Invited review/chapter- Infectious Disease Clinics of North America

Chapter 9

Title: Viral Hepatitis: Aetiology, Epirdemiology, transmission, diagnostics, treatment and prevention

Running Title: Viral Hepatitis

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KEYPOINTS

- Viral Hepatitis due to Hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D (delta) virus (HDV) and hepatitis E viruses (HEV) affects hundreds of millions of people globally.
- Hepatitis may present with a range of clinical features from asymptomatic, or acute with relatively rapid onset, or chronically. A large proportion of infected people are asymptomatic and are unaware of having an infection that can result in liver cirrhosis and liver cancer.
- Whilst hepatitis is associated with significant morbidity, most deaths from viral hepatitis are due to hepatitis B and hepatitis C.
- The development of new diagnostics and highly effective, pangenotypic direct-acting antivirals (DAAs) provide opportunities to cure and eradicate chronic hepatitis C virus (HCV) infection globally

SUMMARY

Viral hepatitis is a major global public health problem affecting hundreds of millions of people and is associated with significant morbidity and mortality. Five major biologically unrelated hepatotropic viruses cause most of the global burden of viral hepatitis: Hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C viruses (HCV), hepatitis D (delta) virus (HDV) and hepatitis E viruses (HEV). HBV, HCV, HDV, and occasionally HEV, can also produce chronic infections, whereas HAV does not. HBV and HCV are associated with significant chronic morbidity. Most deaths from viral hepatitis are due to hepatitis B and hepatitis C. An estimated 257 million people were living with HBV and 71 million people were living with HCV. HDV is a defective viral particle which is clinically relevant only in presence of HBV. HEV causes acute hepatitis in normal hosts but can cause protracted and chronic hepatitis in immunosuppressed patients. HAV and HEV can produce major outbreaks with severe consequences on the welfare of local communities, and HEV is increasingly recognized as a cause of chronic liver disease in the immunosuppressed Most people are asymptomatic and are unaware of having an infection that can result in liver cirrhosis and liver cancer. The development of new diagnostics and highly effective, pan-genotypic direct-acting antivirals (DAAs) provide opportunities to cure and eradicate chronic hepatitis C virus (HCV) infection globally.

INTRODUCTION

Viral hepatitis is a major global public health problem (**Figure 1**) affecting hundreds of millions of people and is associated with significant morbidity and mortality (**Figure 2**). Five biologically unrelated hepatotropic viruses cause most of the global burden of viral hepatitis: Hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C viruses (HCV), hepatitis D (delta) virus (HDV) and hepatitis E viruses (HEV). HBV, HCV, HDV, and occasionally HEV, can also produce chronic infections, whereas HAV does not. HBV and HCV are associated with significant chronic morbidity. Most deaths from viral hepatitis are due to hepatitis B and hepatitis C. Globally, an estimated 257 million people were living with HBV and 71 million people were living with HCV. The first Global hepatitis report [1,2] published in 2017 indicated that in 2015, 1.4 million persons died from the consequences of viral hepatitis infection. More than 90% of this burden was due to cirrhosis and hepatocellular carcinoma (HCC), which are consequences of chronic hepatitis B (CHB) and chronic hepatitis C (CHC). In 2015, the United Nations adopted a resolution calling for specific action to combat viral hepatitis as part of the Agenda for achieving Sustainable Development Goals 2030, followed with the World Health Organization's (WHO) first global elimination strategy for viral hepatitis in 2016. [3]

We review the epidemiology, biology, clinical features, treatment and prevention of viral hepatitis. We also review new agents for treatment of hepatitis C allowing the conceptual framework permitting the development of elimination programmes, and the rich pipeline of potential new therapies for HBV and HDV that may allow cure in future years. Recent outbreaks of HAV and HEV and the increasing recognition of atypical presentations are highlighted.

