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*MINIREVIEWS*

# Viral hepatitis: A brief introduction, review of management, advances and challenges

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## Abstract

Viral hepatitis represents a major public health hazard and is associated with significant global mortality. Over the last decade, there have been significant developments in the prevention and treatment of viral hepatitis. These changes have led to a situation whereby global elimination has become a realistic goal, fully endorsed by the World Health Organization (WHO). By 2030, the WHO aims to reduce viral hepatitis mortality by 65% and reduce new infections by 90% by 2030. These are ambitious targets and will only be met through a sustained programme. This will require expertise from hepatologists and virologists and the fields of public health and primary care. In this article, we review the causes of viral hepatitis, its management through prevention and treatments, and the most pressing challenges and recent advances.

**Key Words:** Viral Hepatitis; Management; Direct-acting antivirals; Advances; Challenges



**Core Tip:** Viral hepatitis represents a major public health hazard and is associated with significant global mortality. The aim of this article is to provide a concise description of the management, advances and challenges in the field of hepatitis caused by hepatotropic viruses A-E.

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## INTRODUCTION

Viral hepatitis has a high prevalence and is a leading cause of death worldwide, accounting for 1.34 million deaths worldwide in 2015[1]. Lots of different viruses are known to cause liver inflammation, including hepatotropic viruses named A to E. Most of these result in acute self-limiting disease; however, hepatitis B (HBV), HCV, HDV and HEV can become chronic (Table 1). Other viruses (such as Cytomegalovirus and Epstein-Barr virus) can also cause hepatitis as part of a systemic infection. This review considers only hepatitis caused by hepatotropic viruses.

Hepatitis A and E are transmitted through the faecal-oral route by contact with contaminated food or water[2]. In contrast, hepatitis B, C and D are transmitted through bodily fluids[3].

Chronic hepatitis is defined as chronic inflammatory reaction in the liver, as reflected in liver function tests and histology for at least 6 mo[4]. Chronic hepatitis B/C/D/E is defined as the presence of virus (in blood, or in stool for HEV) for more than 6 mo after the new onset of infection. Acute liver failure (ALF) is a syndrome of severe hepatic dysfunction associated with encephalopathy and/or coagulopathy. The American Association for the Study of Liver Diseases (AASLD) define it as "evidence of coagulation abnormality, usually an international normalized ratio above 1.5, and any degree of mental alteration (encephalopathy) in a patient without pre-existing liver disease and with an illness of less than 26 wk' duration"[5]. Globally viral hepatitis remains a large causal contributor to ALF[6] and accounts for the majority of ALF in Asia and Africa[7]. Viral induced ALF is associated with mortality of 18%-91% (with a combined mortality of 50%) in low income countries compared with 3%-45% (with combined mortality of 26%) in upper middle income countries[7].

## EPIDEMIOLOGY

### *HAV*

The World Health Organization (WHO) estimated in 2005, 126 million people were affected[8]. Unsurprisingly, the highest rates of HAV infection are found in areas with poor sanitary conditions[9].

### *HBV*

Roughly 30% of the world's population show evidence of current or past infection with HBV[10]. Globally, most HBV infections occur through vertical mother-to-child and early-life horizontal transmission[11].

There are 5 phases of chronic HBV infection[12]. (1) Phase 1: High replicative state with hepatitis B e-antigen (HBeAg)-positive (previously known as 'immune tolerant'). High HBV-DNA levels > $10^6$ IU/mL, often normal or slightly increased alanine transaminase (ALT) levels; minimal or no inflammatory changes on liver biopsy; (2) Phase 2: HBeAg-positive chronic HBV. Variable HBV-DNA levels, higher ALT than the previous phase; moderate/severe inflammatory changes on liver biopsy. Can last for months to years; (3) Phase 3: HBeAg-negative chronic HBV (previously known as 'inactive carrier'). Generally, low HBV-DNA levels, normal ALT; the severity of fibrosis depends on the previous stage, but active inflammation is low; (4) Phase 4: HBeAg-negative chronic hepatitis. Variability in HBV-DNA level, ALT and inflammatory changes on liver biopsy. The annual spontaneous clearance of chronic HBV is about 1%[13]; and (5) Phase 5: Occult infection [Hepatitis B surface antigen (HBsAg)-negative]. Undetectable/very low serum HBV DNA with hepatitis B core antibody (Anti-HBc), with or without hepatitis B surface antibody and normal ALT. HBsAg loss before the development of cirrhosis is associated with minimal risk of cirrhosis and improved survival. Immunosuppression may lead to HBV reactivation in these patients.

