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Viral hepatitis in persons living with HIV in the post-COVID era

Vicente Soriano[1]*, Víctor Moreno-Torres[1,2], Carmen de Mendoza[2], Octavio Corral[1], and Pablo Barreiro[1,3]

[1]UNIR Health Sciences School, Madrid; [2]Puerta de Hierro University Hospital, Madrid; [3]Isabel Zendal Emergency Hospital, Madrid, Spain

Abstract

Coinfection with hepatitis viruses A to E is frequent in persons living with HIV (PLWH) and causes significant morbidity and mortality. Oro-fecal transmissible hepatitis A and E mostly produce acute self-limited episodes in poor income regions and in non-vaccinated travelers. In high-income countries, outbreaks of hepatitis A occur in men having sex with men (MSM) and chronic hepatitis E is occasionally reported among PLWH with severe immunodeficiency. Chronic hepatitis B, C, and D are frequent in PLWH in highly endemic regions and globally in persons who inject drugs (PWID) and MSM. Progression to liver cirrhosis and development of hepatocellular carcinoma (HCC) is major clinical complications in coinfected patients. Current estimates for PLWH are of 38 million worldwide. Roughly 12% have chronic viral hepatitis (5 million). Coinfection figures are of 5-10% for HBV (2-4 million), 4% for HCV (1.5 million), and 15% of HBsAg+ for HDV (0.5 million). Oral direct-acting antivirals (DAA) cure almost all treated patients with hepatitis C. However, given that there is no protective HCV immunity, PLWH with high-risk behaviors may experience HCV reinfection episodes. Tenofovir is the drug of choice in PLWH with chronic hepatitis B, given its dual effect on HIV and HBV. Lifelong oral tenofovir suppresses HBV replication and ameliorate liver damage. However, the risk of HCC persists even in the absence of cirrhosis. Finally, HDV causes the worst of viral hepatitis with faster progression to cirrhosis and HCC. An entry inhibitor, bulevirtide, has recently been approved and another drug, lonafarnib, is completing Phase 3 trials. Combination antiviral therapy for hepatitis D could improve dramatically the poor prognosis of HIV-HDV coinfected patients. The resumption of good medical practices in PLWH after the big disruption caused by COVID-19 will reduce the burden of viral hepatitis coinfections. Renewed efforts on HAV and HBV vaccination of susceptible individuals and earlier and wider prescription of antiviral therapy for HBV, HCV, and/or HDV coinfection should be prioritized in PLWH. The benefits of innovative strategies for viral hepatitis, including pre-exposure prophylaxis or use of long-acting antivirals, warrant further consideration in PLWH.

Keywords

*Correspondence to:
Vicente Soriano
E-mail: vicente.soriano@unir.net

Introduction

Coinfection with hepatitis viruses is frequent in persons living with HIV (PLWH). This is largely explained by the sharing of transmission routes. Outbreaks of acute viral hepatitis among youth engaged in high-risk behaviors, especially among persons who injected drugs (PWID) and men having sex with men (MSM) were frequent in the 80s and 90s[1]. Following the widespread use of HBV vaccines, acute episodes of hepatitis B and delta declined. Since the 2000s, however, outbreaks of acute hepatitis A[2] and acute hepatitis C[3] have been reported in PLWH, especially among MSM.

The biggest clinical burden of viral hepatitis in PLWH is attributed to chronic hepatitis B, C, and delta. Progression to liver cirrhosis and development of hepatocellular carcinoma (HCC) is a major cause of morbidity and mortality in coinfected patients[4-6].

Current estimates from UNAIDS for PLWH are of 38 million worldwide, of whom 25 million live in Sub-Saharan Africa[7]. Roughly 1.5 million new HIV infections occur each year. Despite the increased uptake of antiretroviral treatment, approximately 15% of HIV individuals are not treated. This is mostly due to difficulties in access to medical care (especially in poor income countries) or because infected individuals are not aware of their status (persons neither tested nor diagnosed). This subset of untreated but infected subjects does not benefit from antiretrovirals individually (and, therefore, may progress to AIDS) and it is the major source for HIV transmission to others. Given that PLWH that are treated and have undetectable viral load are no longer infectious[8], an effect known as undetectable=untransmittable (U=U)[7], antiretroviral therapy is nowadays recommended to everyone HIV-positive and given as early as possible upon diagnosis[9].

The current HIV-1 pandemic can be split into three major forms. The first mostly affects Sub-Saharan Africa and is the largest, with estimates of 25 million PLWH. Heterosexual transmission is the predominant mechanism of contagion. Women are slightly more affected than men (roughly 55%). Although mother-to-child transmission has drastically declined, HIV infections in children and adolescents continue to occur in poor regions. The second HIV pandemic form mostly affects North America and Europe, but also Japan and Australia, with estimates of 3 million PLWH. MSM and PWID are by far the most affected high-risk populations. The third HIV pandemic form mostly occurs in Latin America and Asia. It evolves heterogeneously between the two prior forms, affecting sexually active individuals with a variable and larger weight of MSM and PWID (Fig. 1).

Since the mid 90s, immunodeficiency directly caused by HIV has become rare among PLWH thanks to the advent of triple combination antiretroviral therapies[8,9]. As indirect result, coinfection with viral hepatitis soon emerged as an important cause of clinical complications and shorter survival in PLWH[4-6]. Given shared transmission routes, nowadays chronic viral hepatitis continues to be among the most frequent causes of morbidity and mortality in PLWH[10,11]. This is particularly true in Sub-Saharan Africa, where high prevalence rates occur along with low access to antiviral therapies[12]. In Western countries, the advent of effective antiviral therapies for HBV and HCV and high HBV vaccine coverage have reduced the clinical burden of hepatitis coinfections in PLWH[11]. However, migration flows from highly endemic regions, HBV vaccine waning and HCV reinfections keep viral hepatitis as a major issue in PLWH. Figure 2 records graphically the global epidemiological burden and intersection of HIV and viral hepatitis.