1. Viral Hepatitis A

a. Virology and pathogenesis

HAV is single strain positive sense RNA virus belonging to *Hepatovirus* genus [4] and consists of six genotypes. Genotypes I to III infect humans. [5] HAV is present in the host in two forms: naked virions (shed in the faeces), and quasi-enveloped virions (that circulate in the blood). Both forms are infectious and the synthetic genome-length RNA is infectious itself. [5] HAV does not have a significant direct cytopathic effect and most liver damage is due to the host immune response. Cellular immunity appears responsible for viral clearance after primary infection whilst humoral response has a direct role in the prevention of infection. Deficits of cellular immune response, such as HIV infection, can produce longer shedding (and infectivity) but without an apparent increase of symptom severity. [6,7]

b. Natural history

HAV causes an acute self-limiting hepatitis that normally resolves spontaneously. The average incubation period is between 2 and 4 weeks (but can be up to 8 weeks). [11] Clinical manifestations are characterized by the appearance of dark urine and sometimes clay-colored stool often accompanied or followed by jaundice. [8] The proportion of asymptomatic infections range between 30% in adults up to 90% in children under the age of 5 years. [5,11] Fulminant hepatic failure (FHF) is rare, and occurs more frequently among people older than 50 years and those with liver comorbidities. FHF is due to an excessive host response, associated with a reduction in viral load but a marked increase of INR, bilirubin and ALT. [5,6] Several studies suggested that HAV superinfection may lead to clearance of HBV and HCV chronic hepatitis. [5] Relapse of acute hepatitis A occurs in 3-20% of cases and prolonged or persistent cholestasis post-infection, although HAV is not associated with chronic infection. Rarely HAV has extra-hepatic manifestations such as pancreatitis, rash, acute kidney injury with interstitial nephritis or glomerular nephritis, pneumonitis, pericarditis, hemolysis, acute cholecystitis, mononeuritis, Guillan-Barre, encephalitis and central myelitis. HAV infection can precipitate auto-immune hepatitis.

c. Global epidemiology and transmission route

HAV infects between 1 and 2 million people annually. [9] Mortality rates are low at 0.3% [5,6,10]. HAV is a human infection transmitted by the feco-oral route via contaminated food and water and oro-anal sex . [11,12]. In *high endemic areas* with poor sanitation HAV is mainly a waterborne infection. In these settings ≥90% of the population have anti-HAV IgG by the age of 10 years, thus Large epidemics are paradoxically infrequent since most people contract AHA during childhood as asymptomatic infection or have mild infection. [9] In *intermediate endemic areas* HAV is mainly transmitted through contaminated food and water. These areas include countries with transitional economies or geographical settings. In these areas the prevalence of anti-HAV IgG is ≥50% by age 30 but <50% at the age of 15 years. The wide circulation of HAV causes large-scale outbreaks. [9,12,13] In *low endemic areas* HAV infections are associated with travel to high endemic areas and with oro-anal sex. Infection rates are very low and <50% of people older than 30 are immune to HAV [9]. Due to the heterogeneity of transmission modes, [14] AHA may occur as: sporadic cases in travelers, [15] small epidemic clusters [16,17] and large epidemics associated with special alimentary habits, [18] sexual behaviors [19] or special populations. [20] HAV vaccination in low and intermediate endemic settings is shifting the age to a disease of adults rather than early childhood.[21] Foodborne outbreaks are becoming more frequent in high-income countries and amongst the HIV-infected population, men who have sex with men, [19] the homeless and intravenous drug users. [20]

d. Diagnosis

Serology remains the gold standard for diagnosis of AHA. Anti-HAV IgM is recommended for new infection and can be detected at the same time as symptom onset. Anti-HAV IgG represent past infection and generally persists for life. Detection of HAV RNA, and analysis of clinical viral variant, may be useful for the molecular investigation of epidemic clusters. [5,11] HAV RNA is present in blood and feces soon after infection (whilst an individual is asymptomatic) until 1-2 week after symptoms onset. Longer shedding in feces can occur in children and those Infected with HIV. HAV is also shed in saliva and urine but no assays are available to detect this. [22]

e. Treatment and Prevention

There is no specific therapy for hepatitis A. The majority of cases require no specific treatment. [10] Liver transplantation is an option in the rare cases of FHF. Pre-exposure prophylaxis can prevent HAV infection. Two types of HAV vaccines are currently available: formaldehyde-inactivated vaccines and live attenuated vaccines (available only in China and India). [9,23] Traditionally, a two-dose schedule is recommended but, in healthy individuals, high level of immunity can be also achieved with a single dose.[9,24-25] Inactivated HAV vaccine is also available in combination with typhoid vaccine or HBV vaccine (three doses). Serological response to the inactivated vaccine may be diminished in those infected with HIV [26] and in older adults. [27] Targeted vaccination might be the most cost-effective intervention in low endemic areas, [9,28] while universal vaccination campaigns in intermediate endemic areas.[29] In high HA endemic settings, universal vaccine campaigns should be implemented along with improving sanitation and provision of safe drinking water. Sub-optimal vaccine campaigns can lead to an increment of the age of exposure with an increased incidence of severe clinical presentations. [5,9,11,12,13] Postexposure prophylaxis with either inactivated vaccine or specific anti-HAV IgG is effective when administered within 2 weeks of exposure. The inactivated vaccine is noninferior to specific anti-HAV IgG, and confers long-lasting immunity. [30]

