and could provide an additive antiviral effect to RBV in monotherapy [101]. However, a case of a liver transplant patient chronically infected with HCV and HEV, who was treated with Sofosbuvir and Daclatasvir, has recently been published. After treatment, the patient achieved SVR against HCV but remained chronically infected with HEV [102]. Likewise, the case of a patient receiving immunosuppressive treatment for chronic lymphatic leukaemia and who was chronically infected by HEV genotype 3 with a detectable HEV viral load despite treatment with RBV was reported. The addition of Sofosbuvir initially resulted in a negative HEV viral load in the patient, but with the subsequent recurrence of low-level viraemia [103]. Similarly, the combination of Sofosbuvir +

RBV for 12 weeks failed to eradicate HEV in a patient coinfecting with HIV/HBV and with liver cirrhosis and neurological symptoms secondary to a chronic HEV infection, after the prior failure of treatment with pegylated interferon and RBV [104].

[Figure 2](#) summarises the recommended management algorithm for the treatment of chronic hepatitis E.

Figure 2. Recommended management algorithm for the treatment of chronic hepatitis E.



## RECOMMENDATIONS:

- *In patients with pharmacological immunosuppression and chronic hepatitis due to HEV, immunosuppressive therapy should be reduced or discontinued if the clinical situation permits. The persistence of HEV-RNA in the blood and faeces should be re-evaluated at 12 weeks (AII).*
- *In the case of persistent HEV-RNA after the reduction of immunosuppression or in those cases in which this measure is not feasible, antiviral treatment should be initiated (AII).*
- *In immunosuppressed patients of non-pharmacological causes, such as HIV-infected individuals, antiviral treatment should be considered from the beginning (AII).*
- *The antiviral treatment will consist of the administration of RBV 600 mg per day for 12 weeks (AII).*
- *At 4 weeks, the presence of HEV-RNA in the serum should be evaluated, and treatment should be prolonged to 24 weeks if the viral load is positive (BII).*
- *If the viral load at week 4 is negative, the presence of HEV-RNA in the faeces and serum should be evaluated after 12 weeks of treatment, and treatment can be suspended if HEV clearance has occurred (BII).*
- *In the case of viral persistence, treatment should be continued until completing 24 weeks (BII).*
- *In all cases, the presence of HEV-RNA in the faeces and serum should be evaluated 12 weeks after completing treatment (AII).*

- *In the absence of SVR after a previous 12-week treatment, retreatment with RBV should be considered for 24 weeks (BIII).*
- *In those patients with an absence of SVR after treatment with RBV for 24 weeks, there are no current alternative treatment options that can be recommended, except for pegylated interferon in the specific scenario of liver transplantation (CIII).*

#### **4.3. Extrahepatic manifestations**

The information available on the role of treatment in the natural history of extrahepatic manifestations associated with HEV infection is limited to the publication of isolated cases treated with RBV. In neurological manifestations, although the effectiveness of RBV in the published cases has varied, some experts have recommended assessing its use [105]. Similarly, the curing of a patient with cryoglobulinemia associated with HEV after the use of RBV has been reported [91].

#### **RECOMMENDATIONS:**

- *Given the suspicion of extrahepatic manifestations related to HEV infection, antiviral treatment with RBV can be considered following the same guidelines as for chronic hepatitis E (CIII).*

## **5. HOW SHOULD WE FOLLOW-UP ON A PATIENT DIAGNOSED WITH HEPATITIS E VIRUS INFECTION?**

HEV infection, which depends in large part on the characteristics of the host and the virus itself, can evolve in an acute or chronic manner as well as present a wide range of clinical manifestations, ranging from asymptomatic or subclinical to fulminant hepatitis, with or without extrahepatic manifestations. Thus, an individualised clinical follow up is required for each patient ([Figure 3](#)).

### **5.1. Acute infection**

Spontaneous healing without complication is the usual outcome among immunocompetent patients [105]. As such, only a clinical-analytical outpatient follow-up assessment should be performed, with liver function tests on the 2<sup>nd</sup>, 4<sup>th</sup>, and 8<sup>th</sup> weeks as well as a new microbiological test 3 months after diagnosis to confirm HEV-RNA negativisation in the plasma or serum of these patients. Although the chronification of acute HEV infection in immunocompetent patients is rare, the possibility must be considered [31, 106].

Regarding special populations with acute HEV infection (e.g., pregnant women, people with malnutrition, and patients with underlying liver disease), a closer clinical-analytical follow-up assessment should be performed, given the more serious course of this condition [107-109]. This follow up should consist of weekly liver function tests during the first month. If evidence exists of liver failure,

then one should proceed to hospital admission in an intensive care unit and initiate treatment with RBV (see Chapter 4 of this Consensus Document).

Acute infection with HEV genotypes 1 and 2 during the 2<sup>nd</sup> and 3<sup>rd</sup> trimester of pregnancy is associated with an increase in the number of abortions, premature births, increased perinatal mortality, and acute fulminant hepatic failure [10-14]. These effects translate into a high maternal mortality rate, ranging from 21.8% as described by Kumar et al. in a retrospective study in India [110] to 42% as described by Tsega et al. in Ethiopia [111]. The mechanisms of this greater aggressiveness have not been fully elucidated. It might be related to the hormonal and immunological changes that are characteristic of pregnancy, in which cellular immunity decreases such that pregnant women become more vulnerable to the effects of infection [110]. However, this theory contrasts with the results of Kumar et al., who found much higher mortality rates associated with HEV than other hepatotropic viruses (21.8%, 0%, and 6% for HAV, HBV, and HCV, respectively); thus, the type of virus seems to play a decisive role [110]. Because RBV is contraindicated in pregnant women, only supportive treatments with close maternal-foetal monitoring, weekly liver function tests, and foetal monitoring on demand (depending on disease evolution) are possible. If evidence exists of liver failure, then the patient must be admitted to the intensive care unit for advanced life support and, if necessary, a liver transplant request.

The vertical transmission of HEV is high with a foetal-perinatal mortality rate ranging between 15% and 50% [11,112]. No evidence exists that permits the

recommendation of a strategy of care for pregnant women with HEV; thus, decisions must be made individually.

HEV has been isolated in breast milk during the acute phase of the infection [113]. In one case-control study (healthy pregnant women versus infants with HEV infection during the 3<sup>rd</sup> trimester of pregnancy), no case of HEV transmission was observed after a mean follow-up time of 8 months among the 86 children born to asymptomatic infected mothers who were breastfed. However, four cases of transmission were observed among the children of the six symptomatic mothers, even though all were formula-fed [114].