**Table 1 Comparison of hepatotropic viruses hepatitis A-E**

| Hepatitis | A | B | C | D | E |
|---|---|---|---|---|---|
| Viral structure | Naked, ssRNA (Picornavirus) | Envelope, dsDNA (Hepadnavirus) | Envelope, ssRNA (Flavivirus) | Envelope, ssRNA (-ve) (Deltavirus) | Naked, ssRNA (Hepevirus) |
| Transmission | Faecal-oral | Parenteral, sexual | Parenteral, sexual | Parenteral, sexual | Faecal-oral |
| Incidence | 1.4 million | > 250 million[88] | > 80 million | About 12 million (prevalence)[89] | 20 million |
| Chronic infection | No | About 90% of infants infected; about 2%-6% adult infected | 70% (55%-85%) | < 5% of those infected with HBV, > 80% of superinfection)[90] | No (very rarely in immunosuppressed adults)[91] |
| Other disease associations | None | HCC, cirrhosis | HCC, cirrhosis | Cirrhosis, fulminant hepatitis | None (cirrhosis in chronic HEV infection) |
| Treatment | Supportive | Viral suppressive therapy (see criteria for commencement of treatment below) | Eradication therapy DAA (gold standard) | PEG-IFN (sparse data) | Supportive |

HBV: Hepatitis B virus; HEV: Hepatitis E virus; HCC: Hepatocellular carcinoma; DDA: Direct-acting antiviral.

The HBV genome incorporates into the host genome and is postulated to have an oncogenesis effect contributing to hepatocellular carcinoma (HCC) development[14]. Assay of the novel (or "emerging") biomarker hepatitis B core-related antigen (HBcrAg) is helpful in monitoring patients with chronic HBV infection. Serum HBV DNA correlates with HBcrAg. In patients with undetectable HBV DNA or loss of HBsAg, HBcrAg can still be detected[15]. Decreasing HBcrAg titres are associated with positive outcomes for chronic HBV infected patients[16].

### HCV

It is estimated 1.75 million people were newly infected with HCV in 2015[17]. It is the most common bloodborne infection in the USA and the western world[18]. Ninety per cent of HCV infections will progress to chronic liver disease[19]. The most common risk factor for HCV contraction is intravenous drug use, accounting for 80% of cases, with receipt of blood products representing 10.8%[20]. Other less common routes of transmission include organ transplantation, haemodialysis and tattooing.

The WHO estimated that 71 million people were living with chronic HCV infection in 2015[21]. This, however, is not reflected in diagnoses: Only 20% of those who were estimated to be infected were diagnosed in 2016[21], and only 13% of these were treated with direct-acting antivirals (DAAs).

Eighty per cent of HCV infections are found in 31 of 194 countries, with the highest incidences found in Eastern Mediterranean and Eastern European countries[22].

Due to this propensity of the virus to develop into fibrosis, cirrhosis, and HCC, the death rate from HCV is rising despite a reduced incidence. Chronic HCV is often complicated by extra-hepatic diseases such as cryoglobulinemia associated vasculitis, renal disease, and type 2 diabetes[23]. These factors reinforce the importance of treating HCV.

### HDV

The incidence and prevalence of HDV is largely uncertain[21]. Some estimate 12 million cases globally; however, there is speculation this could be even higher with cases as high as 60 million[24].

### HEV

Twenty million infections of HEV are estimated annually with about 3 million of these causing symptomatic disease[25]. This is predominantly found in south and east Asia, with genotypes 1-4 of 8 affecting humans[26]. This is predominantly transmitted through the faecal-oral route; however, other more recently discovered modes of transmission include blood transfusion, zoonotic infections (through consumption of infected meats) and organ transplants[27].