In this review, we will update current knowledge and epidemiological information for each of the hepatitis viruses in PLWH. We will end discussing new strategies aimed to reduce the burden of HIV-hepatitis coinfections in the new post-COVID era, acknowledging the global negative impact of the coronavirus pandemic on both HIV and hepatitis care.
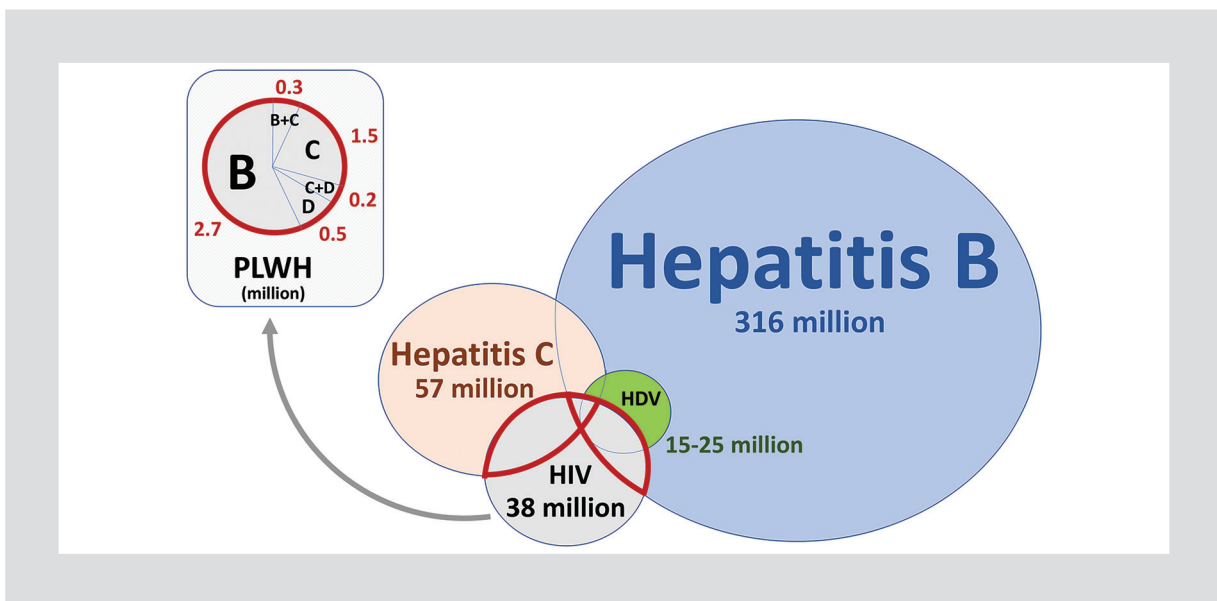
Hepatitis A

The hepatitis A virus (HAV) is a small single stranded RNA non-enveloped virus. It is mostly transmitted by the fecal-oral route. Poor hygiene, contaminated water and food, and oral-anal sex favor HAV contagion. There are three human genotypes (I-III). Dogs are the closest animal reservoir. Table 1 summarizes the main differential features of hepatitis viruses.

Natural HAV immunity is lifelong. A protective effective vaccine was marketed two decades ago. Although one shot provides short-term protection, two shots are recommended to attain long-lasting immunity, what is particularly true for patients with immune dysfunction, including PLWH[13-16]. Hepatitis A generally cause mild symptoms in children but in adults may produce fever, asthenia, nausea, and jaundice. It never evolves to chronicity. Despite presenting as an acute self-limited illness, HAV particles may be eliminated by feces for
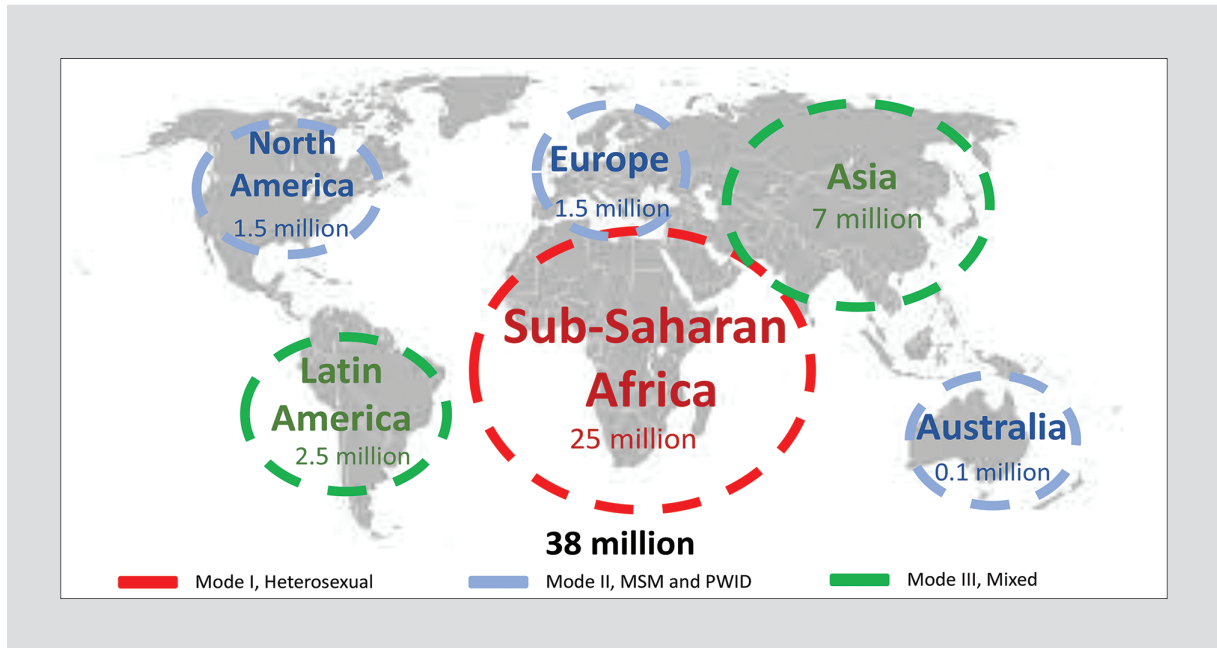
Figure 1. *Major epidemiological forms of the HIV-1 pandemic.*
MSM: men having sex with men; PWID: persons who inject drugs.

