Advances in hepatitis B therapeutics

Vicente Soriano, Pablo Barreiro, Edward Cachay, Shyamasundaran Kottilil, José V. Fernandez-Montero and Carmen de Mendoza

Abstract: Despite the availability of both effective preventive vaccines and oral antivirals, over 250 million people are chronically infected with the hepatitis B virus (HBV). Globally, chronic hepatitis B is the leading cause of hepatocellular carcinoma, which represents the third cause of cancer mortality, accounting for nearly 1 million annual deaths. Current oral nucleos(t)ide therapy with tenofovir or entecavir suppresses serum HBV-DNA in most treated patients, but rarely is accompanied by HBsAg loss. Thus, treatment has to be given lifelong to prevent viral rebound. A broad spectrum of antivirals that block the HBV life cycle at different steps are in clinical development, including entry inhibitors, cccDNA disrupters/silencers, translation inhibitors, capsid assembly modulators, polymerase inhibitors and secretion inhibitors. Some of them exhibit higher potency than current oral nucleos(t)ides. Drugs in more advanced stages of clinical development are bulevirtide, JNJ-6379, ABI-H0731, ARO-HBV and REP-2139. To date, only treatment with ARO-HBV and with REP-2139 have resulted in HBsAg loss in a significant proportion of patients. Combination therapies using distinct antivirals and/or immune modulators are expected to maximize treatment benefits. The current goal is to achieve a ‘functional cure’, with sustained serum HBsAg after drug discontinuation. Ultimately, the goal of HBV therapy will be virus eradication, an achievement that would require the elimination of the cccDNA reservoir within infected hepatocytes.

Keywords: antiviral therapy, bulevirtide, cccDNA, chronic hepatitis B, combination therapy, gene editing, hepatitis delta, resistance

Received: 2 March 2020; revised manuscript accepted: 18 September 2020.

Introduction

Hepatitis B virus (HBV) is a small size, partially double stranded DNA virus of 3200bp that primarily infects human hepatocytes. Following acute HBV exposure in adults, immunity generally controls virus replication and expression, clearing HBV-DNA and hepatitis B surface antigen (HBsAg) from the bloodstream, and evoking markers of an immune response (anti-HBc and anti-HBs). However, HBV covalently closed circular dna (cccDNA) remains in a small proportion of hepatocytes, as a sign of past infection and, occasionally, it reactivates causing hepatitis B flare-ups.1

The majority of chronic HBV infections globally are acquired perinatally or during early childhood, as at that age viral persistence with chronic infection is a more frequent outcome. The world health organization (WHO) estimates that 257 million people are chronically infected with HBV and that hepatitis B causes 887,000 deaths annually.2 Despite an effective HBV vaccine being available since 1982, global HBV vaccine coverage is low, the birth dose globally being given only to 37%.2 Highly endemic HBV regions include South-East Asia and Sub-Saharan Africa, where over 5% of adults are hepatitis B surface antigen (HBsAg) carriers.2 In China alone, more than 90 million people harbor persistent serum HBsAg. Ongoing migration from endemic areas to better resourced countries in North America and the European Union account for more than half of new HBV diagnoses in western countries.1–4 Despite the high prevalence of chronic hepatitis B, only 10% of carriers are diagnosed globally and the proportion treated is below 1%.
The current goal of hepatitis B therapy is to reduce the risk of progression to cirrhosis, ameliorate extra-hepatic complications, diminish the development of hepatocellular carcinoma and prevent ongoing transmission.\(^1\) Using pegylated interferon alpha or nucleos(t)ide analogues, reduction of HBV-DNA generally occurs, the viral load becoming undetectable in a large proportion of treated patients. Having undetectable serum HBV-DNA correlates with normalization of liver enzymes, reduces risk of developing cirrhosis and liver cancer, and halts transmission.\(^1\) However, HBsAg loss is rarely seen, the amount of HBV covalently closed circular DNA (cccDNA) within the nuclei of hepatocytes is not affected, and the integration of HBV-DNA within the chromosomes of infected cells is not prevented. The ability to produce and secrete large amounts of viral subunit antigens (HBe, HBs) in chronic hepatitis B leads to exhaustion of HBV-specific T and B cell immunity. Most of these antigens are found in the bloodstream as defective viral particles, contributing to the immune tolerance state. This unique pathogenic mechanism for hepatitis B supports the theory that the restoration of specific HBV immunity could help to control the infection.\(^1\)\(^,\)\(^5\)