## DIAGNOSIS

The diagnoses of viral hepatitis are primarily made through both serological and molecular assays[28,29]. Serological tests can be either rapid diagnostic tests (field use) or laboratory-based enzyme immunoassays (Table 2).

There is a difficulty in diagnosing viral hepatitis as a cause of ALF. A study in Germany found nearly 50% of cases of HEV causing ALF were misdiagnosed as drug induced liver injuries[30]. Serological testing of HEV alone is often insufficient and molecular testing with polymerase chain reaction needs to be considered more[31].

## PREVENTION

Interventions to mitigate contraction of viral hepatitis include sanitation, vaccination, harm reduction policies and safe blood supply practices.

### *Sanitation*

Sanitation has improved worldwide, resulting in reduced annual numbers of diarrheal diseases and of HAV and HEV infections[32].

### *Vaccination*

An effective HAV vaccine has existed since 1992. Adopting wide-scale HAV vaccination depends on socioeconomic conditions. Thirty-four countries have successfully introduced or are planning to introduce universal childhood HAV vaccination as of 2019[33].

The widespread introduction of a universal childhood HBV vaccine (3 doses) has reduced acute and chronic HBV infection worldwide. In 2013, 183 of 194 countries had introduced the HBV vaccine, and worldwide coverage with three HBV vaccine doses was estimated at 81%[34]. The use of antivirals in pregnant mothers with high HBV levels and immunoglobulins with HBV vaccination in infants born within 12hrs can prevent vertical transmission[35,36].

### *Needle and syringe programmes*

Needle and syringe programmes are known to reduce the incidence of HIV without increasing the frequency of persons injecting drugs[37]. The data for reducing HCV incidence are equivocal; as HCV is more efficiently transmitted the aim would be for individuals to inject for the first time in the facility with clean needles and not contract HCV[38].

### *The advent of standardised HEV testing in meat*

HEV infection has increased 10-fold over the past 10 years in Europe. Food-borne infections are linked predominantly with pig meat but also wild boar and deer meat. Currently the only prevention or control option is heat treatment and adequate cooking. Presently the awareness of HEV infection risk associated with undercooked pork is poor and could be optimised[39].

## REVIEW OF MANAGEMENT

Management of acute viral hepatitis is mainly supportive except in the instance of ALF, which requires urgent referral to a liver transplant centre to evaluate liver transplantation.

### *Treatment*

**HAV:** Supportive management is the mainstay of treatment for HAV, which commonly resolves spontaneously.

**HBV:** When considering management of HBV, one must remember that the virus itself is not cytopathic. Therefore, the clinical outcome following infection depends on the complex interplay between host immune response and viral replication. Acute HBV treatment is mainly supportive. The goal of therapy in chronic HBV is viral suppression to improve/stop liver inflammation and reduce the risk of cirrhosis, HCC and other complications[12,40].

**Table 2 Diagnosing hepatitis A-E**

| Hepatitis | Serological testing | Molecular testing (*via* PCR), quantitative |
|---|---|---|
| A | Anti-HAV IgM (acute); Anti-HAV IgG (previous infection, vaccination); Note incubation period of 28 d[92] | HAV RNA |
| B | Anti-HBc (contact with HBV infection); HBsAg (current infection) appears 1-3 wk post exposure, duration > 24 wk denotes chronicity; Anti-HBS (vaccination, cleared HBV infection); HBeAg (high replication phase (> 10000 IU/mL); Anti-HBe (low replication phase (< 10000 IU/mL); Note incubation 90 d (ranges 45-160 d); Window period 1: first about 8 d of infection; Window period 2: clearance of HBsAg during this period Anti-HBc IgM is detectable[93] | HBV DNA |
| C | Anti-HCV: Note incubation 6-7 wk (ranges 2 wk to 6 mo)[93] | HCV RNA |
| D | Anti- HDV IgG | HDV RNA |
| E | Anti-HEV IgM and IgG and IgA | HEV RNA |

HBV: Hepatitis B virus; HCV: Hepatitis C virus; HDV: Hepatitis D virus; HEV: Hepatitis E virus; PCR: Polymerase chain reaction; HBsAg: Hepatitis B surface antigen.

