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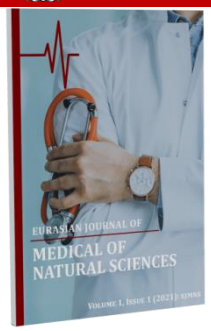

VIRAL HEPATITIS, THE RELEVANCE OF IMPROVING THEIR DIAGNOSTIC METHODS AND PROMISING PREVENTIVE MEASURES

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ABSTRACT

This review focuses on the most important research topics that deal with issues that are currently being solved, those that remain unresolved, and future research directions. For the hepatitis A virus, we will address epidemiology, molecular surveillance, new susceptible populations, as well as environmental and food detections; for the hepatitis B virus, we will discuss host factors related to disease, diagnosis, therapy, and vaccine. Viral hepatitis, which is caused by infection with the hepatitis A, B, C, D, and E viruses, is a significant public health issue and a substantial cause of morbidity and mortality. As for the hepatitis D virus, we describe diagnostic methodology, pathogenesis, and therapy; for the hepatitis E virus, we will discuss epidemiology (including new emerging species), diagnosis, clinical aspects, treatment, vaccine development, and environmental surveillance; and for the hepatitis C virus, we will concentrate on pathogenesis, immunological response, direct action antiviral treatment in the context of solid organ transplantation, problems associated with the development of hepatocellular carcinoma, direct action antiviral resistance due to selection of resistance-associated variants and vaccination. The aforementioned underscores novel issues pertaining to hepatitis E globally, indicating the necessity for additional epidemiological, clinical, and virological research to better comprehend the various HAV, HBV, HCV HDV and HEV scenarios and effects globally.

Introduction. Liver inflammation brought on by a viral infection is referred to as viral hepatitis. There are now five known viruses that specifically target the liver, typically through several pathways. Acute hepatitis in certain viral infections may recover on its own without treatment, but in other cases, the illness may develop into a chronic one. The deployment of

preventive measures, the creation of vaccines and passive immunization techniques, and, more recently, the development of promising and successful treatments—at least for certain types of viral hepatitis—were all results of significant medical advancements in recent decades. Basic research on viruses and the relationship between viruses and cells has produced breakthroughs that have allowed us to combat a problem that looked insurmountable a century ago [1, 2, 3,]. Though viral hepatitis remains a global public health concern that affects millions of people and causes thousands of deaths due to acute and chronic infection, cirrhosis, and liver cancer, the most important research topics at the moment and future research directions that can maximize practical impact in the field of viral hepatitis are highlighted in this review. Hepatitis prevention and treatment advancements are perhaps the epitome of successful translational research [4, 5, 6]. Due to their high impact, HBV and HCV have been identified as important targets for lowering the incidence of liver diseases, especially chronic liver disease. While 75–85% of HCV patients progress to chronic disease, increasing the risk of serious complications like liver cirrhosis and hepatocellular carcinoma, nearly 90% of neonates and up to 5% of adults infected with HBV develop chronic infection. Nevertheless, the interest in HBV/HCV has overshadowed other viral types; among these, the emerging hepatitis E virus (HEV) is a major problem in high-income regions. Initially believed to be self-limiting, HEV may cause persistent infections globally due to its diverse propagation, especially in patients with compromised immune systems [7, 8, 9, 10]. Many countries' efforts to eradicate viral hepatitis are likely to have uneven results due to a lack of funding, diagnostic tools, drugs, and policies with differing degrees of efficacy. These differences have been made worse by the COVID-19 pandemic, especially in low- and middle-income nations. Viral hepatitis initiatives and other public health goals have been harmed in the short and medium term by the delay in economic, social, and health recovery. Therefore, the death and transmission rates provide serious obstacles to the worldwide eradication of viral hepatitis by 2030. Some countries made its first commitment to the GHSS plan in 2016 when its first document outlined the strategy's goals of reducing HCV-related morbidity and mortality through high-risk population-focused health promotion, prevention, diagnosis, and treatment programs. As members of the National Network of Viral Hepatitis Researchers, we have closely monitored the strategic actions as they have been developed, recognizing the progress and assessing the obstacles that may threaten the 2030 goal's success [11-18]. In order to identify the advancements, difficulties, and possible prospects supporting the global effort to eradicate viral hepatitis, this paper offers a fundamental summary of viral hepatitis and Mexico's local reaction to the global drive. Viral hepatitis is a worldwide public health issue that impacts millions of individuals and results in thousands of fatalities from liver cancer, cirrhosis, and acute and chronic infections. There are still important topics that need to be covered even if the clinical and epidemiological features of hepatitis A, B, C, D, and E virus infections are well understood. The most significant research themes, unresolved problems, and potential future research avenues that can optimize practical impact in the field of viral hepatitis are the subject of this review [20-26].