#### **RECOMMENDATIONS:**

- *Follow up is recommended for immunocompetent patients with acute HEV infection over 12 weeks to determine HEV-RNA status at the end of this period (AII).*
- *It is recommended that patients with acute HEV infection with clinical evidence of liver failure be admitted to an intensive care unit to start HEV treatment (AIII).*
- *Weekly liver function tests and close foetal monitoring are recommended for pregnant women with acute HEV infection under gynaecological advice (AII).*
- *Formula-feeding is recommended for women with acute or chronic HEV infection (CIII).*



## 5.2. Chronic infection

Acute infection with HEV, especially amongst immunosuppressed patients, can progress to chronicity [115]. Cases of rapid progression to cirrhosis and liver failure have been described [41]. Once chronic infection has been confirmed in a patient with HEV infection, it should be treated as indicated in the specific chapter of this document. Whether the patient has reached SVR must be evaluated at the end of treatment. In the case of a non-immunosuppressed patient who has reached SVR, no new virological studies (HEV-RNA) are required. In the case of an immunosuppressed patient, it is advisable to perform HEV-RNA detection (faeces and blood) every 6 months during the first year, given the risk of late recurrence [98]. In cases in which, after achieving SVR, immunosuppression persists and the risk of exposure to HEV is maintained (professional ...), the annual determination of HEV-RNA in the blood is recommended because no evidence suggests that HEV infection provides immune protection against new infections.

On the other hand, the Panel considers that, by analogy with chronic infections with other hepatotropic viruses, all patients with chronic HEV hepatitis and stage F3 or F4 liver fibrosis should indefinitely maintain clinical, analytical, and ultrasound follow-up assessments every 6 months to screen for hepatocarcinoma, even amongst those who have achieved SVR. In addition, the annual determination of the transient elastography of the liver is recommended. Importantly, validated cut-off points for stratifying the degree of fibrosis in patients with chronic HEV infection using transient elastography of the liver do not exist. Therefore, the use of the proposed cut-off points for HCV and HBV is

recommended. The indication for a histological study via liver biopsy should be performed individually.

#### **RECOMMENDATIONS:**

- *It is recommended that patients with chronic HEV infection and SVR with persistent immunosuppression receive biannual HEV-RNA treatment during the first year (AII).*
- *The annual determination of HEV-RNA in the blood is recommended for immunocompromised patients in whom, after reaching SVR, the risk of exposure to HEV is maintained (professional ...), given the risk of reinfection (BII)*
- *Biannual ultrasound tests are recommended indefinitely for hepatocarcinoma screening amongst patients with chronic HEV infection and stage F3 or F4 liver fibrosis, even after reaching SVR (CIII).*

#### **5.3. Infection with extrahepatic manifestations**

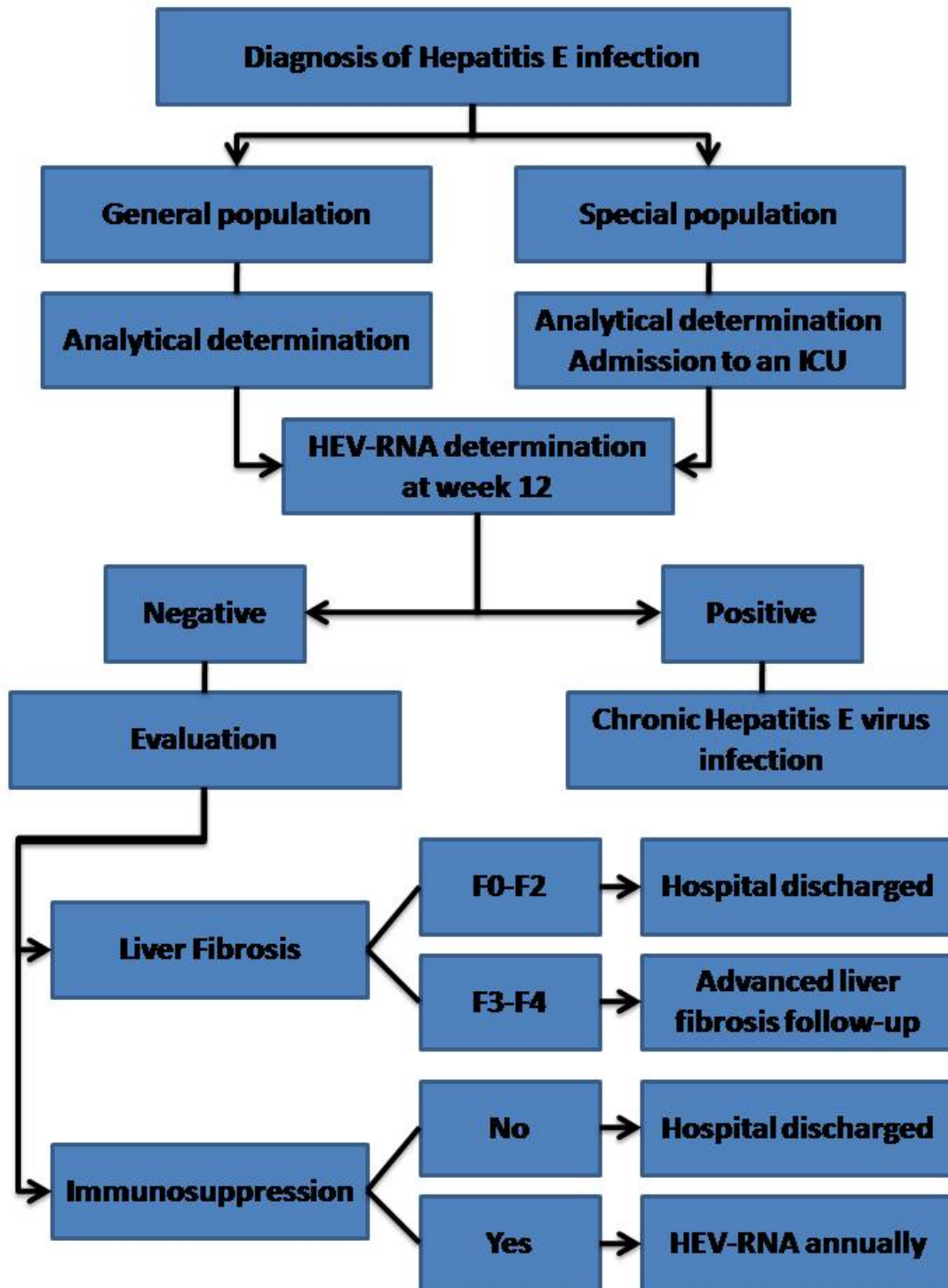
The extrahepatic manifestations most frequently described during the course of the HEV infection are neurological manifestations. Of these neurological manifestations, GBS and amyotrophic neuralgia stand out because of their frequency, with cases of meningitis, encephalitis, myelitis, and multiple mononeuritis that can occur in isolation or jointly also having been described [17]. The close relationship between GBS and amyotrophic neuralgia with HEV, observed in prospective studies, requires the screening of HEV for all patients with these entities (see Chapter 2 of this document) [61, 62, 116]. The

determination of HEV-RNA in the CSF (in addition to the plasma and/or faeces) of all cases with neurological manifestations should be considered. No prospective studies have demonstrated the benefit of HEV treatment in these patients. In the absence of evidence, we believe that the same treatment and follow-up guidelines recommended for patients without extrahepatic manifestations should be followed (see Chapter 4 of this document). Furthermore, no solid evidence regarding the efficacy of steroids and/or immunoglobulins exists, and the results of isolated cases are insufficient and contradictory; therefore, their use remains controversial [104].