2. Viral Hepatitis B

a. Virology

HBV is an enveloped, partially double-stranded DNA virus belonging to *Orthohepadnavirusgenu*s. It is classified in into ten genotypes (A–J). [31] The genome consists of 3020–3320 nucleotides (for the full-length strand) and 1700–2800 nucleotides (for the short length-strand). It contains 4 genes that encodes for 5 main proteins including: the polymerase (gene P); HBcAg (core protein on gene C), HBeAg (envelope antigen created by a different splicing of gene C); HBsAg (surface antigen on gene S) and HBx (a replication co-factor on gene X). [32] The HBV genome exists in different forms in infected individuals. The Dane particles are the infective enveloped visions. The covalently closed circular DNA (ccc-DNA) episomial nucleic acid moieties in the nucleus (5–50 molecules per infected cell) serve as an intra-nuclear transcriptional template for the synthesis of viral RNAs.

Finally, HBV may also exist as proviral DNA integrated in the nucleus (that has roles in the pathogenesis of chronic infection and oncogenesis). [33]

b. Natural history

Acute hepatitis B (AHB) occurs 45-180 days after exposure to HBV. The rate of symptomatic infection is associated with age: being less than 10% in children and about 50% in adults. FHF is rare, occurring in up to 1-4% of cases depending of patient's clinical background. [34] HBV may persist after acute infection and produce chronic hepatitis B (CHB) infection which is inversely associated with age: >90% in infants and <10% in those who develop AHB in adulthoods. The natural history of CHB is schematically divided into five phases. [35]

1) HBeAg positive chronic infection is a long period of asymptomatic infection that is frequent among young subjects and especially those perinatally infected. This phase is characterized by high viral replication (HBeAg and HBsAg positivity with high HBV DNA levels) and minimal (if any) liver damage.

2) HBeAg positive chronic hepatitis may immediately follow an acute infection or may start after several decades of chronic infection. This phase is characterized by sustained viral replication (HBeAg and HBsAg positivity with high HBV DNA levels) and significant liver damage.

3) HBeAg-negative chronic infection follows the loss of HBeAg and is characterized by suppression of viral replication with minimal on-going liver inflammation (HBV DNA levels less than 2000 U/L and normal plasma transaminases). This phase is associated with a low risk of liver disease progression.

4) HBeAg-negative chronic hepatitis may directly follow an acute hepatitis or start after decades of chronic HBeAg positive infection. This phase is characterized by the absence of HBeAg and persistent viral replication and liver damage (HBV DNA levels more than 2000 U/L and raised plasma transaminase levels).

5) HBsAg-negative phase is characterized by negative serum HBsAg and positive antibodies to HBcAg (anti-HBc), with or without detectable antibodies to HBsAg (anti-HBs). If HBsAg loss has occurred before the onset of cirrhosis, minimal risk of liver disease progression occurs. However, this phase can be associated with positive viraemia, known as ''occult HBV infection". HBV DNA can integrate into the hepatocyte genome, and all patients with CHB are at risk of HCC (hepatocellular carcinoma) regardless the level of liver damage.

c. Global epidemiology and transmission route

HBV only causes disease in humans. It is transmitted through sexual contact, via blood and vertically from mother to child. HBV infectivity is very high. HBV genotypes are congruent with distinct geographic distribution and mode of transmission. Genotypes A is frequent in Africa, North America and western European countries. It is more common among subjects with sexually acquired infection and it is associated with high rates of HCC. Genotypes

B and C are common in Asia where they are associated with perinatal infection. Genotype D predominates in the Mediterranean basin, Middle East and Central Asia; it has been historically associated with HBeAg-negative cirrhosis and HCC. Genotype E is an African genotype and has been correlated with high rates of HBeAg positivity and perinatal transmission. Genotype F is associated with high rates of HCC in South America and the Arctic Circle. Genotype H has not been well studied, and genotype G is usually found in a recombinant form, mostly with genotype A. Genotype I has recently been reported in Vietnam and Laos. The latest HBV genotype J, has been identified in the Ryukyu Islands in Japan.[31]

d. Diagnosis

HBsAg is the primary marker of active disease. Anti-HBc antibodies reflect virus exposure with either active or resolved natural infection. HBeAg reflects active viral replication. Anti-HBsAg antibodies represent the marker of immunity in vaccinated people and or resolved infection after natural exposure. Quantification of HBV DNA in blood is recommended for monitoring therapy and for diagnosis of occult hepatitis. Raised alanine transaminase levels indicate active liver inflammation.

