Hot News

Less hepatic decompensation events but rising liver cancer in hepatitis B patients on long-term nucleos(t)ide therapy

Despite the existence of a vaccine and several oral antivirals, chronic hepatitis B virus (HBV) infection is the leading cause of liver cancer worldwide. The WHO estimates that there are 290 million people with chronic hepatitis B on the planet and that HBV causes about 1 million deaths each year (Polaris Observatory. Lancet Gastroenterol Hepatol 2018). In Spain, a recent study has warned about the increase in hospitalizations for hepatitis B, largely driven by a disproportionate incidence of liver cancer (Ramos-Rincón et al. Aliment Pharmacol Ther 2022).

The study examined 73,939,642 nationwide hospital admissions in Spain during the past two decades, from 1997 to 2017. A total of 129,634 (0.17%) included HBV as diagnosis. Most HBV admissions recorded chronic hepatitis B, being acute HBV anecdotal. In-hospital death occurred in 6.4%. The rate of HBV hospitalizations significantly increased over time with a transient drop around 2007, coincident with the arrival of new potent oral antivirals, entecavir, and tenofovir (Fig. 1). The median age of HBV hospitalizations steadily increased during the study period, from 44 to 58 years (Fig. 2). Although the proportion of HBV hepatic decompensation events has declined, the rate of liver cancer continues to rise. The small subset of patients with hepatitis delta superinfection increasingly and disproportionately accounts for hepatic decompensation events and liver cancer (Fig. 3).

These figures for hepatitis B contrast with the current favorable prognosis of hepatitis C virus (HCV) infection, which is declining globally, thanks to the cure given by the new oral direct-acting antivirals. The WHO estimates that the number of HCV infected patients has fallen to 58 million from 75 million a decade ago. Three months of oral medication eradicates HCV infection in most treated patients. Since then, the risk of cirrhosis and liver cancer is drastically reduced. In fact, hospitalizations in Spain for complications of cirrhosis due to HCV have decreased significantly since 2015 (Ramos-Rincón et al. J Viral Hepat 2022).

For more than 20 years, HBV vaccination has been carried out in all newborns in Spain. Thus, many of the new diagnoses of chronic hepatitis B are made in immi-

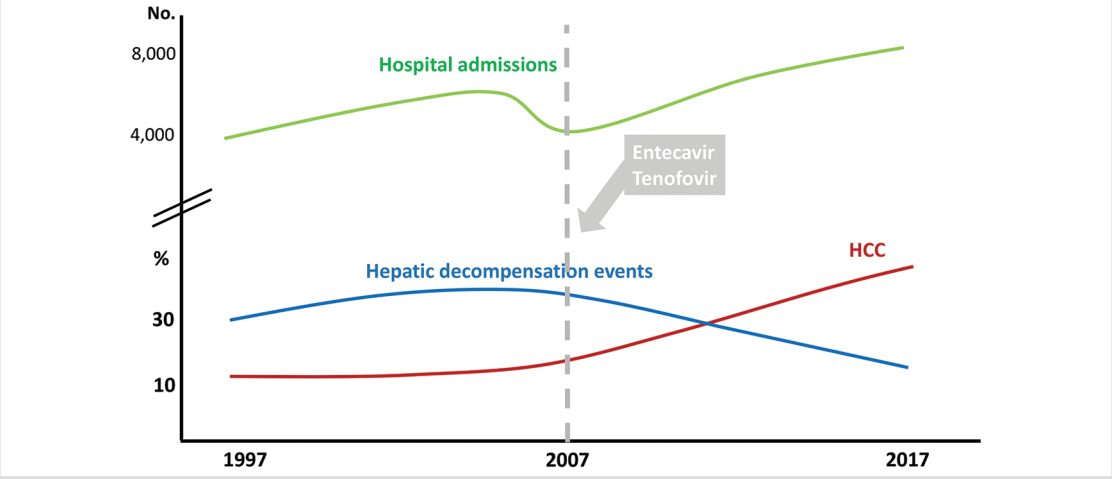

Figure 1. *Hospital admissions in patients with hepatitis B in Spain over two decades (adapted from Ramos-Rincon et al. Alim Pharmacol Ther 2022).*