#### **RECOMMENDATION:**

- *Treatment and follow up of HEV infection is recommended for cases of extrahepatic manifestations following the same recommendations cited for acute or chronic infection, depending on the case (CIII).*

Figure 3. Proposed algorithm for the management of HEV infection



## **6. WHAT MEASURES SHOULD BE RECOMMENDED FOR PREVENTING INFECTION WITH THE HEPATITIS E VIRUS?**

### **6.1. General measures in the general population and the immunosuppressed population**

The risk of acquiring HEV infection varies depending on the geographical location and the genotypes circulating in each region. Similar to all other communicable diseases, the simplest measures for preventing them are based on avoiding contact with sources of infection. In Europe, the main HEV exposure routes come from the intake of pork products, insufficiently cooked game animals (particularly the livers), and blood transfusions and their derivatives [4, 26, 122]. In travellers to developing countries in Asia, Africa, and Latin America and in the inhabitants of these countries, infections are also produced by this zoonotic route, although the main source is contaminated water and the products contaminated by it, causing large epidemic outbreaks [122]. Considering these facts, it is essential to conduct information and awareness campaigns in the general population and amongst health workers, emphasising the acquisition pathways. Advice should be offered to the general population and, particularly in our setting, to immunosuppressed people (including patients with HIV infection with low levels of CD4+ lymphocytes, solid organ transplants, haematopoietic precursor receptors, or patients with rheumatoid arthritis under immunosuppressive treatment, amongst others) and people who have chronic liver disease, because of the high risk of the infection becoming chronic or of having an accelerated or

serious course of infection [38, 122, 123]. These people should be aware of the need to follow a strict diet, in which liver and other pork products or under-cooked game animals or sausages and raw molluscs, such as mussels and other bivalves, are absent. Furthermore, on a global scale, it would be advisable to establish the scope of the presence/inclusion of products infected by HEV in the food chain to control this zoonosis.

There is little information on the stability and persistence of HEV in light of the physical and chemical changes in food and contaminated water. There are strong indications that HEV could remain infectious at the temperatures used in some cooking regimens, with conflicting results in the literature. Considering the current existing data and until the generation of conclusive studies, it seems appropriate to recommend the cooking-heating of food at a temperature  $\geq 70^{\circ}\text{C}$  for a minimum of 30 minutes [124].

#### **RECOMMENDATIONS:**

- *The prevention of HEV infection should be based on offering information aimed at avoiding contact with sources of infection (All).*
- *On trips to developing countries, to avoid contact with HEV, general hygienic practices should be adopted, such as washing the hands with clean or sanitised water before handling food. Do not drink water or consume ice of unknown purity. The consumption of fruit not peeled by oneself and of raw foods in general should be avoided (All).*
- *In addition to adopting the basic hygienic measures recommended for the general population, people at high risk of developing a severe*

*course of infection or the chronification of it (cirrhotic and transplanted) must be specifically informed of the risk involved in eating pork products and undercooked game animals, including sausages, and to avoid the consumption of these products (AII).*

- *People at high risk of developing a severe course of infection or the chronification of it should subject food to cooking-heating at a temperature  $\geq 70^{\circ}\text{C}$  for a minimum of 30 minutes (AI).*

## **6.2. Other populations and contacts**

The high risk that pregnant women have of developing fulminant hepatitis when they contract HEV infection caused by genotypes 1 and 2 has already been highlighted in other sections of this document. For this reason, special emphasis should be placed on strict adherence to hygienic measures when travelling to developing countries [125, 126].

Person-to-person HEV transmission requires a higher infective dose than, for example, that required for HAV transmission. In any case, the use of standard precautions to avoid transmission in the family environment and in contacts with patients in the healthcare environment seems reasonable.

Although sexual transmission is not a typical form of hepatitis E acquisition, HEV is eliminated by faeces, so barrier measures should be used in sexual relations, at least during the acute period of infection and/or in patients with chronic infection [127].

Although breastfeeding does not appear to be a relevant transmission route, a case of the isolation of HEV in breast milk has been reported, which suggests that it could be a potential transmission route. Therefore, it would be advisable to avoid breastfeeding (at least in industrialised countries) during the course of the disease or until the presence of HEV in breast milk is excluded [114].

#### **RECOMMENDATIONS:**

- *Given the serious and even fatal course that pregnant women may suffer, women travelling to areas of high endemicity of HEV genotypes 1 and 2 should receive information and should adhere to hygienic standards to avoid contact with HEV (AII).*
- *Patients suffering from acute or chronic HEV infection should use barrier measures in their sexual relations (AIII).*
- *Formula-feeding should be recommended in women with acute or chronic HEV infection (CIII).*

#### **6.3. Vaccines**

At least 11 experimental vaccines have been evaluated in non-human primates, although to date, clinical trials in humans have been developed for only 2 of these vaccines. In both cases, these are recombinant vaccines against genotype 1 [128-130], and one of them (Hecolin<sup>®</sup>), developed by Xiamen Innovax Biotech Co., Ltd., China, has been available on the market (China) for people over 16 years of age. The manufacturer recommends it for individuals at high risk of infection, including people who work with animals, food handlers, members of



the armed forces, women of childbearing age, and travellers to endemic areas. The phase 3 clinical trial that permitted its licensing assessed 112,604 people between 16 and 65 years of age in the Chinese province of Jiangsu [129]. The participants were randomised 1:1 to receive 3 doses of 30 µg of purified hepatitis E recombinant antigen of 239 amino acids, corresponding to amino acids 368–606 of ORF2, which encodes the HEV capsid protein from a Chinese HEV genotype 1 strain expressed in *Escherichia coli* and is absorbed in 0.8 mg of aluminium hydroxide in 0.5 ml of saline buffer, or to receive a placebo (hepatitis B vaccine), IM (intramuscularly), at 3 timepoints (0, 1, and 6 months). The primary objective was the prevention of hepatitis E from day 31 of the end of the third dose, up to 12 months afterward. In the per protocol analysis, the efficacy of the group in which the recombinant vaccine was used against HEV was 100%. In the placebo group, 15 patients developed hepatitis. Referring to the safety data of the clinical trial, the percentage of local adverse effects at 72 hours after the administration of each dose was 2.8% in the vaccine group and 1.9% in the placebo group. Both groups presented the same percentage of adverse systemic effects during the first 72 hours after the administration of the vaccine and placebo (1.9%). There were also no differences in serious adverse effects in the 30 days or in the follow-up of 19 months. None of the events that led to hospitalisation or death were related to the administration of the vaccine [129]. Although pregnancy was a criterion for exclusion from the clinical trial, 37 pregnant women received a total of 53 doses of vaccine, which was well tolerated, except for 1 patient who reported pain at the vaccine injection site. There was no spontaneous abortion in these women. In the women who continued with their pregnancy (did not choose to have an abortion), there were

no problems with the delivery or in the newborns, who had weights similar to those of the placebo group [131].