e. Treatment and Prevention

A rich pipeline of novel therapies are shown in **Table 1**. These range from therapeutic vaccinations and other strategies to adapt the immune response (e.g. check-point inhibitors), to agents that directly target steps in the virus life-cycle (for instance entry inhibitors, capsid inhibitors, therapies to decrease sAg production/release and therapies that target the HBV nucleic acid (such as siRNA). It is probable that a combination of such new therapies will be needed to induce long-term off-treatment viral control, HBsAg loss or loss of ccc-DNA.

The main goals of antiviral therapy are sustained suppression of HBV replication and hepatic inflammation, thereby decreasing progression to cirrhosis and hepatocellular carcinoma. Severe AHB, characterized by coagulopathy or a protracted course, can be treated with nucleos(t)ide analogues. Patients should be considered for liver transplantation in the case of FHF. Long-term administration of nucleos(t)ide analogues with high barrier to resistance (i.e., entecavir, tenofovir disoproxil or tenofovir alafenamide), represents the treatment of choice for patients with CHB. [35] Pegylated interferon-alfa treatment can also be considered in mild to moderate CHB. Therapy is indicated if there is evidence of significant HBV replication and elevated plasma transaminases, or significant hepatic fibrosis (all cirrhotic patients with detectable HBV DNA should be treated). Other indications for HBV therapy include the prevention of mother to child transmission in pregnant women with high viremia and the prevention of HBV reactivation and flares in patients requiring immunosuppression and chemotherapy. [36]

Universal vaccination of children (using the recombinant anti-HBV vaccine) is most effective intervention to control HBV globally. Perinatal vaccination of infants born to mothers with HBV, catch-up vaccination programmes, sterile medical and other equipment, safe sexual practice and mitigation measures for persons who inject drugs (PWID) should be included in hepatitis control programmes.[37] Pharmacological treatment of HBV infection with nucleos(t)ide analogues or interferon may be indicated but has only a low impact as a public health intervention (with rates of clearance below 3%). [35]

f. HDV coinfection

HDV is a defective virus (virusoid) that can replicate only in persons with HBV infection. HDV can be transmitted either via simultaneous infection with HBV (coinfection) or via infection superimposed on CHB (superinfection). It is estimated that globally about 5-10% of patients with CHB are coinfected with HDV with higher prevalence in PWID populations [38] High-prevalence areas include the Mediterranean basin, Middle East, Indian Subcontinent, Japan, Taiwan, Greenland, the Horn of Africa, West Africa, the Amazon Basin and certain areas of the Pacific. HDV epidemiology and potential intervention for control are the same of HBV. [39]

3. Viral Hepatitis C

a. Virology

HCV is an enveloped positive sense single-stranded RNA virus belonging to *Flaviviridae*. It is currently classified in into eight genotypes (1–8). [40-41-42] The genome consists of 9,600 nucleotides within a unique ORF encoding for a unique polyprotein. This large pre-protein is cleaved by cellular and viral proteases into the 10 viral mature proteins. Structural proteins are assembled into mature viral particles and include the core protein (C) and the two envelope proteins (E1 and E2) that are important for cell entry. Non-structural (NS) proteins are essential for viral replication within the host but are not assembled into mature viral particles. The p7 protein is in the endoplasmic reticulum and plays a role in virus morphogenesis. NS2 integrates with the cellular membrane and has protease activity for viral particle maturation. NS3 is located within the endoplasmic reticulum and forms a heterodimeric complex with NS4A. NS3/NS4A complex has serine protease activity (NS3 N-terminal domain) and helicase activity (NS3 C-terminal domain). NS4B is located within the endoplasmic reticulum where it contributes to a structure known as the membranous web that plays an important role in viral particle assembly. NS5A binds to endoplasmic reticulum and plays a role in viral replication through modulation of cell signaling pathways and the interferon response. NS5B is the RNA dependent RNA polymerase.