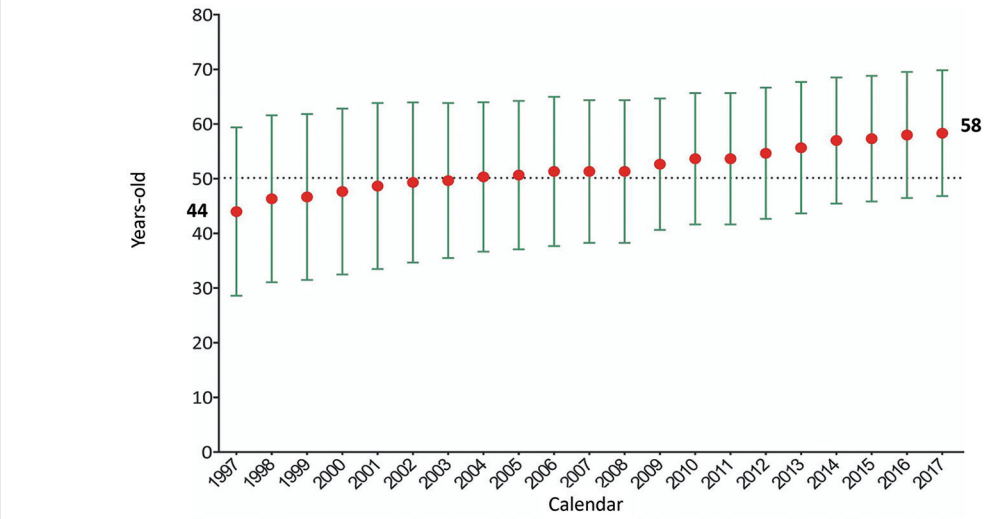

Figure 2. *Median age of patients hospitalized with hepatitis B in Spain over time (adapted from Ramos-Rincon et al. Alim Pharmacol Ther 2022).*

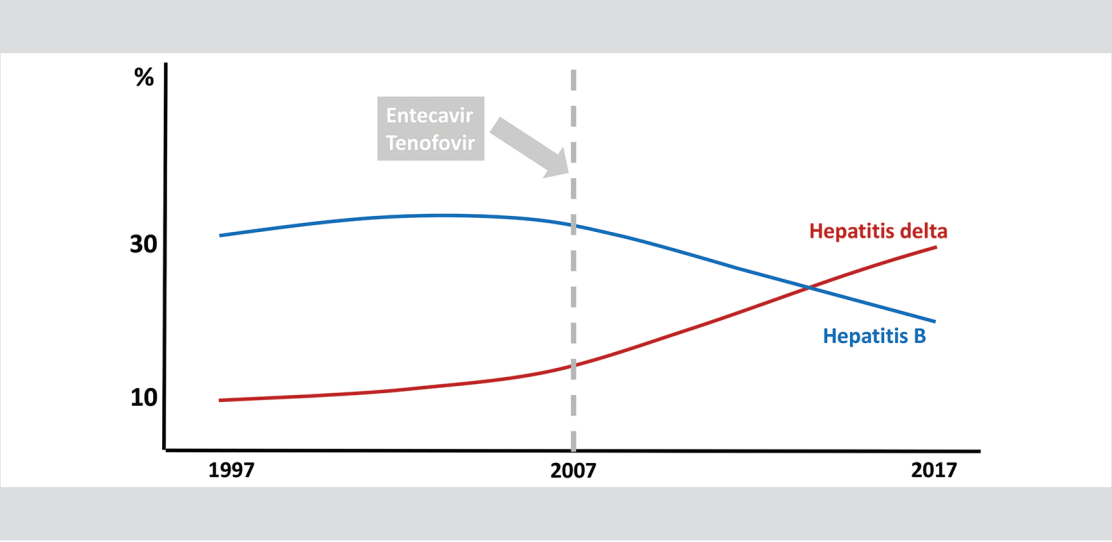

Figure 3. *Hospital admissions in (adapted from Ramos-Rincon et al. Alim Pharmacol Ther 2022) in Spain over two decades (adapted from Ramos-Rincon et al. Alim Pharmacol Ther 2022).*

grants who come from HBV endemic regions in Africa, South America or Asia. Oral HBV antiviral medication with tenofovir or entecavir allows to reduce viral load to undetectable levels in almost all treated patients, but HBV is not eliminated from infected hepatocytes. It remains hidden, silent, inside the nucleus as cccDNA. If the treatment is suspended, viral rebound occurs. Therefore, HBV antiviral treatment is lifelong, such as insulin for diabetics or antiretrovirals for HIV patients.

Nowadays, HBV is largely sexually transmitted, so people with sexual promiscuity are the most exposed to infection. Subjects who use intravenous drugs are also prone to HBV infection. It is important to underline that a small proportion of previously HBV vaccinated subjects may lose immune protection, so they may suffer acute hepatitis B if they are engaged in high-risk exposure practices. Therefore, it is important to screen all adults for hepatitis B markers at least once in their lives. A good

moment is when they come into contact with the health system for any reason. If they do not have protective HBV antibodies, they should be vaccinated. New trivalent HBV vaccines that are more effective have just been marketed. By contrast, if subjects harbor positive HBsAg, they should be considered for oral antiviral therapy and their close contacts tested (Weng et al. CDC. MMWR 2022).