In the follow-up performed at 54 months [132], 60 cases of hepatitis E were registered. Seven cases were reported in the vaccinated group (0.3 cases per 10,000 persons/year) and 53 cases in the placebo group (2.1 cases per 10,000 persons/year), which signifies an efficacy of 86.8% for the vaccine after 4.5 years. Regarding the development of antibodies against HEV, 87% of a randomised sample that was seronegative at the beginning of the trial was positive at the end of the follow-up. Only 9% of the individuals in the placebo group developed antibodies. Most of the vaccinated subjects had detectable antibodies against HEV at the end of the 4.5-year follow-up, although the antibodies decreased rapidly in the first 2 years. Notably, most of the cases that developed hepatitis E in the vaccinated group were infected by genotype 4, and the vaccine had been made with genotype 1. It was expected that since all the genotypes belong to the same serotype there would have been cross-protected, the efficacy of this vaccine should be explored against other genotypes [132]. Studies of cost-effectiveness that have been developed in China have shown that vaccination can be efficient, not only in the age group in which the clinical trial has been conducted but also in elderly populations [133]. The WHO has stated its position through the *Global Advisory Committee on Vaccine Safety* (GACVS), which reviewed the safety of Hecolin® in 2014, and concluded that the safety data derived from the different trials (phase I, II, and III) conducted with this vaccine in healthy subjects were reassuring. However, there are not enough data in children under 16 or in people over 65. There are no data in people with underlying

diseases or with immunosuppressive conditions, nor are there data in patients undergoing transplantation or with chronic liver diseases. The effect when administered with other vaccines and the degree of protection against HEV genotypes other than genotype 1 is unknown [134]. The GACVS does not make a recommendation for the introduction of the vaccine for routine use in populations where epidemic outbreaks or sporadic cases occur. This Committee leaves the decision to the local authorities. The GACVS recommends conducting a post-commercialisation trial to provide more data and discouraging routine use in children under 16 years old, people over 65 years old, patients with chronic liver disease, patients on solid organ transplant lists, pregnant women, or travellers. People who plan to travel to an area where an epidemic is occurring (e.g., aid workers and health workers) should be evaluated individually, and vaccination could be an option [134]. A vaccine developed by Glaxo-Smith-Kline and the United States Army has not been commercialised, although the clinical trial that was conducted demonstrated it to be effective and safe [128]. The panel that writes this Consensus Document endorses the recommendations of the GACVS on the use of the commercialised vaccine.

#### **RECOMMENDATIONS:**

- ***There is a recombinant vaccine marketed in China (Hecolin<sup>®</sup>) that has been shown to be safe and effective in healthy people over 16 and under 65 years of age (AI).***
- ***Routine vaccination is not recommended in children under 16 years old, people over 65 years old, patients with chronic liver disease,***

*patients on solid organ transplant lists, pregnant women, or travellers (CIII).*

- *Vaccination should be considered individually in people who plan to travel to an area where an epidemic is occurring (e.g., aid workers and health workers) (CIII).*

## References

- [1] Aspinall EJ, Couturier E, Faber M, et al. Hepatitis E virus infection in Europe: surveillance and descriptive epidemiology of confirmed cases, 2005 to 2015. *Euro Surveill* 2017; 22(26): pii: 30561. doi: 10.2807/1560-7917.ES.2017.22.26.30561. [1]
- [2] World Health Organization. Global hepatitis report, 2017. Disponible en: <http://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/>
- [3] European Food Safety Authority. Public health risks associated with hepatitis E virus (HEV) as a food-borne pathogen. Disponible en: <https://www.efsa.europa.eu/en/efsajournal/pub/4886>
- [4] Domanović D, Tedder R, Blümel J, et al. Hepatitis E and blood donation safety in selected European countries: a shift to screening? *Euro Surveill* 2017; 22(16): pii: 30514. doi: 10.2807/1560-7917.ES.2017.22.16.30514. [119]
- [5] Kish MA. Guide to development of practice guidelines. *Clin Infect Dis* 2001; 32: 841-4.
- [6] López-López P, Zafra-Soto I, Ruiz-Torres L, et al. Diagnóstico de infección aguda por hepatitis e genotipo 3 mediante detección viral en saliva. *Enferm Infecc Microbiol Clin*. 2017; 35(Supl C): 8.
- [7] Doting MHE, Weel J, Niesters HGM, Riezebos-Brilman A, Brandenburg A. The added value of hepatitis E diagnostics in determining causes of hepatitis in routine diagnostic settings in the Netherlands. *Clin Microbiol Infect* 2017; 23: 667-71.
- [8] Hoofnagle JH, Nelson KE, Purcell RH. Hepatitis E. *N Engl J Med* 2012; 367: 1237-44.

- [9] Donnelly MC, Scobie L, Crossan CL, Dalton H, Hayes PC, Simpson KJ. Review article: hepatitis E-a concise review of virology, epidemiology, clinical presentation and therapy. *Aliment Pharmacol Ther* 2017; 46: 126-41.
- [10] Gurley ES, Hossain MJ, Paul RC, et al. Outbreak of hepatitis E in urban Bangladesh resulting in maternal and perinatal mortality. *Clin Infect Dis* 2014; 59: 658-65.
- [11] Patra S, Kumar A, Trivedi SS, Puri M, Sarin SK. Maternal and fetal outcomes in pregnant women with acute hepatitis E virus infection. *Ann Intern Med*. 2007; 147: 28-33.
- [12] Pérez-Gracia MT, Suay-García B, Mateos-Lindemann ML. Hepatitis E and pregnancy: current state. *Rev Med Virol* 2017; 27: e1929.
- [13] Anty R, Ollier L, Peron JM, et al. First case report of an acute genotype 3 hepatitis E infected pregnant woman living in South-Eastern France. *J Clin Virol* 2012; 54: 76-8.
- [14] Tabatabai J, Wenzel JJ, Soboletzki M, Flux C, Navid MH, Schnitzler P. First case report of an acute hepatitis E subgenotype 3c infection during pregnancy in Germany. *J Clin Virol* 2014; 61: 170-2.
- [15] Chau TN, Lai ST, Tse C, et al. Epidemiology and clinical features of sporadic hepatitis E as compared with hepatitis A. *Am J Gastroenterol* 2006; 101: 292-6.
- [16] Goel A, Aggarwal R. Advances in hepatitis E - II: Epidemiology, clinical manifestations, treatment and prevention. *Expert Rev Gastroenterol Hepatol* 2016; 10: 1065-74.
- [17] Lachish T, Erez O, Daudi N, Shouval D, Schwartz E. Acute hepatitis E virus in pregnant women in Israel and in other industrialized countries. *J Clin Virol* 2015; 73: 20-4.

- [18] Wedemeyer H, Pischke S, Manns MP. Pathogenesis and treatment of hepatitis e virus infection. *Gastroenterology* 2012; 142: 1388-97 e1.
- [19] Lee WM. Etiologies of acute liver failure. *Semin Liver Dis* 2008; 28: 142-52.
- [20] Fontana RJ, Engle RE, Scaglione S, et al. The role of hepatitis E virus infection in adult Americans with acute liver failure. *Hepatology* 2016; 64: 1870-80.
- [21] Crossan CL, Simpson KJ, Craig DG, et al. Hepatitis E virus in patients with acute severe liver injury. *World J Hepatol* 2014; 6: 426-34.
- [22] Scobie L, Dalton HR. Hepatitis E: source and route of infection, clinical manifestations and new developments. *J Viral Hepat* 2013; 20: 1-11.
- [23] Singh S, Mohanty A, Joshi YK, Dwivedi SN, Deka D. Outcome of hepatitis E virus infection in Indian pregnant women admitted to a tertiary care hospital. *Indian J Med Res* 2001; 113: 35-9.
- [24] Kumar Acharya S, Kumar Sharma P, Singh R, et al. Hepatitis E virus (HEV) infection in patients with cirrhosis is associated with rapid decompensation and death. *J Hepatol* 2007; 46: 387-94.
- [25] Kamar N, Bendall R, Legrand-Abravanel F, et al. Hepatitis E. *Lancet* 2012; 379: 2477-88.
- [26] Blasco-Perrin H, Madden RG, Stanley A, et al. Hepatitis E virus in patients with decompensated chronic liver disease: a prospective UK/French study. *Aliment Pharmacol Ther* 2015; 42: 574-81.
- [27] Dalton HR, Bendall RP, Pritchard C, Henley W, Melzer D. National mortality rates from chronic liver disease and consumption of alcohol and pig meat. *Epidemiol Infect* 2010; 138: 174-82.