The main purpose of the presented analytical manuscript is a brief overview of many years of scientific research on viral hepatitis, the relevance of improving their diagnostic methods and promising measures for their prevention.

Transmission and epidemiology: Both new and old problems. Given that the most common ways for HAV to spread are through contaminated water consumption and contact with infected people, the epidemiology of HAV is evolving in nations that are strengthening their public health and sanitation regulations, despite its complexity. For HAV, three circulation patterns have been identified in the past: (1) The transmission pattern is person-to-person, outbreaks are rare because of high immunity from prior childhood infection, and the peak age of infection in early childhood is often asymptomatic in high endemicity areas from low- and middle-income countries, where the incidence fluctuates from low to high over time and between regions [23-26]. The incidence is high, the peak age of infection is in late childhood/adolescence or in young adults who are often symptomatic, the transmission pattern is also from person to person, related to food and water, and because of this, outbreaks are common in areas of moderate endemicity from middle-income countries (regions where sanitary conditions vary); and (3) in areas of low endemicity from high-income countries, the incidence is low, the peak age of infection is in young adulthood, the transmission pattern is from person-to-person, and also via food and water; outbreaks are common because of low immunity from prior childhood infections [18-22]. Although immunization is advised by the WHO, it is not usually administered to visitors to endemic areas, which leads to an increase in hepatitis A incidence in this population. Furthermore, new viral strains were introduced when the virus was transferred from endemic areas—often without vaccine coverage—to non-endemic areas due to the movements of immigrants in several parts of the world, such as South America. This group should be administered immunoglobulin (Ig) G anti-HAV screening; thus, patients who test negative should be offered immunization [25, 26].

Table 1. Epidemiology of viral hepatitis.

№	**Types of viral hepatitis**	Infected in years old	Diagnosed in %	Treated in %	Complications in %	Mortality in mln
1.	HAV	0-18	1,5-2	100	0	0
2.	HBV	5-65	45-48	80	20	3-5
3.	HCV	5-65	35-40	90	10	1-2
4.	Others	5-65	10-18,5	75-80	5-8	0,5-0,8

Hepatitis testing goals. The first step towards accessing both prevention and treatment is the testing and identification of HCV and CHB infections. Providing services for care and treatment. People with CHB or HCV infection can get the care and therapy they need to stop or slow the progression of liver disease if they are identified early. Understanding one's HBV status is crucial for choosing ART regimens that include TDF as well as for keeping an agent active against HBV when a treatment switch is necessary since withdrawal symptoms might cause acute or chronic liver disease flare-ups. Additionally, testing offers a chance to connect to measures that help prevent transmission, like risk behavior counseling and the distribution of hepatitis prevention supplies (like sterilized needles and syringes). B vaccine. Troubles with hepatitis testing. Most people who are coinfected with HBV or HCV are misdiagnosed and are unaware of their infection, even though there is a substantial burden of disease from HBV and HCV infections as well as HIV–HBV and HCV coinfection, as well as advancements and prospects

for treatment. Less than 5% of those infected with CHB or HCV are thought to be aware of their condition [1-11].

Diagnosis of hepatitis. Although a combination of molecular and serological assays may be necessary to confirm infection and track treatment in patients with chronic infections, the diagnosis of hepatitis E infection can be made directly using techniques that allow for the detection of viral antigens and nucleic acid as well as IgG and IgM HEV-specific antibodies. The specificity and sensitivity of laboratory diagnostic methods for HEV detection differ, which is a crucial factor to take into account when utilizing any of them and when comparing them [1,4,7,8]. The PCR test is currently the gold standard for HEV-RNA amplification. To rule out other viral hepatitis and other liver disease causes (autoimmune, toxic, etc.), a differential diagnosis should be made in the event of acute hepatitis E. Both stool samples, when virions are shed for a longer duration, and serum samples, where the viremic phase is brief, can be used for HEV-RNA detection. Although it is not widely utilized, HEV antigen can also be identified in serum, feces, or urine utilizing double-antibody sandwich enzyme immunoassay techniques. IgM anti-HEV detection is another method for diagnosing acute hepatitis. It is important to note that the timing of the sample extraction and diagnosis is critical [4, 14, 17, 19]. False negative results for viral RNA detection could come from this sampling delay. Specific IgM testing is helpful in these situations. The diagnosis of chronic infections is made by looking for HEV-RNA in blood for longer than six months using RT-PCR (and/or its variations Nested-PCR and RT-PCR). The discovery of HEV IgM and IgG should be regarded cautiously since the titer of antibodies against HEV may be lower in these patients and immunocompromised individuals. Even though it is not done frequently, determining the viral genotype is crucial for viral surveillance, understanding clinical and epidemiological patterns, and tracking the entry of new strains or genotypes in a particular area [20-24]. Due to the accurate diagnosis of viral hepatitis in the early stages, as with pathologies of the desired viral etiology, a sharp decrease in the development of complications is achieved and, in turn, a decrease in the likelihood of these complications, as well as a decrease in mortality from existing complications (Fig. 1.).