A final consideration for hepatitis B concerns the risk of hepatitis delta virus superinfection. Individuals with chronic hepatitis B, even if asymptomatic, can become superinfected with HDV anytime. Uniquely HDV is a defective virus that only infects patients carrying hepatitis B. Coinfection produces the most severe form of chronic viral hepatitis, with progression to cirrhosis in more than half of cases. Unlike hepatitis B, there is no vaccine against HDV and only recently bulevirtide, a new antiviral that is administered subcutaneously, has shown to be effective, although viral rebound occurs uniformly on drug discontinuation (Wedemeyer et al. Lancet Infect Dis 2022).

It is necessary to exclude the presence of hepatitis delta in all patients with chronic hepatitis B, since the prognosis and treatment are very different. The small group of patients with hepatitis delta in Spain increasingly accounts for a disproportionate proportion of hospitalizations for liver cancer (Ramos-Rincón et al. Hepatol Int 2022). Therefore, advances in antiviral therapy against HDV are a priority. Hopefully, using combination therapies, hepatitis D might be cured in the near future (Soriano et al. Future Microbiol 2022).

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Controversy around SARS-CoV-2 Reinfections

The end of the SARS-CoV-2 pandemic may be announced in coming months, but this milestone will not mean that the virus has been eradicated, rather that the level of immunity in most of the World population is strong and perdurable enough to make reinfections less severe. As for other emerging respiratory viruses, the influenza agent as best example, the expected shift of COVID is from pandemic to endemic, from a potentially life-threatening infection to a common cold in most cases.

Factors that affect the risk of symptomatic reinfection are the intensity of immune response after prior infection or vaccination, and any significant antigenic change in the emerging SARS-CoV-2 variants (Holmer et al. Ann Intern Med 2022). In a recent study, the protection of vaccination against reinfection was lower for the Omicron as compared with the previous variants, and declined from 60% to 20% beyond 4 months of the last dose (Nielsen et al. PLoS Med 2022). With respect to the frequencies, recent estimates place the risk of reinfection with the Omicron variant in 2.99/10,000 individuals per day of follow-up. Of note, people 20–60 years old and healthcare workers had increased incidence of reinfections in another study (Piazza et al. Vaccines [Basel] 2022).

A recent study has challenged the view that SARS-CoV-2 reinfections are clinically milder than primoinfections, therefore questioning the close end of the pandemic. In a large, retrospective, and observational study, records from the electronic health-care database of the US Department of Veterans Affairs (VA) of more than 440 thousand people with a single infection, and from more than 40 thousand people with several infections, in more than 90% of cases one reinfection, were reviewed and compared with more than 5 million controls (Bowe et al. Nat Med 2022). Surprisingly enough, compared to those with no reinfection, those who had reinfection exhibited an increased risk of all-cause mortality (HR = 2.17, 95% CI = 1.93–2.45), and excess burden of all-cause mortality estimated at 19.33 (95% CI = 15.34–23.82) per 1000 persons at 6 months; the incidence of hospital admissions and of chronic complications was also greater after reinfections than after primoinfections. Furthermore, there was a rising hazard of adverse health outcomes as the number of infections increased. The poorer outcome of recurrent infections was seen in the acute and post-acute phases of reinfection, lasting for at least 6 months. The lag between primary and recurrent infection and the vaccination status did not affect the risk of complications after reinfection. These results are in sharp contrast to other large studies. For example, in a prospective and cohort study done in more than 1 million vaccinated individuals from 465 U.S. health-care facilities, the adjusted odds ratio of severe.

COVID in people with a past history of infection as compared with naïve individuals was 0.27 (95% CI = 0.09–0.84) (Yek et al. MMWR 2022).

Some critics may be done to try explaining these unexpected results, pointing at reinfections as more complicated than primoinfections. First, the age of the population taken from the VA cohort is significantly high, average age was over 60 years old and most

were male individuals, what may make recurrent infections more serious than in younger people due to accelerated loss of immunity. Second, among those with reinfections, 87% of people were not vaccinated and an additional 3% had followed suboptimal vaccination protocols, further contributing to the scarcity of immune protection in the face of reinfection; the rate of vaccination was greater, around 40%, among people with no reinfection. However, more importantly, the retrospective collection of data from clinical records probably has contributed to a bias of selection; at least from routine practice, people with first episodes of infection are more symptomatic than those with reinfection. Asymptomatic IgG-nucleocapsid seroconversion may occur in around 40% of cases of primary SARS-CoV-2 infection (Akinbami et al. MMWR 2022). If, as expected, milder COVID happens after recurrent infection, the number of cases in the reinfection group should have been greater than the number of cases recorded, which were the most severe, what may have overestimated the severity of reinfections.