- [28] Nanji AA, French SW. Relationship between pork consumption and cirrhosis. *Lancet* 1985; 1: 681-3.
- [29] Colson P, Borentain P, Queyriaux B, et al. Pig liver sausage as a source of hepatitis E virus transmission to humans. *J Infect Dis* 2010; 202: 825-34.
- [30] Riveiro-Barciela M, Sauleda S, Quer J, et al. Red blood cell transfusion-transmitted acute hepatitis E in an immunocompetent subject in Europe: a case report. *Transfusion* 2017; 57: 244-7.
- [31] Hewitt PE, Ijaz S, Brailsford SR, et al. Hepatitis E virus in blood components: a prevalence and transmission study in southeast England. *Lancet* 2014; 384: 1766-73.
- [32] Tedder RS, Ijaz S, Kitchen A, et al. Hepatitis E risks: pigs or blood-that is the question. *Transfusion* 2017; 57: 267-72.
- [33] Rivero-Juarez A, Camacho A, Merchante N, et al. Incidence of liver damage of uncertain origin in HIV patients not co-infected with HCV/HBV. *PLoS One* 2013; 8: e68953.
- [34] Kamar N, Garrouste C, Haagsma EB, et al. Factors associated with chronic hepatitis in patients with hepatitis E virus infection who have received solid organ transplants. *Gastroenterology* 2011; 140: 1481-9.
- [35] Unzueta A, Rakela J. Hepatitis E infection in liver transplant recipients. *Liver Transpl* 2014; 20: 15-24.
- [36] Giordani MT, Fabris P, Brunetti E, Goblirsch S, Romano L. Hepatitis E and lymphocytic leukemia in Man, Italy. *Emerg Infect Dis* 2013; 19: 2054-6.
- [37] Versluis J, Pas SD, Agteresch HJ, et al. Hepatitis E virus: an underestimated opportunistic pathogen in recipients of allogeneic hematopoietic stem cell transplantation. *Blood* 2013; 122: 1079-86.



- [38] McPherson S, Elsharkawy AM, Ankcorn M, et al. Summary of the British Transplantation Society UK Guidelines for Hepatitis E and Solid Organ Transplantation. *Transplantation* 2018; 102:15-20.
- [39] Barrague H, Condat B, Petitdidier N, et al. Chronic hepatitis E virus infection in a cirrhotic patient: A case report. *Medicine (Baltimore)* 2017; 96: e7915.
- [40] Gonzalez-Tallon AI, Moreira Vicente V, Mateos Lindemann ML, Achecar Justo LM. Chronic hepatitis E in an immunocompetent patient. *Gastroenterol Hepatol* 2011; 34: 398-400.
- [41] Pineda JA, Cifuentes C, Parra M, et al. Incidence and natural history of hepatitis E virus coinfection among HIV-infected patients. *AIDS* 2014; 28: 1931-7.
- [42] Rivero-Juarez A, Cuenca-Lopez F, Martinez-Peinado A, et al. Rural habitat as risk factor for hepatitis E virus seroconversion in HIV-infected patients: A prospective longitudinal study. *Zoonoses Public Health* 2017; 64: e60-e64
- [43] Merchante N, Parra-Sanchez M, Rivero-Juarez A, et al. High prevalence of antibodies against hepatitis E virus in HIV-infected patients with unexplained liver disease. *Enferm Infecc Microbiol Clin* 2015; 33: 532-5.
- [44] Rivero-Juarez A, Martinez-Duenas L, Martinez-Peinado A, et al. High hepatitis E virus seroprevalence with absence of chronic infection in HIV-infected patients. *J Infect* 2015; 70: 624-30.
- [45] Neukam K, Barreiro P, Macias J, et al. Chronic hepatitis E in HIV patients: rapid progression to cirrhosis and response to oral ribavirin. *Clin Infect Dis* 2013; 57: 465-8.

[46] Teshale EH, Grytdal SP, Howard C, et al. Evidence of person-to-person transmission of hepatitis E virus during a large outbreak in Northern Uganda. *Clin Infect Dis* 2010; 50: 1006-10.

[47] Lewis HC, Wichmann O, Duizer E. Transmission routes and risk factors for autochthonous hepatitis E virus infection in Europe: a systematic review. *Epidemiol Infect* 2010; 138:145-66.

[48] Mirazo S, Ramos N, Mainardi V, Gerona S, Arbiza J. Transmission, diagnosis, and management of hepatitis E: an update. *Hepat Med* 2014; 6: 45-59.

[49] Schlosser B, Stein A, Neuhaus R, et al. Liver transplant from a donor with occult HEV infection induced chronic hepatitis and cirrhosis in the recipient. *J Hepatol* 2012; 56: 500-2.

[50] Pourbaix A, Ouali N, Soussan P, et al. Evidence of hepatitis E virus transmission by renal graft. *Transpl Infect Dis* 2017;19(1).

[51] European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Reflection paper on viral safety of plasma-derived medicinal products with respect to Hepatitis E virus.

[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2016/06/WC500209354.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/06/WC500209354.pdf). (último acceso Diciembre, 2017).

[52] Slot E, Hogema BM, Riezebos-Brilman A, Kok TM, Molier M, Zaaijer HL. Silent hepatitis E virus infection in Dutch blood donors, 2011 to 2012. *Euro Surveill* 2013; 18(31).

[53] Cleland A, Smith L, Crossan C, et al. Hepatitis E virus in Scottish blood donors. *Vox Sang* 2013; 105: 283-9.

[54] Sauleda S, Ong E, Bes M, et al. Seroprevalence of hepatitis E virus (HEV) and detection of HEV RNA with a transcription-mediated amplification assay in blood donors from Catalonia (Spain). *Transfusion* 2015; 55: 972-9.

[55] Piron M, De la Torre Rial C, Bes M, et al. Infección por el virus de la hepatitis E: incidencia y características epidemiológicas en donantes de sangre. *Blood Transfusion* 2017; 15 (Suppl 2): s292

[56] Ojea A, Gonzalez I, Blanco L, et al. Prospective study of prevalence of hepatitis E virus in donors from North-Spain. 27<sup>th</sup> Regional Congress of the ISBT. June 17-21, 2017. Copenhagen, Demark. Abstract P-409

[57] European Pharmacopoeia: human plasma (pooled and treated for virus inactivation). *European Pharmacopoeia* 5.0 2014; 01/2005/1646. [http://library.njucm.edu.cn/yoadian/ep/EP501E/16monographs/17monographs k/human plasma for fractionation/0853e/pdf](http://library.njucm.edu.cn/yoadian/ep/EP501E/16monographs/17monographs%20k/human%20plasma%20for%20fractionation/0853e/pdf) (último acceso Diciembre 2017).