b. Natural history

Humans are the only natural host of HCV. The incubation period of HCV infection is 14-180 days. Only less than 15% of infected people develop acute disease. Viral clearance occurs naturally in about 15% of these whilst the

remainder develop chronic hepatitis C (CHC). About one third of CHC patients develop cirrhosis over the subsequent 30 years, especially males with co-infections [43-44] such as HBV, *Schistosomiases*, HIV, alcoholics, obesity, insulin resistance. [45] Once cirrhosis occurs, there is a 1–5% annual risk of developing HCC and 3–6% risk of hepatic decompensation. Development of ascites is associated with a 1-year survival of 50%, spontaneous bacterial peritonitis, [46] variceal hemorrhage [47], hepatic encephalopathy and hepatorenal syndrome. CHC also induces extrahepatic metabolic and immunologic disorders. [48] HCV may have a direct role in the pathogenesis of insulin resistance and affects lipid metabolism pathways. HCV circulates in blood associated with lipoproteins forming "lipoviroparticles" and uses low-density lipoprotein receptors for hepatic cell entry. HCV affects lipid metabolism in three ways: a) enhancement of lipogenesis, b) reduction of lipoprotein degradation and c) impairment of lipoprotein export (liver steatosis). [49] Chronic stimulation of B-cells by HCV may lead to type 2 or 3 mixed cryoglobulinaemia, ischaemia, kidney injury and vasculitic syndromes. Persistent antigenic stimulation may induce malignant transformation of B-cells resulting in lymphoma. HCV is epidemiologically associated with auto-immune conditions [50] such porphyria cutanea tarda, Sjögren's syndrome, lichen planus and inflammatory arthritis.

c. Epidemiology and routes of transmission

Hepatitis C is transmitted from person-to-person mainly through the blood-borne route. Modes of transmission include use of contaminated needles in PWID. Perinatal transmission occurs in about 3%-10% of children born to HCV -infected mothers. [51] Increased risk of HCV through sex has been reported only for HIV positive men who have sex with men.[3] Different genotypes have different geographical distributions. [52] Genotype in Europe and North America accounts for >60% of HCV infections. Genotype 2 is locally endemic to west Africa and Latin America, [53] Genotype 3 in India and Pakistan, and genotype 6 in Thailand, [54] Myanmar, Laos and Vietnam. [55] Genotype 4 is predominant in North Africa and the Middle East and has been associated with an iatrogenic epidemic in Egypt. [56] Genotype 5 in Southern Africa occurs in up to 40% of HCV infections. [57] Genotype 7 was isolated in Democratic Republic of Congo in 2014. [41] Genotype 8 was reported in 2018 among Punjabi people living in Canada. [42]

d. Diagnostics

Diagnosis of infection is carried out by a combination of serology (anti-HCV IgG) and detection of HCV RNA in blood. Anti-HCV IgG are the biomarker for lifelong contact with infection while HCV RNA in essential for the diagnosis of active infection. Non-protective anti-HCV IgG may indeterminately persist after resolution of infection. HCV RNA is also crucial for monitoring response to anti-HCV therapy. Recently HCV-Ag has been proposed as substitute of HCV RNA testing in settings with low diagnostic capability. Laboratory tests for distinguishing between acute and chronic infection require validation. [58]

e. Treatment and prevention

Multiple direct-acting antivirals (DAAs), target specific steps within the HCV replication cycle, targeting specific nonstructural proteins. Four classes of DAAs, which are defined by their mechanism of action and therapeutic target are nonstructural proteins 3/4A (NS3/4A) protease inhibitors (PIs), NS5B nucleoside polymerase inhibitors (NPIs), NS5B non-nucleoside polymerase inhibitors (NNPIs), and NS5A inhibitors. European [59] and North American guidelines [60] recommend therapy for CHC using combination therapy comprising 2 or 3 DAAs. Treatment duration and DAA combination may change according to stage of liver diseases, genotype and previous failure with interferon. Infection clearance may be obtained in almost all naïve patients with 8 to 12 weeks while patients with cirrhosis may need longer therapy. All HCV RNA positive subjects should be initiated as soon as possible in patients with decompensated liver diseases who are not eligible for liver transplantation and those eligible for liver transplantation and MELD score < 18. **Table 2** shows recommended interferon and ribavirin free treatment for patients with CHC. Patients with MELD > 18 who are eligible for liver transplant might at best be treated after transplantation.