Figure 2. *Intersection between HIV and viral hepatitis globally.*
PLWH: persons living with HIV.

long periods after clinical recovery, especially in immunosuppressed individuals[17].

Most countries in Africa, Asia, and Latin America show high endemicity for HAV. Travelers from North America, the Europea n Union, Japan, Australia, New Zealand, and a few other high-income countries are recommended to be vaccinated before going overseas.

Local outbreaks of hepatitis A in adults have been reported in high income countries among MSM, linked to anal sex[18-21]. These surges are a reminder of inadequate vaccination for this preventable viral disease. In a cohort of more than 3000 PLWH in Texas, < 10% of patients susceptible to HAV had been vaccinated after 2 years in care. MSM and those with HBV or HCV

Table 1. Main differential features of viral hepatitis

	HAV	HBV	HCV	HDV	HEV
Genome (nt)	RNA (7.5 Kb)	DNA (3.2 Kb)	RNA (9.6 Kb)	RNA (1.7 Kb)	RNA (7.2)
Genotypes	3 (I-III)	10 (A-J)	6 (1-6)	8 (1-8)	4 (1-4)
Major transmission	Orofecal	Sexual, Parenteral, vertical	Parenteral, sexual	Sexual, Parenteral	Orofecal
Risk populations	Poor hygiene, MSM	MSM, PWID, MSP	PWID, MSP	PWID, MSM, MSP	Poor hygiene Not cooked meat
Chronicity	No	Yes (> 90% in newborns; < 5% in adults)	Yes (75%)	Yes (more in superinfection than in coinfection)	Rare (immunosuppressed)
Clinical features	Jaundice more frequent in adults	High risk of liver cancer with age	Reinfections after cure following new exposures	Faster progression to cirrhosis	25% risk of stillbirth and/or death in pregnant women
Antivirals	No	Yes	Yes	Yes	No
Vaccines	Yes	Yes	No	No	Yes (China)

PWID: persons who inject drugs; MSM: men who have sex with men; MSP: multiple sex partners, HAV: hepatitis A virus, HBV: hepatitis B virus, HCV: hepatitis C virus, HDV: hepatitis D virus, HEV: hepatitis E virus

infection were more likely receive HAV vaccination[11]. A Spanish cohort of 272 HAV-susceptible PLWH also reported low HAV vaccine uptake, with only 38% undergoing vaccination over a 10-year period. Nearly 10% of those vaccinated did not show HAV seroconversion, and one individual lost HAV antibodies. Several HAV outbreaks occurred during follow-up, 60% in non-immunized MSM[11].

To examine optimal strategies for HAV re-vaccination in those with ineffective initial vaccination, a Taiwanese study randomly assigned 102 PLWH to 1 or 2 HAV vaccine shots after initial non-response or seroreversion. There was no significant difference in seroconversion with 1 dose (79%) versus 2 doses (84%). Those with prior seroreversion responded to either 1 or 2 doses, but the latest led to a 2-fold higher HAV antibody level at week 24[11].
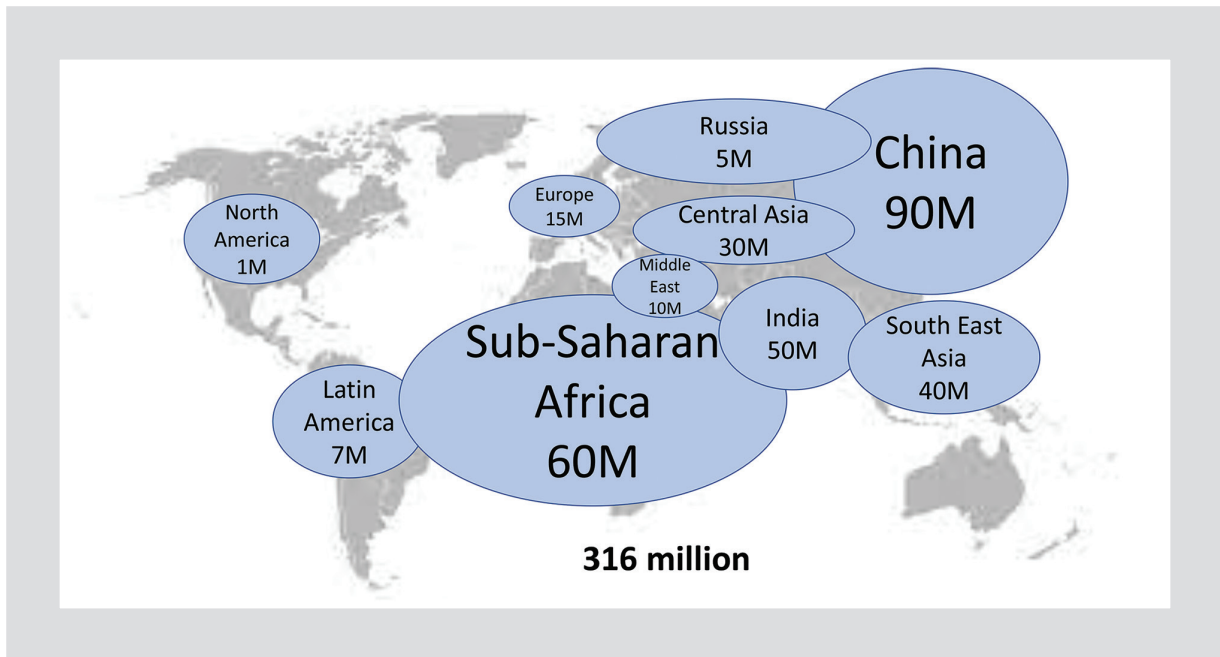
Hepatitis B

The hepatitis B virus (HBV) is a small partially double stranded DNA enveloped virus that uses the NTCP receptor to enter hepatocytes. There are ten HBV gen-

otypes (named A to J), each with a characteristic geographic distribution and differential pathogenicity[22].