Antiviral choices include tenofovir, entecavir, lamivudine, adefovir and telbivudine[41]. The treatment of chronic HBV depends on multiple factors, including the severity of inflammation/fibrosis, cirrhosis, ALT, E-Ag status, age and family history of HCC. The aim of chronic HBV therapy is the chronic sustained inhibition of viral replication, as curative rates are very low.

Table 3 sets out the recommended European Association for the Study of the Liver (EASL) guidelines for the treatment of those with chronic HBV.

Pegylated interferon-a (PEG-IFN-a) is a first line treatment option in chronic HBV infection. The advantage of PEG-IFN-a over nucelos(t)ide analogues is the finite treatment course, together with superior rates of HBsAg and HBeAg seroconversion[42]. However use of PEG-IFN-a is associated with greater adverse effects including psychiatric, neurologic and endocrinological, effects[43].

**HCV:** Acute HCV infection often results in mild acute illness lasting 2-12 wk, with less than 25% of infections identified clinically[44]. Eighty to ninety per cent go on to develop chronic HCV infection with 10%-20% of patients developing complications, including cirrhosis and HCC over decades[45]. DAAs are the mainstay of HCV treatment currently (Table 4). DAAs are highly effective at clearing the virus in > 90% of people. Sustained virologic response (SVR) is defined as aviremia 24 wk post completion of antiviral therapy for HCV infection[46]. However, there is some evidence to support the determination of SVR at 12 wk[47]. SVR at 24 wk remains the gold standard. EASL and the AASLD recommend that all HCV patients (both naïve and treatment-experienced) be offered therapy. Different genotypes respond better to different DAAs (Table 5). Pan-genotypic HCV drug regimens, including (sofosbuvir/velaptasvir) and (glecaprevir/pibrentasavir), can be used to treat patients without identifying their HCV genotype, simplifying therapy[48].

**HBV/HDV:** HDV is a major cause of severe acute and chronic hepatitis[49]. HDV requires the presence of HBV infection for its own viral cycle. HBV/HDV co-infection results in chronicity in 2% of cases; however, superinfection of HDV is associated with 90% chronicity. HDV is a highly pathogenic virus resulting in the most severe chronic hepatitis and the development of cirrhosis within 10 years of infection in 80% of cases[50]. Pegylated interferon can be used as a treatment, although significant data are lacking[51]. Currently HDV treatments are in phase II and III trials.

**HEV:** HEV infection is usually self-terminating in immunocompetent individuals, typically with detectable serum/stool HEV RNA present for approximately three weeks. In acute self-limiting disease, symptomatic management and management of cholestasis is the primary treatment.

Chronic hepatitis E infection is associated with genotypes 3, 4, 7[27,52]. In endemic areas, the faecal-oral route is the main mode of transmission, while in the developed world food-borne transmission is most common. Most chronic HEV infections are reported in developed countries and thus zoonotic transmission is assumed (through consumption of contaminated meat). Immunocompromised individuals are at an increased risk of contracting chronic HEV infection[53]. The high virulence of genotype 1 may increase the risk of chronic infection. Ribavirin is the agent of choice in

**Table 3 European Association for the Study of the Liver 2017 clinical practice guidelines on the management of hepatitis B virus infection[12]**

| Clinical practice guidelines |
|---|
| All patients with HBeAg-positive or -negative chronic hepatitis B, defined by HBV DNA (2000 IU/mL, ALT) upper limit of normal (ULN) and/or at least moderate liver necroinflammation or fibrosis, should be treated (Evidence level I, grade of recommendation 1) |
| Patients with compensated or decompensated cirrhosis need treatment, with any detectable HBV DNA level and regardless of ALT levels (Evidence level I, grade of recommendation 1) |
| Patients with HBV DNA (20000 IU/mL, and ALT) 2 × ULN should start treatment regardless of fibrosis degree (Evidence level II-2, grade of recommendation 1) |
| Patients with HBeAg-positive chronic HBV infection, defined by persistently normal ALT and high HBV DNA levels, may be treated if they are older than 30 years regardless of the severity of liver histological lesions (Evidence level III, grade of recommendation 2) |
| Patients with HBeAg-positive or HBeAg-negative chronic HBV infection and family history of HCC or cirrhosis and extra-hepatic manifestations can be treated even if typical treatment indications are not fulfilled (Evidence level III, grade of recommendation 2) |

HBV: Hepatitis B virus; HBeAg: Hepatitis B e-antigen; ALT: Alanine transaminase.