[58] Baylis SA, Terao E, Blumel J, Hanschmann KO. Collaborative study for the establishment of the Ph. Eur. Hepatitis E virus RNA for NAT testing biological reference preparation batch 1. *Pharmeur Bio Sci Notes* 2017; 2017:12-28.

[59] Farcet MR, Lackner C, Antoine G, et al. Hepatitis E virus and the safety of plasma products: investigations into the reduction capacity of manufacturing processes. *Transfusion* 2016; 56: 383-91.

[60] Yunoki M, Tanaka H, Takahashi K, et al. Hepatitis E virus derived from different sources exhibits different behaviour in virus inactivation and/or removal studies with plasma derivatives. *Biologicals* 2016; 44: 403-11.

[61] Pischke S, Hartl J, Pas SD, Lohse AW, Jacobs BC, Van der Eijk AA. Hepatitis E virus: Infection beyond the liver? *J Hepatol* 2017; 66: 1082-1095

- [62] Dalton HR, van Eijk JJJ, Cintas P, et al. Hepatitis E virus infection and acute non-traumatic neurological injury: A prospective multicentre study. *J Hepatol* 2017; 67: 925-32.
- [63] van Eijk JJJ, Dalton HR, Ripellino P, et al. Clinical phenotype and outcome of hepatitis E virus-associated neuralgic amyotrophy. *Neurology* 2017; 89: 909-917.
- [64] Davern TJ, Chalasani N, Fontana RJ, et al. Acute hepatitis E infection accounts for some cases of suspected drug-induced liver injury. *Gastroenterology* 2011; 141: 1665-72
- [65] Dalton HR, Fellows HJ, Stableforth W, et al. The role of hepatitis E virus testing in drug-induced liver injury. *Aliment Pharmacol Ther* 2007; 26: 1429-35.
- [66] Sanjuan-Jimenez R, Robles-Díaz M, Sanabria J, et al. Prevalence of hepatitis E markers in Spanish patients with suspected drug-induced liver injury. Presented at the 68th Annual Meeting of the American Association for the Study of Liver Diseases, Washington, DC, October 20-24, 2017. Abstract 793.
- [67] Zhao C, Wang Y. Laboratory diagnosis of HEV Infection. *Adv Exp Med Biol*. 2016; 948:191-209.
- [68] Geng Y, Zhao C, Huang W et al. Detection and assessment of infectivity of hepatitis E virus in urine. *J Hepatol* 2016; 64: 37-43.
- [69] Fujiwara S, Yokokawa Y, morino K, Hayasaka K, Kawabata M, Shimizu T. Chronic hepatitis E: a review of the literature. *J Viral Hepat* 2014; 21: 78-89.
- [70] Huang S, Zhang X, Jiang H, et al. Profile of acute infectious markers in sporadic hepatitis E. *PLoS One* 2010; 5: e13560.
- [71] Kamar N, Dalton HR, Abravanel F, Izopet J. Hepatitis E Virus Infection. *Clin Microbiol Rev* 2014; 27: 116-38.

[72] Zaki MEL-S, Found MF, Mohamed AF. Value of hepatitis E virus detection by cell culture compared with nested PCR and serological studies by IgM and IgG. *FEMS Immunol Med Microbiol*. 2009; 56:73-9.

[73] Zhang H, Rao H, Wang J, et al. Role of HEV antigen detection for diagnosis of acute hepatitis E. Presented at the 68th Annual Meeting of the American Association for the Study of Liver Diseases, Washington, DC, October 20-24, 2017. Abstract 760.

[74] Zhang F, Li X, Li Z et al. Detection of HEV antigen as a novel marker for the diagnosis of hepatitis E. *J Med Virol* 2006; 78: 1441-8.

[75] Wen GP, Tang ZM, Yang F, et al. A valuable antigen detection method for diagnosis of acute hepatitis E. *J Clin Microbiol* 2015; 53: 782-8.

[76] Protzer U; Böhm F, Longerich T, et al. Molecular detection of hepatitis E virus (HEV) in liver biopsies after liver transplantation. *Mod Pathol* 2015; 28: 523-32.

[77] Baylis SA, Hanschmann KM, Blümel J, Nübling CM. Standardization of Hepatitis E (HEV) nucleic acid amplification technique-based assays: an initial study to evaluate a panel of HEV strains and investigate laboratory performance. *J Clin Microbiol* 2011; 49: 1234-9.

[78] Abravanel F, Chapuy-Regaud S, Lhomme S, et al. Performance of two commercial assays for detecting hepatitis E virus RNA in acute or chronic infections. *J Clin Microbiol* 2013; 51: 1913-6.

[79] Avellon A, Morago L, García-Galera del Carmen M, Muñoz M, Echevarria JM. Comparative sensitivity of commercial tests for hepatitis E genotype 3 virus antibody detection. *J Med Virol* 2015; 87: 1934-9.

[80] Abravanel F, Lhomme S, Chapuy-Regaud S, et al. Performance of a new rapid test for detecting anti-hepatitis E virus immunoglobulin M in

immunocompetent and immunocompromised patients. *J Clin Virol* 2015; 70: 101-4.

[81] Wenzel H, Preiss J, Schemmerer M, Huber R, Jilg W. Test performance characteristics of anti-HEV IgG assays strongly influence hepatitis E seroprevalence estimates. *J Infect Dis* 2013; 207: 497-500.

[82] Harlt J, Otto B, Madden RG, et al. Hepatitis E seroprevalence in Europe: A meta-analysis. *Viruses* 2016; 8: pii: E221.

[83] Khudyakov Y, Kamili S. Serological diagnostics of hepatitis E virus infection. *Virus Res* 2011; 161: 84-92.

[84] Pisanic N, Rahman A, Saha SK, et al. Development of an oral fluid immunoassay to assess past and recent hepatitis E virus (HEV) infection. *J Immunol Methods* 2017; pii: S0022-1759(17)30009-1.

[85] Hyams C, Mabayoje DA, Copping R, et al. Serological cross reactivity to CMV and EBV causes problems in the diagnosis of acute hepatitis E virus infection. *J Med Virol* 2014; 86: 478-83.

[86] Ferguson M, Walker D, Mast E, Fields H. Report of a collaborative study to assess the suitability of a reference reagent for antibodies to hepatitis E virus. *Biologicals* 2002; 30: 43-8.

[87] Germer JJ, Ankoudinova I, Yevgeniy S, et al. Hepatitis E virus (HEV) detection and quantification by a Real-time Reverse Transcription-PCR assay calibrated to the World Health Organization Standard HEV-RNA. *J Clin Microbiol* 2017; 55: 1478-87.

[88] Pischke S, Hardtke S, Bode U, et al. Ribavirin treatment of acute and chronic hepatitis E: a single-centre experience. *Liver Int* 2013; 33: 722-726.

