Medical Research Archives

ESMED
European Society of Medicine

OPEN ACCESS

Published: November 30, 2022

Citation: Chen PH and Han S, 2022. An Update on the Current Management of Hepatitis B Virus in Special Populations, Medical Research Archives, [online] 10(11). https://doi.org/10.18103/mra.v10i11.3315

DOI
https://doi.org/10.18103/mra.v10i11.3315

ISSN: 2375-1924

RESEARCH ARTICLE

An Update on the Current Management of Hepatitis B Virus in Special Populations

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ABSTRACT

Hepatitis B (HBV) in special populations within this article is considered as acute on chronic liver failure due to HBV, coinfection with Hepatitis C (HCV), Hepatitis D (HDV), or Human Immunodeficiency Virus (HIV), and HBV infection in patients who are in immunosuppressive states due to specific therapies and liver transplant recipients. Patients within these special populations are at higher risk of liver-related complications such as fibrosis, accelerated cirrhosis, acute on chronic liver failure, and/or development of hepatocellular carcinoma (HCC). Given their respective complex pathophysiology, specific treatment approaches are required for each population. With the introduction of effective antiviral HBV therapies over the past decade and the respective treatment options for the special population diseases, patient outcomes have seen improvement. With the advent of HCV direct antivirals, treatment of HBV-HCV coinfection has been more successful and consistently shown high rates of sustained virologic response. Treatment of HBV-HDV coinfection remains primarily as interferon-based, though new promising therapies have shown greater improvement in viral suppression. HBV-HIV coinfection has also shown promising results given overlapping mechanisms for treatment and specific regimens should be chosen to decrease risk of resistance. HBV reactivation in patients undergoing immunosuppressive therapies have been reported and guidelines recommend close monitoring and in certain cases, HBV antiviral therapy prophylaxis. With the effective HBV therapies, the perception of HBV as a contraindication for liver transplant has been diminishing and prolonged graft survival with effective antiviral therapies have shown promising outcomes.

Aim

The aim of this article is to review the current literature to help inform clinicians on how to effectively treat and monitor patients within the HBV special populations.

Acute Liver Failure Patients

Acute liver failure (ACLF) is a clinical syndrome of rapid hepatic function loss and often presents with coagulopathy and encephalopathy in a patient without pre-existing cirrhosis[1]. Acute liver failure in the United States is primarily caused by drug related hepatotoxicity such as from excessive acetaminophen[2]; whereas acute hepatitis B (HBV) accounts for approximately 7-19% of cases. In endemic areas like Asia, HBV accounts for up to 21-38% of ACLF cases[3]. Prior data showed that survival rates are between 19-33% for patients with ACLF secondary to HBV (ACLF-HBV) who do not undergo liver transplantation[4], and the 90-day mortality rate ranges from 50 to 70%[5,6]. Specifically, the genotypic presence of precore stop codon (G1896A) and core promoter dual (T1762A, A1764T) variants has been suggested to increase the risk of developing ACLF due to HBV[7]. Liver transplant (LT) is the primary therapeutic option for ACLF due to HBV and has reported survival rates up to 80%[8]. Given the limited option for liver transplants, many studies have investigated the role of HBV antivirals and other experimental approaches such therapies targeting the immune system for ACLF-HBV.

Entecavir (ETV), Lamivudine (LAM), Tenofovir Disoproxil Fumarate (TDF), and Tenofovir Alafenamide (TAF) are the drugs most studied in HBV related ACLF. Tillman et. al previously investigated LAM in ACLF-HBV patients and found that 14 of 17 (82.4%) LAM-treated patients survived without LT[9]. A subsequent prospective study of LAM in 18 HBV-ACLF patients compared to 17 placebo patients showed no statistically significant benefit of LAM, though the LAM group showed improvement in bilirubin (32% vs 26.5%), alanine aminotransferase (ALT) normalization (48% vs 35%) and hepatitis B surface antigen (HBsAg) clearance (67% vs 48%) when compared to placebo[10]. Chen et. al. prospectively studied patients with ACLF-HBV treated with ETV (n = 106) and LAM (n = 215). The ETV group achieved better virological suppression (HBV DNA <300 copies/ml) than the LAM group both at week 24 (p = 0.043) and week 48 (p = 0.007), but when adjusting for baseline factors, the study concluded that neither antiviral drug was associated with better overall or liver-related mortality rate[11].

A prospective study of TDF in 27 patients with ACLF-HBV showed that it reduces HBV-DNA viral levels (P <0.01) and improved Child Turcotte Pugh (CTP) and Model for End-Stage Liver Disease (MELD) scores (P <0.01) when compared to placebo[12]. At the 90-day follow-up, one of eight (12.5%) TDF-treated patients lost HBsAg and three of five (60%) TDF-treated patients lost HBeAg compared to no patients, respectively, in the placebo group[12]. Another prospective study of 40 ACLF-HBV patients by Li et al. compared ETV, TAF, and TDF in the treatment of HBV-ACLF. At week 48, 8 (80%) patients in the TAF group, 6 (60%) patients in the TDF group, and 17 (85%) patients in the ETV group survived without liver transplantation, but these survival differences were not statistically significant (P = 0.251)[13]. Finally, in a double blind, randomized phase III trial of ACLF-HBV patients comparing TAF and TDF, Agarwal et. al. showed that at week 48 and week 96, TAF was equally efficacious as TDF in suppressing HBV, but demonstrated improved renal and bone safety[14]. Given high resistance rates associated with LAM, ETV and TDF/TAF are favored in the treatment of ACLF-HBV[12,15,16].