HIV and HBV coinfected subjects should be treated similarly to HCV mono-infected subjects but modification of antiretroviral therapy may be required before starting DAA treatment, and clinicians need to be alert to HBV flares associated with successful HCV treatment in HBV/HCV coinfected individuals. [59-60] All DAAs are contraindicated in patients receiving cytochrome P450 inducing agents due to the risk of significantly reduced concentrations of DAA. NS3/4A inhibitor are contraindicated in those with decompensated liver disease

Resolution of CHC is associated with remission of HCV extrahepatic manifestations. [49,61] and clearance of HCV may arrest progression of liver disease, and possibly revert fibrosis and hepatic decompensation [62] [63] Since clearance of chronic infection stops further transmission, anti-HCV therapy is considered to be a useful preventing further transmission.

4. Viral Hepatitis E

a. Virology and pathogenesis

HEV is a single-stranded, positive-sense RNA virus belonging to *Orthohepevirus* genus. There are eight HEV genotypes within a unique serotype. HEV-1 and HEV-2 are human viruses, while other HEV genotypes are enzootic viruses mainly found in swine (HEV-3 to HEV-6), rodents (HEV-3 and HEV-4) and camels (HEV-7 and HEV-8). The RNA is made of 7.2 kb and contains three or four ORFs. ORF1 polyprotein contains the replication machinery of the virus including methyltransferase, RNA helicase and RNA-dependent RNA polymerase. ORF2 contains the capsid protein while ORF3 encodes a functional ion channel that mediates the release of infectious viral particles. HEV-1 expresses an additional ORF (ORF4) that produces a nonstructural protein that has a role in

viral replication in human cells. [64] HEV is shed in faces as a non-enveloped virus but exists in a lipid enveloped form in blood. The lipid envelopment is essential for immune escape and viral dissemination to different body compartments. [65] HEV is a non-cytopathic virus and clinical presentations of the infection, including hepatic and extra-hepatic manifestation, are determined by the host immune response. [66]

b. Natural history

HEV1 and HEV2 are transmitted person-to-person, and are generally associated with acute, self-limiting hepatitis. However, HEV1 can cause severe infection in pregnancy, where it is associated with FHF and stillbirth. [67] HEV3, HEV4 and HEV7 are associated with self-limiting hepatitis in immunocompetent hosts, though rarely this can progress to FHF in the elderly. [68] Infection in immunocompromised hosts results in persistent infection associated with rapid progression toward cirrhosis and liver decompensation. [59] The clinical relevance of HEV5, HEV6 and HEV8 is unclear. HEV1 and HEV3 cause a wide range of extra-hepatic manifestations including acute neurological diseases, myositis, renal diseases, acute pancreatitis, arthritis, autoimmune thyroiditis and myocarditis. HEV has been isolated in cerebrospinal fluid suggesting a potential causal link between HEV infection and neurological diseases including Guillain–Barré syndrome, neuralgic amyotrophy, encephalitis and acute myelitis.[69] The immuno-pathological mechanisms associated with the increased HEV virulence during pregnancy, the persistence of infection in immunocompromised hosts and the extrahepatic manifestation are unclear. Whether humoral immunity mediated by anti HEV IgG can protect from re-infection remains to be defined. [70,71]

c. Global epidemiology and transmission route

HEV has received increased attention recent as an emerging infection. [72] Distribution of HEV genotypes is congruent with specific geographical areas and different modes of transmission. [73] HEV1 and HEV2 are human pathogens transmitted largely through the waterborne route causing outbreaks in poor setting in Asia, [74] Africa [75-76] and Latin America. [77] HEV1 and HEV2 cause about 20.1 million new infections annually and 70,000 deaths. [78] HEV3, HEV4 and HEV7 [79] are enzootic viruses associated with small clusters of infection among people with close contact with animals or after consumption of animal products. HEV4 can infect humans and swine and is associated with zoonotic infections in high-income Asian countries. [80] Apart from rare cases of iatrogenic transmission there is no strong evidence of direct person-to-person transmission of HEV other than genotype 1 and 2. [81]

d. Diagnostics

Serological and molecular tests for detecting acute and past HEV infection have been developed for both epidemiologic and diagnostic purposes. Detection of HEV RNA in blood or plasma represents the gold standard for diagnosis of AHE. Serologic tests detecting anti-HEV IgM and HEV antigen. Anti-HEV IgG antibodies can last