[89] Peron JM, Abravanel F, Guillaume M, et al. Treatment of autochthonous

acute hepatitis E with short-term ribavirin: a multicenter retrospective study. *Liver Int* 2016; 36: 328-333

[90] Tavitian S, Peron JM, Huguet F, et al. Ribavirin for chronic hepatitis prevention among patients with haematological malignancies. *Emerg Infect Dis* 2015; 21: 1466-1469.

[91] Del Bello A, Guilbeau-Frugier C, Josse AG, Rostaing L, Izopet J, Kamar N. Successful treatment of hepatitis E virus-associated cryoglobulinemic membranoproliferative glomerulonephritis with ribavirin. *Transpl Infect Dis* 2015; 17: 279-283.

[92] Gerolami R, Borentain P, Raissouni F, Motte A, Solas C, Colson P. Treatment of severe acute hepatitis E by ribavirin. *J Clin Virol* 2011; 52: 60-62.

[93] Kamar N, Izopet J, Tripon S, Bismuth M, Hillaire S, Dumortier J, et al. Ribavirin for chronic hepatitis E virus infection in transplant recipients. *N Engl J Med* 2014; 370: 1111-1120.

[94] Chaillon A, Sirinelli A, De Muret, Nicand E, d'Alteroche L, Goudeau A. Sustained virological response with ribavirin in chronic hepatitis E virus infection in heart transplantation. *J Heart Lung Transplant* 2011; 30: 841-843.

[95] Kamar N, Rostaing L, Abravanel F, Garrouste C, Lhomme S, Esposito L, et al. Ribavirin therapy inhibits viral replication on patients with chronic hepatitis E virus infection. *Gastroenterology* 2010; 139: 1612-1618.

[96] Mallet V, Nicand E, Sultanik P, Cjakvetadze C, Tessé S, Thervet E, et al. Brief communication: case reports of ribavirin treatment for chronic hepatitis E. *Ann Intern Med* 2010; 153: 85-89.

[97] Goyal R, Kumar A, Panda SK, Paul SB, Acharua SK. Ribavirin therapy for hepatitis E virus-induced acute on chronic liver failure: a preliminary report. *Antivir Ther* 2012; 17: 1091-1096.

[98] Kamar N, Lhomme S, Abravanel F, et al. An early viral response predicts the virological response to ribavirin in hepatitis E virus organ transplant patients. *Transplantation* 2015; 99: 2124-2131.

[99] Abravanel F, Lhomme S, Rostaing L, Kamar N, Izopet J. Protracted fecal shedding of HEV during ribavirin therapy predicts treatment relapse. *Clin Infect Dis* 2015; 60: 96-99.

[100] Kamar N, Rostaing L, Abravanel F, Garrouste C, Esposito L, Cardeau-Desangles I, et al. Pegylated interferón-alpha for treating chronic hepatitis E virus infection after liver transplantation. *Clin Infect Dis* 2010; 50: e30-33.

[101] Dao Thi VL, Debing Y, Wu X, et al. Sofosbuvir inhibits hepatitis E virus replication in vitro and results in additive effect when combined with ribavirin. *Gastroenterology* 2016; 150:82-85.

[102] Donnelly MC, Imlach SN, Abravanel F, et al. Sofosbuvir and daclatasvir antiviral therapy fails to clear HEV viremia and restore reactive T cells in a HEV/HCV co-infected liver transplant recipient. *Gastroenterology* 2017; 152: 300-301.

[103] Van der Valk M, Zaaijer HL, Kater AP, Schinkel J. Sofosbuvir shows antiviral activity in a patient with chronic hepatitis E virus infection. *J Hepatol* 2017; 66: 242-243.

[104] Todesco E, Demeret S, Calin R, et al. Chronic hepatitis E in HIV/HBV coinfecting patient: lack of power of sofosbuvir-ribavirin. *AIDS* 2017; 31: 1346-1348.



- [105] Dalton HR, Kamar N, van Eijk JJ, et al. Hepatitis E virus and neurological injury. *Nat Rev Neurol* 2016; 12:77-85.
- [106] Murrison LB, Sherman KE. The enigma of hepatitis E virus. *Gastroenterol Hepatol* 2017; 13:484–91.
- [107] Liu L and Liu Y. Analysis of acute to chronic hepatitis E: 6-10 year follow-up. *Hepato-gastroenterology* 2011; 58: 324-325.
- [108] Festa S, Garbuglia AR, Baccini F, et al. Acute fulminant hepatitis E virus genotype 3e infection: description of the first case in Europe. *Scandinavian Journal of Infectious Diseases* 2014; 46:727–31.
- [109] Mateos-Lindemann ML, Aguilar MD, Galdámez AG, et al. Acute, Chronic and Fulminant Hepatitis E: Ten Years of Experience (2004-2013). *International Journal of Gastroenterology Disorders & Therapy* 2014; 1: 102
- [110] Kumar AS, Kumar SP, Singh R, et al. Hepatitis E virus (HEV) infection in patients with cirrhosis is associated with rapid decompensation and death. *J Hepatol* 2007; 46:387-94.
- [111] Kumar N, Das V, Agarwal A, Pandey A, Agrawal S. Fetomaternal outcomes in pregnant women with hepatitis E infection; still an important fetomaternal killer with an unresolved mystery of increased virulence in pregnancy. *Turk J Obstet Gynecol* 2017; 14: 106-13.
- [112] Tsega E, Krawczynski K, Hansson BG, Nordenfelt E. Hepatitis E virus infection in pregnancy in Ethiopia. *Ethiop Med J* 1993; 31: 173-181.
- [113] Rasheeda CA, Navaneethan U, Jayanthi V. Liver disease in pregnancy and its influence on maternal and fetal mortality: a prospective study from Chennai, Southern India. *Eur J Gastroenterol Hepatol* 2008; 20: 362-4.
- [114] Rivero-Juarez A, Frias M, Rodriguez-Cano D, Cuenca-López F, Rivero A.

Isolation of Hepatitis E Virus From Breast Milk During Acute Infection. *Clin Infect Dis* 2016; 62: 1464.

[115] Chibber RM, Usmani MA, Al-Sibai MH. Should HEV infected mothers breast feed? *Arch Gynecol Obstet* 2004; 270: 15-20.

[116] Kamar N, Selves J, Mansuy JM, et al. Hepatitis E virus and chronic hepatitis in organ-transplant recipients. *N Engl J Med* 2008; 358: 811-7.

[117] Ollier L, Tieulie N, Sanderson F, et al. Chronic hepatitis after hepatitis E virus infection in a patient with non-Hodgkin lymphoma taking rituximab. *Ann Intern Med.* 2009 17; 150:430-1.

[118] Dalton HR, Bendall RP, Keane FE, Tedder RS, Ijaz S. Persistent carriage of hepatitis E virus in patients with HIV infection. *N Engl J Med* 2009; 361:1025-7.

[119] Behrendt P, Lüth S, Dammermann W, et al. Exacerbation of hepatitis E virus infection during anti-TNF $\alpha$  treatment. *Joint Bone Spine* 2017; 84:217-19.