The achievement of a functional cure (undetectable serum HBV-DNA plus HBsAg loss with/ without anti-HBs seroconversion off treatment) is associated with excellent long-term outcomes.\(^5\) However, given that reactivations may occur, the ultimate goal of HBV therapy aims to eliminate the HBV cccDNA from the host (sterilization).\(^5\)\(^\text{-}^\text{8}\) At this time, it seems that the best roadmap for achieving HBV elimination should include a timely sequential intervention of antivirals followed by boosting immune restoration.

All current experimental drugs for hepatitis B treatment are grouped within these two existing categories: (a) direct-acting antivirals, such as nucleos(t)ide analogues; and (b) immune modulators, such as pegylated interferon alpha. Table 1 summarizes the most promising drugs under clinical development as HBV therapy. Hopefully combination therapies will allow the achievement of an HBV sterilizing cure.\(^6\)\(^\text{-}^\text{8}\)

**HBV entry inhibitors**

*Bulevirtide (myrcludex B)*

Bulevirtide (myrcludex B) is a lipopeptide of 47 amino acids corresponding to the pre-S1 domain of HBsAg. It irreversibly binds to sodium taurocholate cotransporting polypeptide (NTCP), the uptake cell membrane transporter that links to HBV and allows entrance into the hepatocyte (Figure 1). Given its mechanism of action, it

| Mechanism of action       | Antiviral family          | Drugs and delivery                        |
|---------------------------|---------------------------|-------------------------------------------|
| 1. Entry inhibitors       | NTCP inhibitors           | Myrcludex [Bulevirtide] [sc]               |
| 2. cccDNA disruptors      | Gene editing: CRISPR/Cas9 | Intravenous administration using vectors  |
|                           | Epigenetic silencers      | GS-5801 [sc]                              |
| 3. Translation inhibitors | siRNA                    | ARC-520, ARB-1467, ARO-B [JNJ-3989], AB-729 [sc] |
|                           | ASO                      | RO-2931, GSK-9404 [sc]                    |
|                           | RNA destabilizers         | AAB-452, RG-7834 [sc]                     |
| 4. Capsid assembly inhibitors | Assembly disruptors      | JNJ-440, JNJ-379, NVR-3778, ABI-H0731, ABI-H2158, AB-506 [oral] |
|                           | Core blockers             | RO-4389, GLS-4 [oral]                     |
| 5. Polymerase inhibitors  | RT chain terminators      | Tenofovir, entecavir, besifovir [oral]    |
| 6. Secretion inhibitors   | NAPs                      | REP-2139, REP-2165 [sc injection planned] |

AS0, anti-sense oligonucleotide; cccDNA, covalently closed circular DNA; HBV, hepatitis B virus; NAPs, nucleic acid polymers; NTCP, sodium taurocholate cotransporting polypeptide; sc, subcutaneous.
causes a dose-dependent increase in bile acids. Bulevirtide is given subcutaneously at doses of 10 mg/day.9 The drug may cause significant clinical drug interactions.10 Bulevirtide produces serum HBV-DNA and HBV-RNA declines, without significant changes in HBsAg.

Studies in patients with delta hepatitis using bulevirtide in combination with peginterferon have shown dual HBV and HDV efficacy.9 No serious side effects have been reported in short-term clinical trials. However, low vitamin D levels and osteoporosis are expected under long-term exposure. The induction of specific antibodies against bulevirtide does not seem to compromise its activity.10 Bulevirtide is moving along the pipeline to phase III studies where extended monotherapy or in combination with interferon are investigated in patients with hepatitis B. The drug was recently approved in Europe as treatment of viremic patients with hepatitis delta. In summary, bulevirtide leads to suppression of both HBV and hepatitis d virus (HDV) replication, without functional cure, but offers hope for synergistic activity in combination with other drugs.