more than 10 years after infection and recognize past infection. There are nine different serology assays for the detection of anti-HEV IgG. [82] Inter-assay concordance is suboptimal and a recent meta-analysis suggested that results from population studies performed with different assays cannot be directly compared. [83] Molecular test for direct assessment of the viral load is the more appropriate in immunocompromised patients. [70] Neurological involvement appears to be directly associated with recent HEV infection and cerebrospinal fluid abnormalities may be found in patients with mild (anicteric) HEV infection.[84-85]

e. Therapy and prevention

AHE does not require treatment. However, pregnant women with acute infection should be strictly monitored as they may develop FHF. HEV3 and HEV4 have been associated in persistent infection in immunocompromised subjects including organ transplant recipients, patients with AIDS and those with haematological malignancies. The mainstay of management is to ensure optimal antiretroviral therapy for HIV infected patients and reduction of immunosuppression in transplant recipients. In patients with persisting HEV replication for >3 months, ribavirin treatment for 12 weeks is recommended. Twelve additional weeks of therapy can be given to non-responders. Non-response to ribavirin may be associated with single nucleotide variants in the virus, which may be present as a baseline minor variant. [86] Therapy with pegylated interferon alpha may be considered in liver transplant recipients who did not respond to ribavirin. [70] Prevention of human HEV genotypes (HEV1 and HEV2) involves providing better sanitation standards in low-income countries. Zoonotic genotype spread (HEV3, 4 and 7) in more affluent settings can be prevented by avoiding the consumption of raw or undercooked meat products, or attempts to decrease the prevalence of this infection via animal husbandry. In the Democratic Republic of China a recombinant vaccine (Hecolin) is available based on a 239 amino acid peptide derived from the Chinese HEV1 strain. The protective efficacy of this vaccine for symptomatic disease has been demonstrated in areas with known circulation of HEV1 and HEV4, but its efficacy against other HEV genotypes is unknown. [87]

5. Conclusion: towards global control of viral hepatitis

Viral Hepatitis due to Hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D (delta) virus (HDV) and hepatitis E viruses (HEV) affects hundreds of millions of people globally. Most deaths from viral hepatitis are due to hepatitis B and hepatitis C. The WHO has set the ambitious target to eliminate viral hepatitis by achieving a 90% reduction of new HBV and HCV infections by 2030. A shift in emphasis from the current focus on individuals to a coordinated public health to interrupt transmission is required to achieve this. Endemic infections may be eradicated by immunizing susceptible subjects or depleting the reservoir of chronically infected subjects by mass treatment. In HBV the former is possible, and the pipeline of future

therapies may allow us to explore the potential of the latter in future years. A major challenge for the elimination of HBV and HCV globally is the lack of guaranteed access to diagnostics, vaccine and drugs.

Tables

Table 1. Current clinical pipeline and therapies for Hepatitis B and Hepatitis D

Hepatitis B Pipeline & Current Therapies				
Life-Cycle Target	**Phase 1**	**Phase 2**	**Phase 3**	**Licensed in US/Europe**
Nucleos(t)ide analogues		CMX 157		Adefovir Entecavir Lamivudine Telbivudine Tenofovir Disoproxil Fumarate Tenofovir Alafenamide
siRNA-based	AB-729 DCR-HBVS	ARB-1467 ARO-HBV RG6004 Vir-2218		
Entry Inhibitor		Myrcludex B		
Capsid Inhibitor	AB-423 AB-506 ABI-H2158 QL-007 RG7907	ABI-H0731 JNJ 56136379 Morphothiadin		
HBsAg Inhibitors		REP 2139 REP 2165		
Anti-Sense Molecules		GSK3228836 GSK33389404		
Immune System Targeting				
Interferons				Interferon alfa-2a Interferon alfa-2b
Therapeutic Vaccines	AIC 649 HB-110 HepTcell INO-1800 TG1050			
Innate Immune Activators	GS9688 RG7854 S9688	Inarigivir RG7795		
Apoptosis Inducers	APG-1387			
Anti-sAg Antibodies		GC1102		
Farnesoid X Receptor Agonist	EYP001			
Hepatitis D Pipeline & Current Therapies				
	Phase 1	**Phase 2**	**Phase 3**	**Licensed in US/Europe**
Varied		Ezetimibe Myrcludex B Lonafarnib REP 2139 REP 2165	Interferon-lambda	Interferon alfa-2a Interferon alfa-2b

Table 2: Recommended Interferon and ribavirin treatment for patients with CHC.