The most recent estimate of the number of individuals with chronic hepatitis B is 316 million, which represents 4.5% of the 8 billion World population[23]. Countries with the largest number of chronic hepatitis B patients are China, India, Nigeria, Indonesia, and the Philippines (Fig. 3).

The prevalence of chronic HBV infection has steadily declined since 1990, particularly in children, following the introduction of universal infant hepatitis B vaccination[22]. The additional contribution of antiviral therapy suppressing viremic and therefore, infectious- carriers are lower and mostly restricted to high-income countries.

In 2016, only 10% of people with chronic HBV infection were diagnosed, and only 5% of those eligible for therapy were receiving antiviral treatment[24,25]. By 2021, the WHO estimated that 30 million people with chronic HBV infection were diagnosed but < 7 million were treated. Hepatitis B produces more than 600,000 deaths annually. Moreover, estimates for liver cancer due to HBV are 40% globally but up to 65% for China[23].

Figure 3. *Hepatitis B. Global geographic distribution and major endemic regions.*

Attaining HBV virologic suppression can take a long time, particularly in HIV/HBV-coinfected individuals. Of 222 starting tenofovir-based treatment in the Swiss HIV cohort, 84% had detectable HBV-DNA and 58% had levels above 2000 IU/mL. HBV viremia persisted in 27% at 2 years and in 18% at their latest follow-up. Persistent viremia was associated with high baseline HBV-DNA level and advanced HIV disease[11].

In the Swiss HIV cohort, of 272 HIV/HBV-coinfected patients, HBsAg loss occurred in 8% during the first 2 years of tenofovir therapy and in 16% after a median of 8.4 years of follow-up, which is higher than generally seen in HBV monoinfection. When HBsAg clearance occurred, more than half (54%) developed anti-HBs antibodies, suggesting durable immunologic control[11].
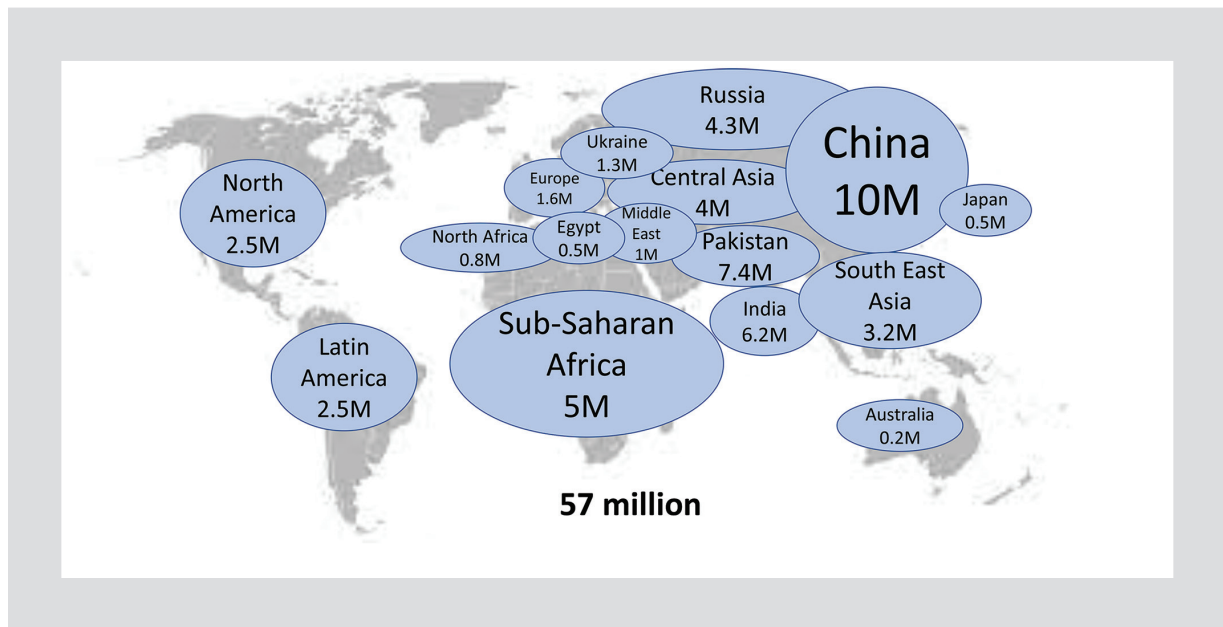
Hepatitis C

The hepatitis C virus (HCV) is a small enveloped particle with one single stranded RNA genome. All the replication cycle of HCV occurs in the cytosol of infected hepatocytes. In contrast with the intranuclear HBV episomal form or the HIV provirus, there is no persistent HCV genomic cell reservoir[26]. This finding explains that therapeutic HCV eradication is feasible with potent antivirals whereas blocking of HBV or HIV replication requires lifelong antivirals.

Following parenteral or sexual exposure, HCV generally causes asymptomatic or mild symptomatic acute hepatitis C. Roughly two-thirds may progress to chronicity[27]. However, individuals with immunosuppression, including PLWH, show an increased risk of chronic hepatitis C along with a faster progression of liver disease[3-5].

There are six major HCV genotypes, each with a characteristic geographic distribution, pathogenicity, and susceptibility to antiviral agents[27]. HCV genotypes 1, 2, and 3 are widely distributed worldwide and produce most infections in North America, the European Union, and Japan. HCV genotype 4 predominates in North Africa and the Middle East. HCV genotype 5 circulates in South Africa and HCV genotype 6 in South-east Asia.

The five countries with the current largest number of chronic viremic hepatitis C patients are China, Pakistan, India, Bangladesh, and Russia (Fig. 4). Egypt is no longer in this list after undergoing a massive treatment campaign a couple of years ago, supported by international agencies and pharma companies[28].