Neutralizing antibodies
HBV entry blocking using high affinity specific neutralizing antibodies that target the pre-S1 region of HBsAg are being investigated by German researchers.11 Specific T-cell responses and antibodies are generated using pre-S1 DNA plasmids as immunogens. Hypothetically, they could mount immune responses as well as block virus binding to NTCP. The benefit of interfering with HBV entry blocking might be more significant than expected, as de novo HBV infection via the hepatocyte receptor NTCP seems to be required to maintain the cccDNA pool.12

**HBV cccDNA disrupters/silencers**
Once established, chronic HBV infection results in the expression of viral proteins from the HBV genetic reservoir within the nuclei of infected hepatocytes. HBV pre-genomic RNA and distinct messenger mRNA (mRNA) are transcribed from the four open reading frames in the cccDNA.6,7,12 Host chromosome integrated HBV genomes also express some viral products, mostly HBsAg (Figure 1).

Disruption of critical HBV genes (i.e. S, X, core and POL) using gene editing has been investigated in vitro and in animal models.13,14 Decreased levels of HBsAg and hepatitis B core antigen (HBcAg) have been demonstrated. Interestingly, the disruption of HBV cccDNA after targeting HBV genomic regions has been recognized in both
episomal DNA and chromosomally integrated HBV sequences. Overall, significant reductions in HBV cccDNA have been reported with minor side effects in the short term.13–16

The delivery of CRISPR/Cas9 with a specific HBV guide RNA (gRNA) of 20bp has been made using nanoparticles or vectors, such as adenov-associated viruses. Major challenges include: (a) persistence of a pool of infected hepatocytes that escape CRISPR/Cas9 action; (b) selection of resistance due to mutations in HBV sequences targeted by the gRNA; and (c) unwanted off-target effects, affecting products of other genes. Selection of escape mutants can be ameliorated using highly conserved viral regions and/or several targets (multiplex approaches).16

New gene editing technologies that directly target HBV cccDNA may cure without killing the infected hepatocytes.12 At this time, the CRISPR/Cas9 system is the most attractive approach because of its simplicity and cost, using gRNAs designed to target specific HBV sequences. Other gene therapy strategies are under study, including a few that intend to silence HBV epigenetically. Inhibition of HBV transcription from cccDNA has been shown with GS-5801, a pro-drug that blocks the activity of lysine demethylase 5, a key epigenetic regulator of the histone complex. Its inhibition increases the methylation of histones and silences HBV cccDNA.12

Gene editing strategies targeting HBV-DNA would generally lead to viral DNA destruction, if mutations are beyond repair. Alternatively, they may modify the viral genome leaving only defective molecules, thus no viral replication/production would be possible. In contrast, epigenetic silencing would not lead to HBV-DNA eradication. Instead, the intact viral genome would still be present in the infected hepatocytes, but it would be transcriptionally silent. Thus, only direct HBV cccDNA targeting could potentially achieve a complete HBV cure.12 Given the difficulties in measuring hepatic HBV cccDNA, several biomarkers have been examined that may correlate with the amount of viral genomes in HBV carriers. At this time circulating pregenomic HBV-DNA has carefully been examined as the best surrogate for assessing the effect of anti-HBV agents on cccDNA.12,14

Figure 2 shows graphically the major goals achievable using distinct HBV therapeutics. Of note, only direct interventions over the HBV cccDNA could lead to complete HBV eradication, and represent the most attractive therapeutic modality. However, agents within this class, as expected, are still in the early stages of clinical development.