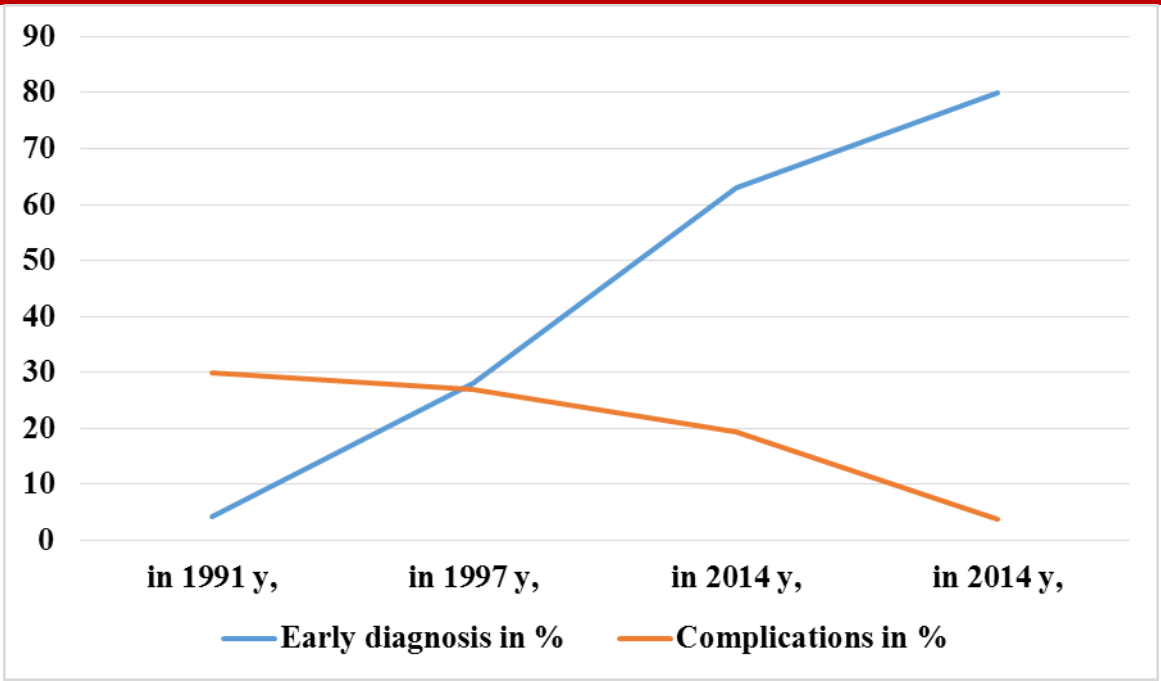

Figure 1. Effectiveness of early diagnosis of viral hepatitis

Antiviral therapy and vaccination. Since the virus is normally eliminated on its own, antiviral treatment is not necessary in cases of acute HEV infection. However, in cases of acute-on-chronic liver failure or severe acute hepatitis E, ribavirin treatment may be explored. For three months, ribavirin monotherapy is advised for chronic infections. When solid organ transplant recipients are diagnosed with persistent HEV infection, it is also recommended that their immunosuppressive dosages be reduced. Serum and stool samples should be evaluated for HEV-RNA after three months. The European Association for the Study of the Liver advises halting ribavirin treatment if RNA cannot be detected. Treatment with ribavirin should be continued for three more months if RNA replication continues. Only one HEV vaccine, Helicon®, has received a license in China, despite the fact that other others have been produced elsewhere [11-19]. The recombinant HEV peptide used in this vaccine is produced from genotype 1, which corresponds to a segment of open reading frame 2, which codes for the HEV capsid protein. People over 16 who are at high risk of contracting HEV infection (such as food handlers, animal husbandry workers, soldiers, women of childbearing age, visitors to endemic regions, etc.) are advised to use it. However, a number of elements of this vaccine, including its efficacy, immunogenicity, and safety, are poorly understood, which restricts its use, particularly in some populations, such as pregnant women, transplant recipients, and those with chronic liver disease [7-10].