From a total of 115 million people with HCV antibodies by 2015, odds were six times higher in PLWH (6.2% rate). The estimated number of PLWH with active HCV infection was 2.3 million before direct acting antivirals (DAA) became widely available[29], of which 1.4 million were in PWID. With the uncertainty of how many PLWH

Figure 4. *Hepatitis C. Global geographic distribution and major endemic regions.*

with hepatitis C have been treated with DAA since then, we estimate that considering high diagnosis rates in PLWH, frequent HCV reinfections, and challenges in medication access, among others, roughly one-third of HIV-HCV coinfected patients have cured hepatitis C by 2023, acknowledging that the highest cure rates should have occurred in resource rich countries. Thus, HIV-HCV coinfection should still affect roughly 1.5 million people, which represents 4% of PLWH worldwide.

In 2013, HCV treatment was transformed by the introduction of oral DAA therapies that cure ≥ 95% of patients. Broad DAA access has a treatment-as-prevention (TasP) effect on primary HCV incidence among PLWH[30]. Response rates in PLWH are as good as in HCV-monoinfected individuals[31]. Hence, HCV in PLWH behaves as a microelimination population on track to meet the WHO's 80% HCV incidence reduction target by 2030[25]. However, it should be noted that HCV reinfections hamper this benefit in certain populations, such as PWID sharing needles and MSM with mutiple sexual partners[30,32].

In an examination of the European HCV care cascade in PLWH, the EuroSIDA cohort reported 90% ever tested for HCV antibodies, with 24% with active infection by HCV-RNA, with highest prevalence (45%) in Central-Eastern Europe. Overall, 65% of those diagnosed had ever been treated and nearly half had been cured[11]. Spain has made some of the most substantial progress toward HCV elimination. In a nationwide

seroprevalence survey, HCV-RNA positivity declined from 22.1% in 2015 to 2.2% in 2019[33].

An important caveat before prescribing DAA is the exclusion of active HBV coinfection. Close monitoring of HBV reactivation is warranted, since hepatic HCV displacement using DAA might result in unwanted HBV surges[34,35].

Hepatitis D

The hepatitis D virus (HDV) is a unique small enveloped virus that requires HBV to complete its replication cycle, since HBsAg is part of the new released HDV particle. Hence, HDV is a defective agent. A recent meta-analysis pointed out that HDV is responsible for 18% of cirrhosis and 20% of HCC in individuals with chronic HBV infection globally. Thus, almost one-fifth of all HBV-related deaths in 2019 were attributable to HDV infection[23].

Eight HDV genotypes have been reported, each with a distinct geographic distribution and pathogenicity[36]. Genotype 1 is prevalent worldwide. Genotype 2 is mostly reported in Russia, Taiwan and Japan. Genotype 3 is common in the Amazon Basin and is associated with more severe forms of liver disease, earlier onset of HCC and outbreaks of fatal acute liver failure. Genotype 4 is reported in the Far East, including Japan and Taiwan. Genotypes 5-8 are reported in Africa[37]; and in Europe among African immigrants.

Sexual transmission and injection drug use are by far the most common routes of contagion for both HIV and HDV[8,38]. However, in regions where any of these viruses are endemic and access to mother-to-child preventive measures are limited, perinatal transmission still occurs[8,38]. The most common situation for HDV is vertically acquired hepatitis B and years later HDV superinfection during childhood or early sexually active adulthood[38].

The WHO has global estimates for hepatitis B and C[24], but it does not have figures of prevalence or mortality for HDV. Despite being a neglected disease, hepatitis delta is included as part of the Global Health Sector Strategy on Viral Hepatitis that in 2016 called for the elimination of all viral hepatitis by 2030, meaning at least 65% reduction in mortality and 90% decline in incidence[25]. Approaches envisioned by the WHO to face the challenge of HDV control have recently been released[39]. Expanding HBV vaccination and HDV testing are key elements of this roadmap. However, specific interventions in target populations as PLWH are scarcely addressed.

During the last couple of years, a vivid discussion in the scientific literature has been around the number of persons with hepatitis delta worldwide[40,41]. The most recent global estimate is 0.7%, which translates in 13% of HBsAg+ patients[42]. Given that only a fraction (less than two thirds) of anti-HDV positive persons replicate the virus, the absolute number of HDV viremic individuals should be between 15 and 25 million people worldwide.

By order, Asia, Africa, South America, Middle East, Eastern Europe and Western Pacific islands are the regions with the largest HDV populations[38,41] (Fig. 5). The five countries with the largest number of individuals with chronic hepatitis delta are China, Nigeria, Pakistan, Mongolia and Romania. Of note, there are no reliable data from Russia and China, where HDV rates are high and underestimated[38,41,43]. Mongolia, a country geographically in between, has one of the greatest HDV rates worldwide (30% of HBsAg+). In the Western Pacific, high HDV rates have been reported in Micronesia, whereas Polynesia and Melanesia depict low HDV rates[44].

Temporal trends in HIV and HDV infections are divergent. The widespread use of antiretroviral therapy has reduced HIV transmission significantly in most regions. However, 1.5 million new HIV infections still occur annually worldwide[8]. The introduction of treatment as early as HIV diagnosis is made and the prescription of antiretrovirals as pre-exposure prophylaxis in HIV-uninfected individuals engaged in high-risk behaviors has largely impacted among MSM[9,45]. For other risk groups, such as PWID, both individual and social challenges frequently preclude them to take all advantages from medical services, including periodic testing, HBV vaccination and access to medications[46]. All these unfavorable factors increase the likelihood of HDV acquisition[47,48].

In a recent survey conducted in Europe, 15% of nearly 2800 PLWH with HBsAg+ had HDV antibodies[49]. However, whereas it was only 5% among MSM, resembling the rate seen in the general HIV-negative population with HBsAg+, it rose to 50% among PWID [49]. These numbers are similar to those reported in prior surveys conducted in PLWH in Europe more than one decade ago[50]. Thus, PWID represents the largest HDV reservoir among PLWH in Europe and North America. In the rest of the world, the contribution of sexual risk groups to the HDV reservoir is greater[51].