**Table 4 Comparing pegylated-interferon therapy to nucelos(t)ide analogues therapy**

| | PEG-IFN | NA |
|---|---|---|
| Route of administration | Subcutaneous | Oral |
| Length of treatment | 48 wk | Long-term in chronic HBV (stopping may be considered in some cases[13]); 8-16 wk in HCV |
| Contraindications | Many (*i.e.*, decompensated disease, comorbidities) | None (dose adjustment according to eGFR) |
| Tolerance | Inferior tolerability | Excellent tolerance |
| Side effects | Significant adverse events (psychiatric, neurologic, endocrinological) | Renal impairment (some DAA)[12] |
| SVR in HCV | 40%-75%[94,95] | > 90%[46] |
| Efficacy in chronic HBV | > 30% HBeAg loss; 3%-5% HBsAg loss[96] | > 11%-18% eAg loss (lower rate of HBeAg seroconversion); Very low HBsAg loss[97] |
| Cost | Expensive | Expensive when given long-term (*i.e.*, chronic HBV infection)[98] |
| Resistance | No | Yes |

PEG-IFN: Pegylated interferon; NA: Nucelos(t)ide analogues; HCV: Hepatitis C virus; HBeAg: Hepatitis B e-antigen; HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; DDA: Direct-acting antiviral.

**Table 5 First-line recommended direct-acting antiviral therapies for hepatitis C patients**

| Genotype | 1 | 2 | 3 | 4 | 5/6 |
|---|---|---|---|---|---|
| DAA schedule (non-cirrhotic) | Sofosbuvir/Ledipasvir; Or Glecaprevir/Pibrentasvir | Sofosbuvir/Velpatasvir | Sofosbuvir/Velpatasvir | Sofosbuvir/Ledipasvir | Sofosbuvir/Ledipasvir |
| Duration | 8-12 wk | 12 wk | 12 wk | 12 wk | 12 wk |
| DAA schedule (cirrhotic) | Sofosbuvir/Ledipasvir | Sofosbuvir/Velpatasvir | Glecaprevir/Pibrentasvir | Sofosbuvir/Ledipasvir | Sofosbuvir/Ledipasvir |
| Duration | 12 wk | 12 wk | 8-16 wk | 12 wk | 12 wk |

DDA: Direct-acting antiviral.

chronic HEV infections[54]. Genotype 1 HEV infection can be severe in pregnancy. It has been associated with preterm labour and a maternal mortality rate of up to 30% in the third trimester[55].

The development of a HEV vaccine (Hecolin), licensed in China, has shown promise and efficacy in preventing HEV genotype 4 infection in healthy individuals 16–65 years[56].

## ADVANCES

### *HAV*

The WHO's 1992 recommendation of universal mass vaccination programmes in countries with a high risk HAV exposure has led to positive outcomes. The introduction of universal vaccination in countries with endemic HAV infections has resulted in decreased incidence of HAV as well as reduced cases amongst non-vaccinated individuals. Incidence reductions of 88% in Argentina, > 95% in Israel, 93% in Panama and 96% in Uruguay were observed over a 5-10 year period post introduction of a vaccination programme[57].

### *HBV*

**WHO elimination strategy:** The WHO and its member states aim to eliminate viral hepatitis by 2030. This is a historic commitment which has allowed for funding and resource advocacy internationally. Undoubtedly the impact of the current global pandemic with COVID-19 coronavirus will adversely impact the provision of resources and funding.