Diagnostic advances and future changes. Technological developments for detecting the hepatitis virus have also opened up new avenues for improving hepatitis diagnosis and tracking treatment response. Simplified single virological assay testing methods, assays for near-patient or point-of-care (POC) use of NAT and core antigen, DBS, multiplex and multidisease platforms, and self-testing for anti-HCV are some examples of future testing trends and advancements.

With the introduction of POC molecular tests, multiplex or polyvalent testing, self-testing, streamlined one-assay testing algorithms, and novel service delivery methods, developments in hepatitis virus detection technologies have opened up new avenues for improving testing referral and treatment [9-17].

Discussion. Epidemiology and transmission: Traditional and contemporary issues. Even though the epidemiology of HAV is complicated, it is changing in nations that are strengthening their sanitation and public health regulations, given that contact with sick people and drinking contaminated water are the most common ways that HAV is spread. In the past, three circulation patterns for HAV have been identified: (1) In low- and middle-income countries with high endemicity, where the incidence fluctuates from low to high over time and across regions, early childhood is the peak age of infection, which is often asymptomatic; the transmission pattern is person-to-person; and outbreaks are rare because of high immunity from prior childhood infection; The incidence is high, the peak age of infection is in late childhood/adolescence or in young adults who are often symptomatic, the transmission pattern is also from person to person, related to food and water, and because of this, outbreaks are common in areas of moderate endemicity from middle-income countries (regions where sanitary conditions vary); and (3) in areas of low endemicity from high-income countries, the incidence is low, the peak age of infection is in young adulthood, the transmission pattern is from person-to-person, and also via food and water; outbreaks are common because of low immunity from prior childhood infections [18-24]. We compiled the most pertinent issues that are now under investigation or that have emerged recently in relation to viral hepatitis in this overview. While a lot has been learned about viral hepatitis in recent years, there are still a lot of unanswered questions. Enhancing diagnosis is essential to maintaining a steady and ongoing epidemiological surveillance of infected populations, learning more about the pathophysiology of each virus, enhancing therapy, and creating or enhancing vaccine efficacy. The most effective way to stop viral hepatitis from becoming a significant public health issue is to implement both local and international initiatives [2-7]. In order to better comprehend the many HEV scenarios and their global ramifications, further epidemiological, clinical, and virological research is required, as the aforementioned emphasizes new issues related to hepatitis E. Hepatitis testing innovations and future directions include ways to increase access, such as using community-based and existing facility-based testing opportunities, near-patient or point-of-care assays for virological markers (nucleic acid testing and HCV core antigen), using dried blood spot specimens with various nucleic acid and serological test assays, using multiplex and multi-disease platforms to enable testing for multiple analytes/pathogens, and possibly self-testing for viral hepatitis [13-20].

Conclusions. The most pertinent issues that are now being examined or that have recently come up in relation to viral hepatitis were compiled in this review. Even though our understanding of viral hepatitis has advanced significantly in recent years, many questions remain. In order to maintain a consistent and ongoing epidemiological follow-up of infected populations, increase our understanding of the pathophysiology of each virus, enhance therapy, and create or boost the effectiveness of vaccines, we must keep striving to improve diagnosis.

Since this is the most effective way to stop viral hepatitis from becoming a significant public health issue, it is crucial to realize that initiatives need to be both local and global.

The aforementioned identifies new global hepatitis E issues, indicating the need for additional epidemiological, clinical, and virological research to better understand the various HEV scenarios and their global ramifications.

The use of current facilities and community-based testing opportunities for hepatitis testing, near-patient or point-of-care assays for virological markers (nucleic acid testing and HCV core antigen), dried blood spot specimens used with various serological and nucleic acid test assays, multiplex and multi-disease platforms to enable testing for multiple analytes/pathogens, and possible self-testing for viral hepatitis are some examples of future directions and innovations in hepatitis testing.

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