[120] Amougou Atsama M, Atangana PJA, Noah Noah D, Moundipa PF, Pineau P, Njouom R. Hepatitis E virus infection as a promoting factor for hepatocellular carcinoma in Cameroon: Preliminary Observations. *Int J Infect Dis* 2017; 64:4-8.

[121] GeurtsvanKessel CH, Islam Z, Mohammada QD, Jacobs BC, Endtz HP and Osterhaus MR. Hepatitis E and Guillain-Barré Syndrome. *Clin Infect Dis* 2013; 57: 1369-1370.

[122] Khuroo MS, Khuroo MS, Khuroo NS. Hepatitis E: Discovery, global impact, control and cure. *World J Gastroenterol* 2016; 22:7030-7045.

[123] Legrand-Abravanel F, Kamar N, Sandres-Saune K, et al. Characteristics of autochthonous hepatitis E virus infection in solid-organ transplant recipients in France. *J Infect Dis* 2010; 202:835

- [124] Johne R, Trojnar E, Filter M, Hofman J. Thermal stability of hepatitis E virus as estimated by a cell culture method. *App Environ Microbiol* 2016; 82: 4225-4231.
- [125] DuPont HL, Ericsson CD. Prevention and treatment of traveler`s diarrhea. *N Engl J Med* 1993; 328: 1821-7
- [126] Khuroo MS, Kamili S. Aetiology, clinical course and outcome of sporadic acute viral hepatitis in pregnancy. *J Viral Hepatol* 2003; 10: 61-69.
- [127] Montella F, Rezza G, Di Sora F, Pezzotti P, Recchia O. Association between hepatitis E virus and HIV infection in homosexual men. *Lancet* 1994; 344: 1433.
- [128] Shrestha MP, Scott RM, Joshi DM, Mammen PM, Thapa GB, Thapa N, et al. Safety and efficacy of a recombinant hepatitis E vaccine. *N Engl J Med* 2007; 356:895-903.
- [129] Zhu FC, Zhang J, Zhang XF, et al. Efficacy and safety of a recombinant hepatitis E vaccine in healthy adults: a large-scale, randomised, double-blind placebo-con- trolled, phase 3 trial. *Lancet* 2010; 376: 895-902.
- [130] Zhang J, Zhang XF, Zhou C, et al. Protection against hepatitis E virus infection by naturally acquired and vaccine-induced immunity. *Clin Microbiol Infect* 2014; 20: O397-O405
- [131] Wu T, Zhu FC, Huang SJ, et al. Safety of the hepatitis E vaccine for pregnant women: a preliminary analysis. *Hepatology* 2012; 55: 2038
- [132] Zhang J, Shih JW, Wu T, Li SW, Xia NS. Development of the hepatitis E vaccine: from bench to field. *Semin Liver Dis* 2013; 33: 79-88.

[133] Xiaoqing Cheng, Yueyuan Zhao, Xuefeng Zhang, Hui Jin, Jie Min. Health economic evaluation of immunization strategies of hepatitis E vaccine for elderly population. *Hum Vaccin Immunother* 2017; 13: 1873-1878.

[134] Hepatitis E vaccine: WHO position paper, May 2015. Disponible en: <http://www.who.int/wer/2015/wer9018.pdf?ua=1> (último acceso Diciembre 2017).

## DECLARATION OF CONFLICT OF INTERESTS

**Ana Avellón:** has received honoraria from Gilead Sciences, Abbvie, Siemens Health Care, Abbott, Diasorin, and Mikrogen for participating in meetings as a speaker.

**Antonio Aguilera:** No conflicts of interest to declare.

**Antonio Rivero Juárez:** has performed consulting work for Gilead Sciences and Roche Diagnostics laboratories; has received honoraria from Bristol-Myers Squibb, Gilead Sciences, Janssen Cilag, ViiV Healthcare, and Merck Sharp & Dohme for participation in meetings as a speaker; and has received scholarships for research from Abbvie and ViiV Healthcare.

**Antonio Rivero:** has performed consulting work for Abbvie Laboratories, BristolMyers Squibb, Gilead Sciences, Merck Sharp & Dohme, and ViiV Healthcare; has received scholarships for clinical research from Abbvie, Bristol-Myers Squibb, Gilead Sciences, Merck Sharp & Dohme, and ViiV Healthcare; and has received financial compensation for lectures from Abbvie, Bristol-Myers Squibb, Gilead Sciences, Merck Sharp & Dohme, and ViiV Healthcare.

**Christian Gortazar:** No conflicts of interest to declare.

**David Rodríguez Lázaro:** No conflicts of interest to declare.

**Federico García:** has performed consultancy work for Abbvie, Gilead Sciences, Merck Sharp & Dohme, Roche Diagnostics, Werfen, ViiV Healthcare, and Hologic and has received research grants from Gilead Sciences, Gilead Sciences, Merck Sharp & Dohme, and Roche Diagnostics.

**Francisco Tellez:** No conflicts of interest to declare.

**Jose Antonio Oteo:** has received honoraria from Bristol-Myers Squibb, Gilead Sciences, Janssen Cilag, Merck Sharp & Dohme, Abbvie, Novartis, Boehringer Ingelheim, Roche, and Pfizer for participating in meetings as a speaker and has received scholarships for research from Gilead Sciences.

**Juan Antonio Pineda:** has received consultancy fees from Abbvie, Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Janssen Cilag, and Merck Sharp & Dohme; has received research grants from Boehringer Ingelheim Pharmaceuticals, Bristol-Myer Squibb, Gilead Sciences, GlaxoSmithKline, Janssen Cilag, Merck Sharp & Dohme, Roche Pharma, and ViiV Healthcare; and has received honoraria for lectures from Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Janssen Cilag, Merck Sharp & Dohme, Roche Pharma, and ViiV Healthcare.

**Juan Macías:** has been a researcher in clinical trials supported by Bristol-Myers Squibb, Gilead, and Merck Sharp & Dohme; has received honoraria for lectures

from Gilead, Bristol-Myers Squibb, and Merck Sharp & Dohme; and has received consultancy fees from Bristol Myers-Squibb, Gilead, and Merck Sharp & Dohme.

**Luis Enrique Morano:** has received honoraria from Bristol-Myers Squibb, Gilead Sciences, Janssen Cilag, Merck Sharp & Dohme, Abbvie, Novartis, Boehringer Ingelheim, Roche, and Pfizer for participating in meetings as a speaker.

**María Teresa Pérez Gracia:** No conflicts of interest to declare.

**Miguel García Deltoro:** has performed consulting work for ViiV Health Care and Janssen; has received financial compensation for lectures from Janssen, MSD, Gilead, and Abbvie; has received funding for meetings and congresses from MSD and Gilead; has participated as a researcher in clinical trials for MSD, Gilead, Janssen, and ViiV; and has received funding for educational programmes and courses from ViiV, Gilead, Janssen, MSD, and Abbvie.

**Nicolás Merchante:** has received financial compensation for lectures from Bristol-Myers Squibb, Gilead Sciences, and Merck Sharp & Dohme; and has received assistance for congress attendance from Janssen Cilag, Merck Sharp & Dohme, Gilead Sciences, and ViiV Healthcare.

**Rafael Granados:** No conflicts of interest to declare.