**Updated HBV treatment guidelines on therapy discontinuation:** International guidelines have outlined endpoints for nucleos(t)ide analogues withdrawal, the optimum of which is loss of HBsAg. This is rarely achieved, however, due to the presence of covalently closed circular DNA (cccDNA). Surrogate markers of efficacy have been developed including viral suppression, transaminases normalisation and HBeAg seroconversion[12]. These markers are associated with cessation of inflammation and fibrosis advancement[58]. These surrogate markers are now considered as potential alternative endpoints: the seroconversion of HBeAg in non-cirrhotic patients with normal ALT levels and viral suppression can discontinue treatment post 1 year[12,59] (or 3 years as per APASL). Over the last year there is growing evidence of the potential benefit of stopping nucelos(t)ide analogue treatment in selected groups, including a greater reduction in quantitative HBsAg seroconversion in those who discontinue nucelos(t)ide analogue treatment[60,61].

### *HCV*

**Advent of DAAs allowing successful HCV eradication:** The advent of DAAs with complete eradication of the HCV is one of the most critical advances in hepatology. Their increased efficacy, safety and tolerability make DAAs a welcome alternative to interferon-based therapy. These treatments now boast SVR rates > 90%.

Interferon-alpha (IFN-a) monotherapy was the mainstay of treatment until the 1990s. The advent of IFN-a and ribavirin combination therapy saw SVR of 38% with a 48-wk course[62]. This was further boosted to an SVR rate of 55% using pegylated-IFN[63]. Increased understanding of the HCV's molecular virology and life cycle enabled the synthesis of the first DAAs, namely the Ns3/4A protease inhibitors telaprevir and boceprevir. These, when used in combination with Peg-IFN and ribavirin, achieved an SVR rate of 65%-75%[64]. Use of this 'triple therapy' gained FDA approval in 2011. Later, sofosbuvir's development achieved 82 and 95% SVR rates when used with ribavirin alone[65]. The use of a DAA therapy alone (sofosbuvir and ledipasvir) demonstrated SVR rates of 94%-99% at 12 wk in three pivotal trials comparing DAA combinations (with and without ribavirin) in both treatment-naïve and treatment-experienced patients[66-68]. There are currently 10 FDA-approved DAAs.

### *HDV*

**Development of new treatments:** Newly developed treatments for HDV are promising. These include viral assembly point inhibitors, virus entry point inhibitors (Bulvertide phase II and III trials NCT03852719, approved by EU in July 2020)[69] and prenylation inhibitors (lonafarnib in combination with ritonavir and Peg-IFN, phase III trials NCT03719313)[70].

### *HEV*

**Improved understanding of its pathogenesis and extra-hepatic manifestations:** Improved understanding and awareness of extra-hepatic manifestations has improved HEV diagnosis and thus treatment. These include conditions such as Guillain-Barré[71,72], cryoglobulinemia's[73], cardiac arrythmias[74] and pancreatitis[75] to name a few.

Development of HEV vaccine in China has proved effect further study is needed to demonstrates it long-term effect[56].

## CHALLENGES

### *HBV*

**Prevention of vertical transmission in African countries:** The first HBV vaccine dose should be administered within 24 h of birth ("the birth dose"). This has proven challenging, particularly in countries where home births predominate. Only 94 of 194 countries have established scheduled birth dose HBV vaccination, with an estimated 38% of children worldwide receiving this crucial dose[1]. This needs to be addressed in an attempt to reduce vertical transmission.

**Difficulty with early diagnosis:** As previously mentioned in this article, HBV is underdiagnosed and indeed people are often diagnosed late in life. In Asia, HBV is the main cause of HCC and the main cause of liver transplantation[76]. Failure to access diagnostics and a lack of screening programmes perpetuate this situation[28].

**Reactivation in the context of Immunosuppression:** HBV reactivation is the reappearance or rise of HBV DNA in those with past or chronic HBV infection. Reactivation may occur in a range of clinical scenarios predominantly in the context of an immunosuppressed state of immunosuppressive therapy. Reactivation of HBV is frequently reported in patients undergoing chemotherapy for haematological malignancies and post hematopoietic stem cell transplants[77].