**HBV translator inhibitors**

RNA interference (RNAi) compounds are short RNA molecules that target the transcripts of viral RNA. They overlap the sequence of the viral mRNAs, triggering their degradation.6–8,10,12 Given that immune exhaustion is a crucial feature of progression to chronic HBV infection, a major obstacle for HBV eradication is believed to be the massive release of HBsAg.1 Thus, RNAi molecules that directly target HBV transcripts may reduce the HBsAg load and lead to reduced budding of viral and subviral particles. In this way, their benefits would be double, derived from acting as direct antivirals and immune boosters, respectively.17

ARC-520 was the first RNAi molecule that entered HBV clinical trials. In a phase II trial, weekly doses of 2mg/kg produced only moderate HBsAg reductions, possibly due to the expression of HBsAg from integrated HBV-DNA, indicating the need for RNAi therapeutics that target viral transcripts regardless of origin, either as episomic cccDNA or integrated chromosomally.18 More recent data have shown that another RNAi named ARC-530 produces a significant and sustained decline in serum HBsAg.18

ARO-HBV (JNJ-3989) contains two RNAi that silence all mRNA produced from HBV cccDNA and host integrated viral DNA (Figure 1). It is administered subcutaneously. It does not cause significant drug interactions.10 In combination with nucleos(t)ide analogues, a mean reduction of 2–3 log10IU/mL in serum HBsAg was seen at 3 months. No serious adverse events were reported.10,12

Single stranded or anti-sense oligonucleotides (ASOs), such as RO-2931 or GSK-9404, are small nucleic acids complementary to their target RNA. Once bound, they promote RNA degradation. New molecules have been engineered to be liver specific and more stable, reducing viral replication and HBsAg, both in vitro and in vivo.10,12,19 Overall, RNAi agents that block the translation of HBsAg will be valuable in combination therapy with other antiviral agents.
Capsid assembly inhibitors

The HBV core protein (HBc) is essential for genome packaging. Capsid assembly inhibitors can reduce the release of infectious viral particles by destabilizing the HBV core protein assembly, leading to the formation of aberrant capsids or morphologically normal capsids without genetic material. These drugs show further benefits inhibiting the recycling of relaxed circular DNA (rcDNA) into the nucleus and thus leading to reductions in the cccDNA pool (Figure 1). Depending on their chemical structure, there are two classes, core blockers and assembly disruptors.

NVR-3778 was one of the first molecules within this class. In a phase I trial, it was given orally twice daily, reducing 1.5–2.0 log₁₀ serum HBV-DNA and HBV-RNA. The effect was more pronounced in combination with peginterferon. However, there was no effect on serum HBsAg levels.

ABI-H0731 blocks the packaging of pre-genomic RNA into nucleocapsids. In addition, it interferes with trafficking of the mature nucleocapsid into the nucleus, resulting in empty capsids, and failure to replenish the HBV cccDNA pool. Oral administration of 300 mg/day seems to be the optimal dose. In one study, dose-dependent activity was reported at 4 weeks, with maximum HBV-DNA and HBV-RNA drops of 4 log₁₀ IU/mL. However, no changes in HBsAg or hepatitis B e antigen (HBeAg) were recorded. Furthermore, baseline polymorphisms at the HBV core gene (T109M) seemed to compromise its activity. Finally, more pronounced effects were seen when the drug was given in combination with nucleos(t)ide analogues. No serious adverse events were recorded but skin rash. ABI-2139, a second generation and more potent CAM is being tested in phase II studies.

JNJ-6379 binds to the HBV core protein (HBcAg) and interferes with assembly and encapsidation of pre-genomic RNA. In addition, it blocks HBV cccDNA formation. Oral doses of 100–300 mg/day have been examined. The drug shows a very long half-life of 120–140h. At week 4, serum HBV-DNA and HBV-RNA mean declines were of 2.0–2.5 log₁₀ IU/mL. However, no effect was recognized on HBsAg neither on HBeAg. Baseline polymorphisms (Y118F) are present in 7% of individuals and might compromise its antiviral activity. No serious adverse effects have been reported to date.

HBV polymerase inhibitors

Nucleos(t)ide analogues (NAs) inhibit the retro-transcription by the viral polymerase and reduce the formation and synthesis of viral DNA from the pre-genomic RNA (pgRNA). RNA enzyme type I (RNAseH) inhibitors produce the accumulation of long RNA:DNA heteroduplexes and block the production of HBV-DNA strands. A rapid decay of serum HBV-DNA occurs after beginning treatment with NAs, whereas the decline of serum HBsAg and of liver cccDNA is slow and incomplete. Moreover, the HBV cccDNA is detected in the liver even after years of treatment. As low-level HBV replication persists despite successful treatment with NAs, naive
hepatocytes can be constantly infected. During long-term NA therapy, continual HBV cccDNA recycling contributes to the replenishment of the intrahepatic pool.\textsuperscript{12,17}