The assessment of asymptomatic infections mostly relies in seroprevalence studies that discriminate IgG-spike (indicative of vaccination and/or infection) and Ig-G-nucleocapsid (indicative of infection). There is no clear data about the specific proportion of asymptomatic people in case of SARS-CoV-2 reinfections, mostly because it is not possible to determine if a serological pattern after SARS-CoV-2 infection in a persons without symptoms corresponds to a first or a recurrent episode. Ad hoc cohorts under prospective study need to be set to respond to this important question that needs to be clarified before affirming with numerical data that reinfections are more severe than primoinfections.

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Envisioning hepatitis delta cure without functional hepatitis B cure

Hepatitis D virus (HDV) is a small defective virus that only produces human infection along with the hepatitis B virus (HBV). HDV requires HBV-encoded envelope proteins for dissemination and *de novo* cell entry. However, it can also spread just by cell division of infected hepatocytes within each patient (Zhang et al. J Hepatol 2022). HDV replicates its 1.7 Kb circular single-stranded RNA genome in the nucleus of hepatocytes, but in contrast with the HBV genome – that persists indefinitely as cccDNA –, there is no lifelong HDV genome reservoir within infected cells. Although the half-life of circulating HDV particles has been estimated around 1.3 days (Shekhtman et al. Sci Rep 2020), at this time, no information exists about the intracellular half-life of HDV-RNA molecules. This is an important question when considering for how long should be given any curative HDV therapeutic strategy.

HDV infection causes the most severe form of either acute or chronic viral hepatitis. Approximately 15-25 million people are chronically infected with HDV worldwide (Stockdale et al. J Hepatol 2020). Simultaneous exposure to HBV and HDV (coinfection) mostly occurs in young persons and frequently produces acute hepatitis with jaundice. Fulminant HBV/HDV hepatitis is uncommon but potentially life-threatening. The majority of patients with acute HBV/HDV exposure resolve the episode without progressing to chronicity. In contrast, HDV super-infection may occur anytime in chronic hepatitis B patients; then, HDV uniformly establishes persistence. Chronic hepatitis delta is characterized by an accelerated course to cirrhosis and more frequent development of liver cancer. No specific antivirals to treat hepatitis delta existed until recently. Interferon alpha has been used for decades, but poor drug tolerance and low efficacy have discouraged its wide use.

The small HDV genome does not codify for any replication enzyme, as do other RNA viruses such as hepatitis C or HIV, for which drugs targeting these molecules (i.e., polymerases or proteases) have successfully been developed. It has been 10 years since the identification of NTCP as the receptor for HBV and HDV entry into hepatocytes (Yan et al. Elife 2012). The search for molecules that interfere with the binding of NTCP and HBV/HDV led to design bulevirtide (formerly known as myrcludex-B). This lipopolypeptide mimics a region of the pre-S1 domain of the hepatitis B surface antigen (HBsAg) and blocks viral entry by inhibitory competition (Lütgehetmann et al. Hepatology 2012; Bogolomov et al. J Hepatol 2016).

The results of the MYR-202 trial (Wedemeyer et al. Lancet Infect Dis 2022) were recently reported. This is a phase 2 study that examined bulevirtide plus tenofovir in patients with chronic hepatitis delta. A total of 120 patients from Germany and Russia were enrolled. Overall 60% (54/90) achieved undetectable HDV-RNA or > 2 log drop at week 24. The investigators and authors from an accompanying comment (Ito & Nguyen; Lancet Infect Dis 2022) argued that since 87% of patients were infected with HDV genotype 1 and 86%