Producing estimates of the global population with HIV and HDV coinfection is difficult. Given that HDV only occurs among HBsAg+ individuals, if we assume that the rate of HBsAg among PLWH ranges from 5% to 10%, and there are 38 million PLWH worldwide, the population with HIV-HBV coinfection will range from 2 to 4 million. Then, if we apply the 15% rate of anti-HDV seen among European PLWH with HBsAg+[49,50], the estimated number of HIV-HDV coinfected persons will range between 350,000 and 700,000 people worldwide.

Double and triple viral hepatitis infections may occur in PLWH, including HBV plus HCV, or HBV plus HDV plus HCV[52]. Classically, these patients exhibit the worst outcomes[53]. Viral interference phenomena may occur with hepatic displacement of one virus when replication of another hepatitis virus takes over. In this situation, antiviral treatment of all replicating viruses should be encouraged[54].

Considering HIV and HDV overlapping geographic distribution, predominant transmission routes, HBsAg+ prevalence, and survival rates, it could be expected that roughly 0.5 million persons might be dually infected worldwide. Two major patterns of HIV and HDV coinfection that exhibit distinct HIV-1 variants and HDV genotypes can be recognized. In North America and Europe, HIV-1 subtype B and HDV genotype 1 are the predominant coinfections, being men more frequently affected than women. MSM and PWID are the largest groups[47,51]. A second pattern of HIV-HDV coinfection occurs in Sub-Saharan Africa, where multiple HIV-1 non-B subtypes circulate and coinfection with HDV
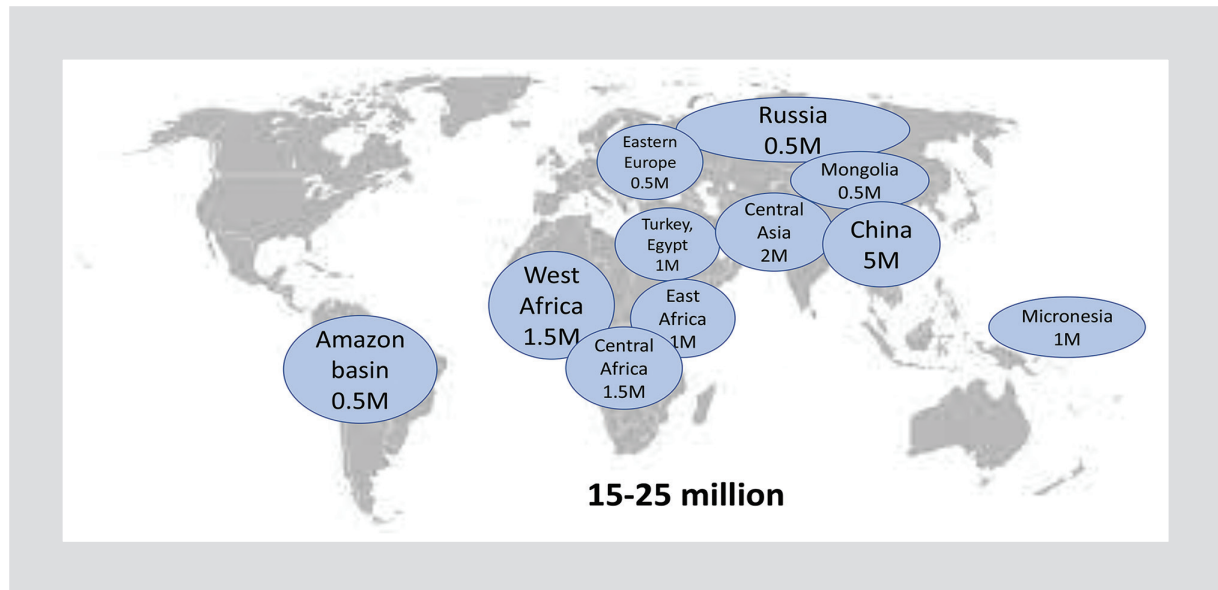
Figure 5. *Hepatitis delta. Global geographic distribution and major endemic regions.*

genotypes 5-8 predominate along with HDV-1. Heterosexual transmission of HIV and HDV is the most common, being women more affected than men[38]. As result of migrant flows, this second pattern of HIV-HDV coinfection is increasingly being recognized in Europe and North America[55,56].

In earlier studies, a severe course of liver disease was described in chronic hepatitis D patients, with faster pace toward liver cirrhosis with subsequent high liver-related morbidity and mortality[57,58]. However, many of those studies included risk groups as PWID or patients with multiple comorbidities, including HIV or diabetes. During the last decade, the epidemiological landscape of hepatitis delta has changed with domestic cases decreasing while increasing the proportion of younger individuals immigrating from endemic regions to low-endemic regions[55,56]. Recent insights into the spectrum of HDV disease have highlighted an indolent course in a substantial proportion of persons with hepatitis delta[59]. However, at diagnosis, up to 30% might already show cirrhosis. Older age, liver cirrhosis, and HIV coinfection are the main predictors of worse clinical outcome for hepatitis delta[56,60].

In PLWH, chronic hepatitis delta has been associated with a disproportionate rate of cirrhosis and poor clinical outcomes. In a case–control study, 26 HIV/HDV-coinfected patients experienced significantly higher rates of hepatitis flares, liver cirrhosis, liver decompensation, and death over a median follow-up of 55 months than matched HIV-monoinfected controls[53]. More recently, two larger studies have examined the risk of liver decompensation and HCC in PLWH with hepatitis delta. In one Spanish study[61], 1147 PLWH (mean age, 42 years; 81% males; 46% PWID, 85% on ART) were followed for a mean of 8 years. Overall, 15 patients died of liver-related complications and 26 developed hepatic decompensation events. The major predictors of hepatic outcomes were HDV coinfection and baseline liver fibrosis. Of note, three out of 17 PLWH with hepatitis delta developed HCC during the study period.