Tenofovir is an adenosine analogue that shows a potent inhibitory effect on HBV replication. Tenofovir alafenamide (TAF) is a pro-drug with a safer kidney and bone profile than tenofovir disoproxil fumarate (TDF), the oldest medication.\textsuperscript{23} A new lipid conjugated formulation is under clinical development, named tenofovir exalidex. It shows an enhanced hepatic targeting that maximizes liver activity while reducing systemic drug exposure.\textsuperscript{12} Preliminary data suggest that it could enhance HBsAg loss and reduce the cccDNA amount.

Given the high cost of oral anti-HBV medications tenofovir and entecavir, their prescription has been limited to date, particularly in developing countries. However, the recent expiration of patent rights for TDF and entecavir has brought the opportunity for expanding their prescription to a larger number of chronic hepatitis B individuals. Acknowledging the experience from the HIV field, where treatment has increasingly moved to earlier disease stages accompanying drug discovery and access to more and stronger medications, the European Association for the Study of the Liver (EASL) guidelines are increasingly favoring ‘test & treat strategies’ for HBV.\textsuperscript{24} Briefly, the principle is that suppression of HBV replication in any given HBsAg-positive patient would be associated with a double benefit, namely an individual’s lower risk of liver complications and a population reduced risk of transmission.

Besifovir is a guanosine analogue developed in South Korea that exerts potent HBV antiviral activity. In a non-inferiority trial, besifovir had antiviral efficacy comparable to tenofovir after 48 weeks of treatment, with durable effects over 96 weeks. Besifovir had a better safety profile than TDF, in terms of bone and renal outcomes.\textsuperscript{25} The only significant side effect of besifovir in initial studies was L-carnitine depletion, which can potentially lead to myonecrosis and hypoglycemia, requiring carnitine supplementation.

**HBsAg release inhibitors**

Secretion inhibitors reduce HBsAg subviral particle release from hepatocytes. These non-infectious particles are partly responsible for the exhaustion of adaptive immune responses in chronic HBV infection (Figure 1). For this reason, it is believed that HBV secretion inhibitors mostly act by restoring the immune function rather than halting viral particle release.\textsuperscript{6–8,10,17} Given this mechanism of action, some nucleic acid polymers (NAPs) can prevent virus budding and reduce HBsAg in a unique way, as non-specific gene targets are used.

REP-2139 is a phosphorus-derivate oligonucleotide that has to be administered subcutaneously.\textsuperscript{26} Other oligonucleotides that have already been approved for other medical conditions are mipomersen (as treatment for homozygous familial hypercholesterolemia), volanesorsen (as treatment for familial chylomicronemia syndrome), and inotersen (as treatment for hereditary transthyretin-mediated amyloidosis). All these compounds bind to plasma proteins and show mean half-lives lasting from weeks to months.

Results from clinical studies with REP-2139 have been promising with regard to HBsAg reduction and HBsAg loss, either alone or in combination with nucleos(t)ides and/or peginterferon alpha.\textsuperscript{26} Although originally dosed as a weekly intravenous administration, subcutaneous formulations are under investigation. Interim data from a larger trial (study 401) involving 40 patients treated with triple therapy (interferon, tenofovir plus REP-2139) showed that 24 patients experienced HBsAg seroconversion at one year. Thrombocytopenia and increases in liver enzymes have been reported in a subset of patients treated with REP-2139.\textsuperscript{27} During 48 weeks of treatment-free follow-up, virological control persisted in 13 of 40 participants (two lost to follow-up after 24 weeks), whereas functional cure persisted in 14 of 40 participants (all completing 48 weeks of follow-up) with persistent HBsAg seroconversion.\textsuperscript{28}

To date, REP-2139 has provided the most promising results for HBV functional cure, with loss of HBsAg and development of anti-HBs in a significant proportion of patients. Phase III studies are ongoing with the new subcutaneous formulation.