**Chronic HBV relapse:** In contrast to HCV, the current antiviral therapy does not have the potential of HBV eradication. cccDNA is a replication template of HBV: The pre-genomic portion can be reverse transcribed into DNA. This cccDNA is not targeted by antiviral nucleot(s)ide analogues and can act as a viral relapse reservoir. The uncertainty of therapy course length is associated with patient compliance, resistance, safety and financial cost. To combat therapy length uncertainty (see Advances section), EASL proposed three endpoints for antiviral treatment of chronic HBV in 2009. These are: (1) HBsAg clearance; (2) HBeAg seroconversion; and (3) Persistent inhibition of HBV DNA replication[12]. However, withdrawal of treatment is still associated with significant relapse rate and the 2015 Chinese guidelines for chronic HBV infection suggest extending therapy for three years post-HBeAg seroconversion[40]. Neither the AASLD nor the EASL advises extending therapy post-HBeAg seroconversion[12,59]. Long-term nucleot(s)ide analogue use can produce resistance and side-effects. A resistance rate of 70% has been reported in patients using lamivudine for 5-years[12]. Long term use of adefovir and tenofovir can result in renal impairment[78].

### *HCV*

**Stigma and inequity:** Harm reduction strategies have been proven to work; however, the failure of implementation may be secondary to the stigma associated with persons injecting drugs. As this group tends not to vote, their concerns are not advocated. Policy makers often overlook such interventions, being swayed instead by voters' issues. Because HCV is relatively asymptomatic, a large proportion of the population are unaware of their diagnosis.

**Access to DAA therapy:** Global access to HBV and HCV therapy remains a problem. This is a multifactorial issue that includes access to diagnostics, therapy affordability and public health issues. Only approximately 1.7-million of the estimated 250 million individuals worldwide with chronic HBV were on treatment in 2015/2016[21]. Of the estimated 71 million people living with HCV, about 20% were aware of their diagnosis and about 5 million were treated with DAAs by the end of 2017[18]. Improved access to affordable non-hospital diagnostics is needed, as well as access to treatment. Attempts to combat these shortcomings include the addition of viral hepatitis diagnostics to the WHO's proposed Essential Diagnostics List in 2016[79]. Development of point of care molecular testing is promising, but this needs to be affordable if it is to be used in low to middle-income countries[80]. Intellectual property or patenting remains a barrier to access to generic therapy and thus, to affordable treatment. Voluntary licencing agreements and those created through the Medicines Patent Pool (MPP) allow the manufacture and sale of generic DAAs, improving affordability. The proposed licensing of pibrentasvir and glecaprevir with the MPP would facilitate access to generic alternatives of important pan-genotypic

therapy for HCV in low to middle-income countries[81]. Licensing of tenofovir and its generics with the MPP has allowed improved access in low to middle-income countries[82]. Further work and support of HCV eradication, and of HBV viral suppression programmes, are needed at both national and global level.

**DAA resistance:** The emergence of resistance to DAAs is a crucial challenge. The HCV high replication rate (estimated at $10^{12}$ copies per day) and the viral protein responsible for replications (RNA-dependent RNA polymerase, RdRp) demonstrates an absence of proofreading; therefore, HCV replication has a high error rate[83]. This results in multiple mutated viruses known as quasi-species, circulating in the blood[84]. Although the mutated viruses/quasi-species have less fitness (*i.e.*, ability to replicate) when an individual is treated with DAAs, one sees the quantity of the wildtype virus fall and the mutated virus rise. These mutated viruses/quasi-species can lead to structural changes in the protein/enzyme that the DAAs act on, thus generating resistance[85]. Resistance-associated-substitutions or RASs confer this resistance. The viral population that carry RASs are known as resistant variant (RAV). This can lead to RAV outgrowing the DAA-sensitive viruses during treatment (known as 'breakthrough') or after treatment (known as 'relapse'). Therefore, the emergence of resistance is also determined by the level of previous therapeutic drug exposure.

**HDV:** Arguably HDV represents the largest challenge in treatment as it confers the most severe acute and chronic hepatitis and thus worst outcomes.

## CONCLUSION

In conclusion, viral hepatitis is due to a group of pathogens that are associated with significant disease complications and morbidity. The increased awareness of viral hepatitis disease burden and the arrival of effective treatments for HBV and HCV have enhanced efforts and calls for action to eradicate viral hepatitis, as outlined by the United Nations WHO 2030 agenda[17,86,87].

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