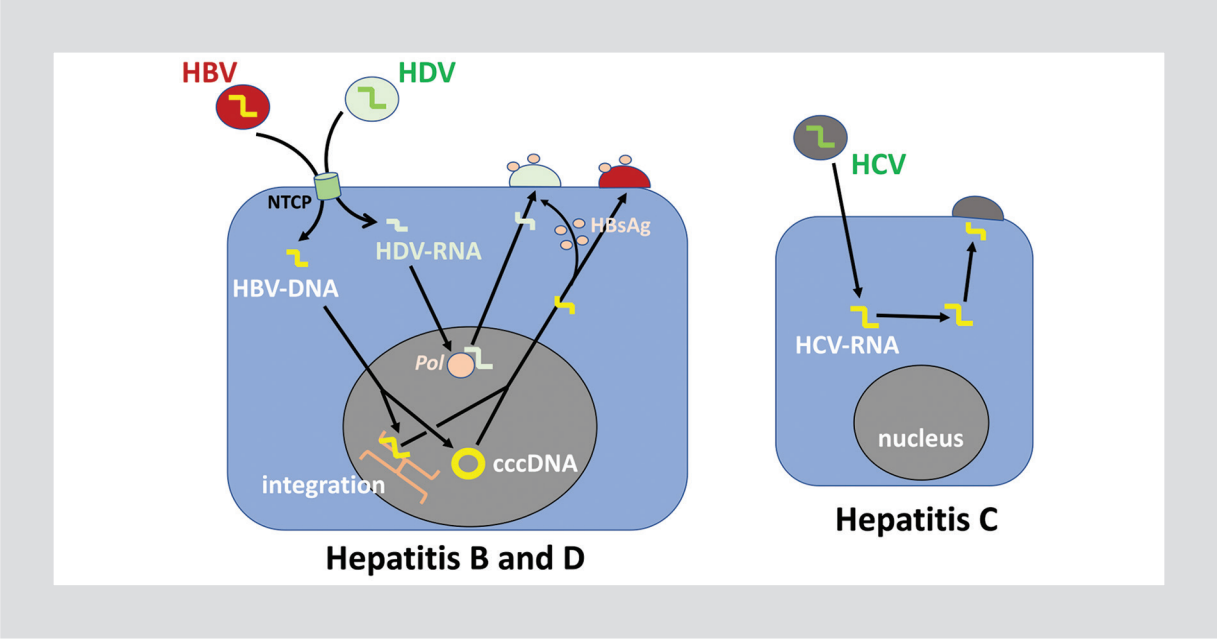

Figure 1. *Biological differences in the replication of hepatitis viruses. NTCP, sodium taurocholate co-transporter polypeptide; Pol, Human RNA polymerase II.*

were white, the results might not be generalizable to patients with other HDV variants and/or ethnicities. Moreover, they pointed out that longer treatment would be needed since all patients experienced HDV-RNA rebound on bulevirtide discontinuation at week 24.

Given the mechanism of action of bulevirtide and tenofovir, we believe that neither HDV variants nor ethnicity should be an important caveat. Furthermore, just extending treatment duration with bulevirtide plus tenofovir would unlikely cure hepatitis delta. Why is that?

First, bulevirtide activity across HDV genotypes. Bulevirtide is an entry inhibitor for hepatitis B and D viruses. It blocks the NTCP receptor at the hepatocyte surface causing inhibitory competition with the physiologic substrate, the bile acids. As defective virus, HDV uses HBsAg as part of its envelope and, in this way, enters hepatocytes using the same receptor that HBV. In this way, no effect on HDV variability should be expected on viral entry. Accordingly, a recent study has shown that bulevirtide is effective across all eight HDV genotypes (Manhas et al. J Hepatol 2022).

Second, HDV cure using bulevirtide. At the MYR-202 trial, the combination of bulevirtide plus tenofovir did not modify serum HBsAg concentrations. Thus, a rebound in serum HDV-RNA on bulevirtide discontinuation was expected. Rather than extending treatment duration, the advent of new anti-HDV agents will be required to achieve HDV elimination. A promising drug, lonafarnib, is completing phase 3 trials as HDV therapy (Yurdaydin et al. Hepatology 2022). It specifically blocks the assembly of HDV virions within hepatocytes. Peginterferon lambda is another antiviral currently been tested in phase 3 studies as hepatitis D treatment (Etzion et al. J Hepatol 2019).

Since there is no stable cell reservoir for the HDV-RNA genome, viral clearance might hypothetically be achieved if complete blocking of viral replication occurs using antivirals for a minimum timeframe (Soriano et al. Future Microbiol 2021). The combination of several specific anti-HDV agents will be required. This is what happens in hepatitis C combining direct-acting antivirals, with cure of nearly all patients treated for 3 months. Hepatitis delta is a unique condition, and clearance of HDV-RNA genomes might occur despite HBV persistence as cccDNA or integrated HBV-DNA within hepatocytes (Fig. 1). Supporting this concept is cases of HDV elimination despite persistence of serum HBsAg following treatment with bulevirtide or lonafarnib plus/minus peginterferon (Lampertico et al. J Hepatol 2022; Yurdaydin et al. Hepatology 2018; Anolli et al. J Hepatol 2022).

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