The second study reported data from the Swiss Cohort[62]. Overall, 15% of 818 HBsAg+ individuals had antibodies to HDV infection, of whom 63% had active HDV replication (detectable and measurable serum HDV-RNA). During a median follow-up of 8 years, PLWH with hepatitis delta were 8 times more likely to die from liver-related causes and 9 times more likely to develop HCC.

Hepatitis E

The hepatitis E virus (HEV) is a non-enveloped agent with a RNA genome. HEV is the most frequent cause of acute viral hepatitis worldwide[63]. Each year produces over 3 million clinical cases, 70,000 deaths, and 3,000 stillbirths, mostly in Asia and Africa[63]. HEV infection mostly affects persons living in resource-limited settings with poor access to clean water and sanitation. Acute hepatitis E can be particularly severe in

pregnant women and neonates[64]. Indeed, HEV is a significant contributor to global maternal mortality, with reported case fatality rates of 20-30%.

Four HEV genotypes have been described. HEV genotypes 1 and 2 cause epidemics of acute hepatitis E and is largely transmitted by fecal contamination of water and food in highly endemic regions for HEV in Asia, Africa and Latin America. In contrast, HEV genotypes 3 and 4 cause sporadic acute hepatitis E cases in Europe and Asia, respectively, frequently following the consumption of non or poorly cooked meat[65]. Hence, in this occasion, hepatitis E is a zoonosis. Precisely, it was in France where the first cases of chronic hepatitis E were described among transplant recipients[66]. Since then, chronic hepatitis E has also been reported among other immunocompromised individuals, including PLWH[67,68].

Hepatitis E may affect other organs than the liver. Extrahepatic complications include Guillain-Barré syndrome, neuralgic amyotrophy, glomerulonephritis, cryoglobulinemia, pancreatitis, thrombopenia, meningitis, thyroiditis, and myocarditis[69]. These manifestations have been associated to either a direct cytopathic tissue damage by HEV replication or to an overwhelming host immune response.

To date, there is a limited availability and usage of diagnostic tools for the serologic and/or molecular diagnosis of HEV, as well as a paucity of antiviral treatment options. Moreover, though an anti-HEV vaccine exists, it is only licensed in China and has not been authorized yet by the WHO for use in endemic settings and/or outbreaks. Ribavirin has been used as treatment of symptomatic or chronic hepatitis E, generally with poor results[70].

Both acute and chronic hepatitis E have both been described in PLWH, especially among MSM[71-73] and in the subset of patients with low CD4 counts, respectively[72]. However, to date, there is no evidence in favor of sexual HEV transmission[74,75].

Interventions to reduce the burden of viral hepatitis in PLWH

Although viral hepatitis will continue to challenge PLWH, the resumption of both preventive and curative strategies promises new hopes after the disruption caused by the COVID-19 pandemic. Renewed efforts should cover all steps of the medical care cascade, from expanding testing and vaccination of susceptible individuals to provision of medications as soon as possible to infected patients (Fig. 6).

Acute viral hepatitis A and E will continue to be a challenge in resource poor settings where these viruses are highly endemic. Although PLWH are not an increased risk for liver disease severity neither with HAV or HEV, protection by HAV vaccines may be lower in immunodeficient individuals and there is a risk for HEV chronification in the subset of PLWH with profound immunodeficiency.

Following the introduction of potent HBV and HCV antivirals, the clinical burden of chronic viral hepatitis has steadily declined globally[23,28]. However, this slowdown seems to have reached a plateau, even after discounting the distraction caused by the COVID-19 pandemic. A similar phenomenon has been noticed with respect to new infections by human retroviruses[76].

There are three major reasons to explain this slowdown in incident cases, one for each of the chronic hepatitis viruses. First, HBV antivirals can control but not cure (eradicate) hepatitis B. The virus stays in the liver of HBsAg+ patients and favors the development of liver cancer even in the absence of cirrhosis. This finding has clearly been demonstrated in a large study performed in Spain examining nationwide hospitalizations over the past 20 years[77].

To push down further new incident hepatitis B, renewed efforts on HBV vaccination are warranted. Immunity waning in PLWH most likely account for unexpected low anti-HBs rates seen in recent studies[78].

Second, given that there is no protective immunity, HCV reinfections are frequent in persons that continue to be engaged in high-risk behaviors, including MSM with multiple sex partners or PWID sharing needles. In these groups, new exposures to HCV may blunt the benefit of any prior curative course of HCV therapy[79-81]. The good news is that prescription for 3 months of oral DAA will cure hepatitis C in almost all patients any time, halting the development of both hepatic and extrahepatic complications[82].