**HBV immunomodulators**

HBV infection triggers both innate and adaptive immune responses that pursue the control of virus replication. In this attempt, patients with chronic hepatitis B experience an exhaustion of their adaptive HBV-specific immune responses.\textsuperscript{1} These patients are not broadly immunosuppressed and,
therefore, the use of immune modulators in hepatitis B should aim the activation of the impaired host immune response specifically towards the virus. Interferon alpha has been the classical molecule exploiting this approach.

Activation of innate immunity has been investigated using toll-like receptors (TLRs) or RIG-1 agonists. Inarigivir (SB9200) is an oral agent that induces the interferon signaling pathway.\(^{10,17}\) In the phase II ACHIEVE trial, 80 chronic hepatitis B patients receiving doses of 50 mg/day produced mean declines in HBV-DNA and HBV-RNA of 1 log\(_{10}\) IU/mL at 3 months. Moreover, the proportion of patients with undetectable viremia increased with a longer duration of therapy and up to one quarter of patients experienced HBsAg loss.\(^{10,17}\) However, the unexpected death of a patient in a phase II trial recently led to termination of inarigivir clinical development.

Two main TLR agonists have been tried as HBV therapy. GS-9620 induces interferon by plasmacytoid dendritic cells, present in the gut and liver. Phase I/II trials, however, failed to show any significant antiviral effect.\(^{29}\) GS-9688 is a TLR-8 agonist that induces IL-12 and IL-18 production from hepatic monocytes and dendritic cells.\(^{30}\) Although phase II studies with GS-9688 have shown only modest effects on HBsAg levels, this molecule holds promise as a part of combination therapy.

Immune therapy for HBV using checkpoint programmed cell death protein type 1 (PD-1) inhibitors have been tried with only modest efficacy. In addition, several therapeutic vaccines have also been tested, generally with poor results, suggesting that boosting the immune system alone in chronic hepatitis B patients is not sufficient to mount an immune response that can lead to functional cure.

**HBV combination therapy**

Following the lessons from the HIV field, the chances of achieving a long-lasting functional cure for hepatitis B, with no rebound after stopping therapy, would be higher using combination therapy with drugs targeting different steps in the virus replication cycle. One of the most attractive approaches is the use of virus entry blockers complemented with maturation inhibitors, such as oral capsid assembly inhibitors.\(^{31}\) Another combination that could act synergistically relies on the use of NAs plus CAMs, because these molecules target critical steps in the HBV replication cycle, and already have been shown to enhance viral load reductions. Whether it would restore HBV immune responses that would result in viral clearance or an additional booster of the immune system will be required is so far unclear.\(^{31}\) The most recent evidence suggests that combination therapy for hepatitis B should both disrupt the HBV replication cycle and restore the immune function against HBV antigens. Pre-clinical studies in animal models support this approach,\(^{31}\) suggesting that sequential interventions using first antivirals and thereafter immune boosters would be the best way to proceed.

### Special patient populations

**Hepatitis delta**

Tremendous progress in the treatment of hepatitis C virus (HCV) infection has occurred in recent years. As a consequence, hepatitis C, the leading indication for liver transplantation for many years now ranks third in the United States. For hepatitis B, the widespread use of nucleos(t)ide analogues has halted liver disease progression in most treated HBsAg carriers, but medication is lifelong and HBV is not eradicated. Based on the above considerations, liver mortality due to HBV or HCV in western countries is declining and increasingly unveiling hepatitis delta as a major responsible agent, as first alerted by two European HIV cohort studies.\(^{32,33}\) Sadly, HDV has been neglected for many years despite the fact that it causes the most severe form of viral hepatitis in humans.