HCV Genotype	Type of Patient	SOF/VEL 1QD	GLE/PIB 3QD	SOF/LDV 1QD	GZR/EBR 1QD	3D [E] 2QD+1BID
1a	Naive without cirrhosis	12	8	8[A C]	12[B]	
	Naive with cirrhosis	12	12	12	12[B]	
	Experienced without cirrhosis	12	8		12[B]	
	Experienced with cirrhosis	12	12		12[B]	
1b	Naive without cirrhosis	12	8	8[A C]	8[A]	8[A]
	Naive with cirrhosis	12	12	12	12	12
	Experienced without cirrhosis	12	8	12	12	12
	Experienced with cirrhosis	12	12	12	12	12
2	Naive without cirrhosis	12	8			
	Naive with cirrhosis	12	12			
	Experienced without cirrhosis	12	8			
	Experienced with cirrhosis	12	12			
3	Naive without cirrhosis	12	8			
	Naive with cirrhosis	12[D]	12			
	Experienced without cirrhosis	12	12			
	Experienced with cirrhosis	12[D]	16			
4	Naive without cirrhosis	12	8	12	12 [B]	
	Naive with cirrhosis	12	12	12	12 [B]	
	Experienced without cirrhosis	12	8			
	Experienced with cirrhosis	12	12			
5	Naive without cirrhosis	12	8	12		
	Naive with cirrhosis	12	12	12		
	Experienced without cirrhosis	12	8			
	Experienced with cirrhosis	12	12			
6	Naive without cirrhosis	12	8	12		
	Naive with cirrhosis	12	12	12		
	Experienced without cirrhosis	12	8			
	Experienced with cirrhosis	12	12			

(Figures within white squares indicated the duration of treatment in weeks. Black square indicates that the treatment is not recommended).

SOF/VEL: Sofosbuvir/velpatasvir; **GLE/PIB**: Glecaprevir/pibrentasvir; **SOF/LDV 1QD**: Sofosbuvir/ledipasvir; **GZR/EBR**: Grazoprevir/elbasvir; **3D**: Ombitasvir/paritaprevir/ritonavir/Dasabuvir; **1QD**: one tablets one time daily; **2QD**: two tablets one time daily; **1BID**: one tablet two times daily.

A: 12 weeks treatment required if patients has Metavir F3 fibrosis
B: recommended only for patients with HCV RNA ≤800,00 IU/mL
C: 12 weeks treatment are needed for those who are Afro-Caribbean in origin, HIV infected or those who have HCV RNA level is <6 million IU/mL
D: only recommended for patients who tested negative for Y93H RAS at baseline, all other patients need addition of Voxilaprevir (VOX) or ribavirin if it is unavailable.
E: 3D is not available in fixed doses combination -it requires Ombitasvir/paritaprevir/ritonavir 2 tablets once daily and 1 tablet of Dasabuvir twice daily.

Figure Legends

Figure 1. Global distribution of deaths due to viral hepatitis. The GBD estimates that in 2017 viral hepatitis has caused about 1.4 million deaths (range 1.2 – 1.6; see figure 2).
This analysis reports
the number of deaths per 100,000 inhabitants due to viral hepatitis in 196 territories all around the world for the year 2017 (fatality rate) for: **(A)** people aged less than 50 years and **(B)** people aged 50 years or more.
The burden of viral hepatitis is the heaviest among older adults as the consequence of late sequalae of chronic infections and severe presentation of acute viral hepatitis. Asia, Egypt, Sub-Saharan Africa are the geographical areas where viral hepatitis took most life in 2017. Fatalities for viral hepatitis in Italy and Japan were still relatively high among older people due historical issues. In contrast Russia and Eastern Europe countries experienced a relatively high number of fatalities among young people; this phenomenon is alarming and potentially associated with the surging number of new infections reported in these areas since the early 1990's
Data source.
Estimates: Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2017 (GBD 2017) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2018. Available from http://ghdx.healthdata.org/gbd-results-tool.
Maps: Esri, HERE, Garmin, Intermap, increment P Corp., GEBCO, USGS, FAO, NPS, NRCAN, GeoBase, IGN, Kadaster NL, Ordnance Survey, Esri Japan, METI, Esri China (Hong Kong), swisstopo, © OpenStreetMap contributors, and the GIS User Community

Figure 2. Global number of deaths associated with viral hepatitis according to clinical conditions. : **(A)** people aged less than 50 years and **(B)** people aged 50 years or more.
Data source. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2017 (GBD 2017) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2018. Available from http://ghdx.healthdata.org/gbd-results-tool.

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