Third, the lack of effective therapy for hepatitis delta explains that chronic HDV infection is taking over hepatitis B or C as cause of morbidity and mortality in PLWH. Chronic HDV infection occurs in roughly 15% of PLWH and hepatitis B[49,50]. As hepatitis delta is the most aggressive of all chronic viral hepatitis, most PLWH with hepatitis delta progress to liver cirrhosis and may develop liver cancer[61,62]. No effective antiviral therapy had been developed until recently to treat hepatitis delta, but the advent of a subcutaneous entry inhibitor, bulevirtide, has opened a new era for hepatitis delta[83] (Table 2).
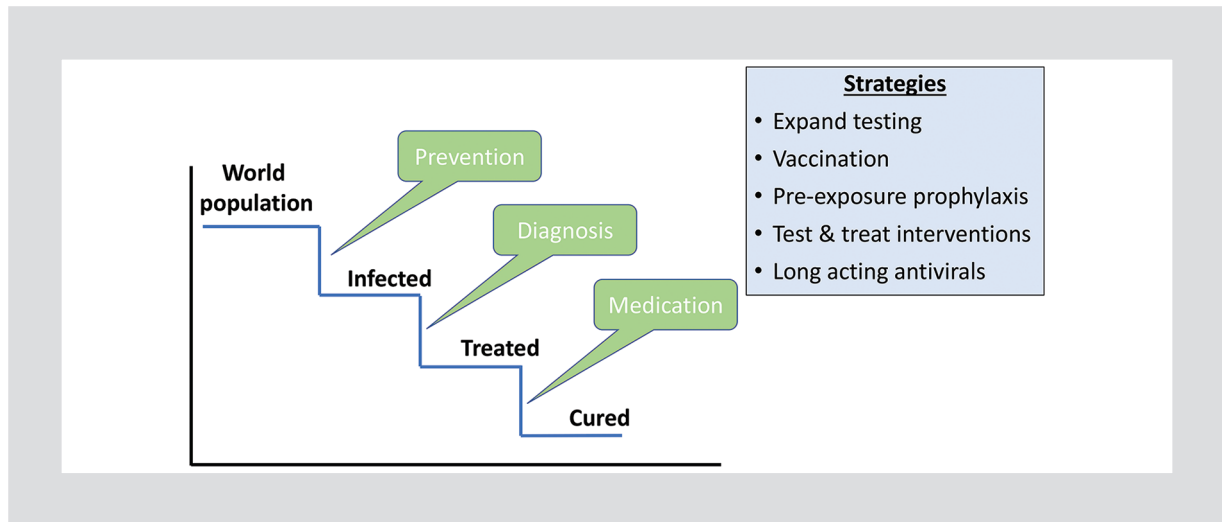
Figure 6. *The cascade of care for viral hepatitis.*

New strategies for viral hepatitis B and C

New approaches merit further consideration for viral hepatitis, based on the good results achieved confronting HIV infection. Among others, we will discuss the use of point-of-care (POC) tests, simpler treatment protocols, pre-exposure prophylaxis, and development of long-acting antivirals.

Rapid tests

Although 10 million hepatitis C patients had received DAA until 2020, only 20% of those infected worldwide had been diagnosed and 13% treated. To address this gap, POC viral load assays have recently been recommended by the WHO for hepatitis C[84]. These tests for diagnosis and treatment monitoring have already shown their benefit on tuberculosis and HIV. The use of POC HCV viral load assays is especially relevant for promoting linkage to care for hard to reach or marginalized populations at high risk of loss to follow-up, and at decentralized HCV testing and treatment sites that might include opioid harm reduction services, primary clinics, prisons as well as STI and HIV clinics[84].

Simpler treatment protocols

The need to simplify HCV treatment approaches, particularly with the availability of low-cost generic drug formulations and to facilitate HCV elimination globally, has pushed studies that could minimize care requests using DAA. In this regard, the results from the real-world ACTG trial MINMON (Minimal Monitoring) are very appealing[85]. The study gave DAA therapy right on confirmation of HCV viremia, routine laboratory evaluations to assess cirrhosis (using the FIB-4 index), and exclusion of active HBV infection. A 12-week course of sofosbuvir/velpatasvir (84 tablets) with no in-person follow-up or laboratory evaluations was made until 12 weeks after completion of treatment. Pre-treatment HCV genotyping was not performed. Remote (telephone) contact was scheduled at weeks 4 and 22. The study enrolled 400 participants globally, of whom 42% were coinfected with HIV. Sustained virologic response was attained by 95% (379/399) of participants, and no serious adverse events were noticed[85].

Pre-exposure prophylaxis

A protective effect of tenofovir on HBV acquisition comes from studies conducted in HIV patients on antiretroviral therapy[86]. Sexually active men having sex with men (MSM) that received tenofovir as part of their antiretroviral regimen had a lower chance of HBV infection than those that did not receive the drug[87,88]. Thereafter, this protective effect was also confirmed in HIV-uninfected persons at risk undergoing PrEP with tenofovir. Based on these findings, the recent increasing trend in HIV therapeutics for using dual regimens sparing tenofovir is worrisome[89]. It might be associated with a rebound of incident HBV infections.

For all these considerations, the use of tenofovir as chemoprophylaxis might be discussed in certain populations to avert breakthrough HBV infections. We

Table 2. Current antivirals for chronic viral hepatitis

	Entry inhibitors	Nucleos(t)ide analogues	Protease inhibitors	NS5A inhibitors	Others*
HBV	Bulevirtide	Tenofovir Entecavir			Bepirovirsen
HCV		Sofosbuvir	Glecaprevir Voxilaprevir	Ledapasvir Velpatasvir Pibrentasvir	
HDV	Bulevirtide				Lonafarnib Interferon λ

*Expected approval soon

postulate that this could be the case for individuals engaged with high-risk behaviors, including PWID sharing needles and MSM with multiple sexual partners. Although HBV vaccines are effective, some individuals experience suboptimal responses and/or waning of antibodies following immunization[90]. Moreover, circulation of HBV vaccine escape mutants is occasionally responsible for paradoxical acute HBV infections in vaccinated individuals[91].

Long-acting antivirals

The advent of long-acting formulations of tenofovir could facilitate its prescription either as treatment or prevention[92,93]. An additional indirect benefit of using tenofovir chemoprophylaxis would derive from reducing the chances of hepatitis delta acquisition, since this virus requires HBV for transmission[94].

In certain risk populations, such as PWID sharing needles and MSM with multiple sex partners, repeated episodes of HCV re-infection (occasionally more than 6)[95] have urged to reconsider the administration of repeated HCV courses. Given that the clinical consequences of chronic hepatitis C are generally seen only after decades of infection, some authors have advised against immediate anti-HCV treatment when high-risk behaviors persist. Against this view is the fact that being viremic means to be a potential source of contagion for others[96,97]. In this scenario, the consideration of sofosbuvir as prevention of new HCV infections in persons engaged in risky behaviors and/or in prisons could be defended. This drug depicts high potency, good safety profile, limited number of drug interactions, and high barrier to resistance. After becoming HCV-RNA negative following a first course of therapy, sofosbuvir chemoprophylaxis could avert HCV re-infections in high-risk individuals. Furthermore, if long-acting forms of HCV drugs become available[98], this option could be even more appealing.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

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