HDV is a defective virus that uses the HBV surface antigen to enter hepatocytes (Figure 3). It is associated with an accelerated course of liver fibrosis progression and an increased risk of hepatocellular carcinoma. The prevalence of HDV infection is measured by a positive anti-HDV test in HBsAg carriers. Global estimates for HDV range from 48 to 74 million people.\(^{34–38}\) High prevalence areas include Central and West Africa, Central Asia, Mongolia, Pakistan, some Pacific Islands, Eastern Europe, the Middle East and Turkey, the Amazonian basin, and Greenland. China accumulates the largest number of HDV-infected people, Pakistan being second.\(^{37,38}\)

Given the dependence of HDV on HBV, drugs active against HBV should indirectly benefit
hepatitis delta. This has been well established using HBV inhibitors of entry, the polymerase and HBsAg secretion.\textsuperscript{11,26–28,39} In contrast, drugs only active against HDV, such as lonafarnib,\textsuperscript{39} may not exert any activity against HBV. On one hand, complete suppression of HDV replication for a while might hypothetically result in HDV eradication despite HBV persistence.\textsuperscript{40} On the other hand, a functional cure for HBV would result in HDV clearance, given that HDV propagation requires HBsAg. As a reference, this unique situation has already been proved using peginterferon alpha with and without NAs.\textsuperscript{41,42}

**HIV coinfection**

Given shared transmission routes, HBV and HIV coinfection is relatively common. Globally, 10% of the 38 million people with HIV infection harbor chronic hepatitis B (Figure 4).\textsuperscript{43} In a large retrospective North American cohort study, that included HIV/HBV-coinfected patients from 1996 to 2010, low CD4 cell counts and sustained detectable HIV-RNA were independent predictors of hepatic complications.\textsuperscript{44} One advantage for HIV-HBV coinfected patients is that many antiretroviral regimens contain medications that are active against both HIV and HBV, such as tenofovir and emtricitabine.\textsuperscript{45}

In an era of newer co-formulated drug options and forthcoming long-acting HIV regimens, clinicians making decisions relative to treatment simplification need to be aware of their patients’ HBV status. For instance, antiretroviral regimens such as co-formulated oral rilpivirine plus dolutegravir or using long-acting formulations of cabotegravir plus rilpivirine have no activity against HBV.\textsuperscript{46} Unless additional HBV drugs are given, inadvertent HBV flare-ups may occur, potentially being severe and causing liver failure.\textsuperscript{43}

**Occult hepatitis B infection**

The presence of serum HBV-DNA in the absence of circulating HBsAg has been associated with both liver disease and transmission.\textsuperscript{47} This population represents a small subset of individuals that were exposed to HBV in the past and that cannot completely control virus replication. In the presence of immune suppression, as in untreated HIV infection, occult hepatitis B infection (OBI) could be more frequent.\textsuperscript{48} Antiviral therapy for OBI has generally been discouraged, but the advent of more potent antivirals might change this view, at least in certain settings; that is, individuals beginning treatment with immunosuppressors. However, major difficulties exist for designing studies that would assess the clinical benefit of antiviral therapy in HBV viremic but seronegative (HBV-DNA-pos/ HBsAg-neg) individuals.

In summary, current antiviral therapy for chronic hepatitis B is effective in suppressing HBV replication, that translates into serum HBV-DNA
undetectability in most treated patients. Newer drugs in the pipeline target different steps of the HBV life cycle and may add the benefit of reducing HBsAg hepatocyte secretion, that would translate into a functional cure. As these new agents make their way through safety and efficacy studies, opportunities exist for the attainment of HBV functional cure combining distinct antivirals. The achievement of significant reductions and eventually elimination of cellular HBV reservoirs, such as cccDNA and integrated HBV-DNA, would require new strategies and/or drugs, most likely combining gene therapies, antivirals and immune modulators. Moreover, improved pharmacokinetic drug formulations; that is, using long-acting antivirals, might provide unique opportunities for enhancing drug exposure and overcoming the worsening of good drug adherence generally associated with prolonged oral therapies.

**Author contributions**

VS reviewed the recent literature on the topic and wrote the original manuscript. PB, SK, EC, JVFM and CdM contributed with suggestions in different areas of their respective expertise on successive drafts. All authors reviewed the final submission.

**Conflict of interest**

The authors declare that there is no conflict of interest.

**Funding**

The authors received no financial support for the research, authorship, and/or publication of this article.

**ORCID iD**

Vicente Soriano  
https://orcid.org/0000-0002-4624-5199

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**Figure 4.** Global distribution of HIV and HBV.

HBV, hepatitis B virus.
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