Other experimental therapies for ACLF-HBV are currently being explored. The role of thymosin alpha 1 (Tα1), an immunomodulatory peptide that acts on toll-like receptors on dendritic cells and T-cells which increases activity of natural killer cells, has been studied in ACLF-HBV patients. Chen et. al. studied 120 patients with ACLF-HBV in a randomized control trial comparing Tα1 monotherapy to standard therapy (ETV or TDF). The 90-day cumulative liver transplantation free survival rate in Tα1 was 75% compared to 53.4% in the standard medical therapy group (P = 0.03), and the incidence of complications such as bacterial infection and hepatic encephalopathy was lower in the Tα1 group (32.1%) compared to the standard treatment group (58.6%) (P = 0.029)[17]. Granulocyte Colony Stimulating Factor (G-CSF) was compared to standard therapy in in a randomized control trial of 114 HBV-ACLF patients, and the G-CSF group was shown at 180 days to have greater survival (72.2 vs. 53.8%, P 0.014)[18]. However, aside from immediately starting antiviral therapy for ACLF-HBV, these newer modalities are still under investigation and cannot be recommended.

Hepatitis C and Hepatitis B Coinfected Patients

Prevalence of Hepatitis C (HCV) coinfection ranges between 7-15% in patients with chronic HBV[19,20],

but the true prevalence is unclear. HBV and HCV viremia in coinfected patients usually demonstrates a fluctuating dominance between the two viruses over periods of time, though HCV typically is more predominant[20,21]. Previous studies have demonstrated HBV-HCV coinfected individuals tend to have more severe liver disease such as a higher risk of fibrosis, cirrhosis, and piecemeal necrosis and an increased incidence of hepatocellular carcinoma (HCC)[21–23]. The introduction of HCV direct acting antivirals (DAAs) has not only improved sustained virologic response rated (i.e., cure) for HCV mono-infected patients, but also dynamically transformed the treatment management of HBV-HCV coinfected individuals.

Given the alternating dominance patterns of HBV-HCV co-infected patients, there were initial concerns about HBV reactivation post-treatment with HCV DAAs. A meta-analysis with a sample size of 779 patients with HBV-HCV coinfection found the incidence of HBV reactivation was similar in those treated with interferon-based treatments (14.5%) compared to DAA (12.2%), but reactivation occurred much earlier (4-8 weeks) in DAAs (12.2%) compared to interferon-based regimens (0%)[24]. Doi et. al. retrospectively identified 159 hepatitis B core antibody (HBcAb)-positive patients who completed 12 weeks of ledipasvir/sofosbuvir or sofosbuvir/ribavirin at multiple centers and identified HBV reactivation (defined as HBV DNA > 20 IU/ml) in 3.4% (5/147) of the patients (2 HBsAg positive and 3 HBsAg negative), though no patient developed HBV associated hepatitis[25]. Another retrospective study in Taiwan and Korea of 103 HBcAb-positive patients treated with HCV DAA showed that no patients developed HBV reactivation[26]. In a multicenter, prospective study of 111 HBV-HCV coinfected patients treated with Ledipasvir and Sofosbuvir for 12 weeks, 31 patients with a baseline HBV DNA < 20 IU/mL had at least 1 episode of elevated HBV DNA during the post treatment phase. Among the 31 patients with a quantifiable HBV viral load, 2 patients had elevated ALT >2 upper limit of normal, and one patient required HBV antiviral therapy due to development of malaise, anorexia, and jaundice[27].

With the emergence of DAAs, treatment of HBV-HCV coinfection has become more tolerable and effective. Reactivation rates of HBV during the treatment of HCV coinfection ranges widely. In 2016, the US Food and Drug Administration issued a black box warning for all HCV patients undergoing DAA, they must first be screened for HBV[28]. For patients with a history of chronic HBV, it is imperative to regularly monitor liver enzymes and serum HBV DNA and to initiate prompt HBV antiviral treatment for clinically significant HBV reactivation. Treatment approaches of HBV-HCV coinfected individuals begin first with identifying the dominant virus and then treating the dominant virus with close monitoring for reactivation of the non-dominant virus[29]. For HBV, ETV or tenofovir-based regimens (TDF or TAF) have been recommended given their high barrier to genetic resistance[30] and routine close monitoring of serum ALT.

Hepatitis D and Hepatitis B Coinfected Patients

There are an estimated 12 million people worldwide with hepatitis D virus (HDV) infection[31], which is about 5% of chronic HBV carriers globally. HDV requires the presence of HBV to express its virulence. It has greatest prevalence in the Mediterranean Basin, South America, and parts of Asia[32], and in the United States and Northern Europe, it is estimated to affect about 1% of patients with chronic HBV. HBV coinfection with HDV is associated with more severe liver disease compared to HBV mono-infection[33]. Vigilant screening and vaccination to prevent chronic HBV infection and effective treatment of active HBV is important given limited effective therapies currently exist to treat HDV[34].

Interferon based therapies have been the mainstay of HDV treatments for decades[35,36], but currently, HDV does not have a US Food and Drug administration approved therapy[37]. Prior studies of pegylated interferon (peg-IFN) therapies with modest sample sizes have shown HDV suppression in roughly 50-57% of HBV-HDV coinfected individuals and a survival benefit with HDV RNA and HBV DNA clearance[35,36,38]. Yurdaydin et. al. compared IFN monotherapy, LAM monotherapy, and combination IFN with LAM in 39 patients and found treatment responses were similar in terms of virologic levels and liver function outcomes across all experimental arms[39]. Another study of 38 HBV-HDV coinfected patients used peg-IFN monotherapy for 72 weeks which resulted in low-level or undetectable HDV RNA in 34% of the patients. However, at 24 weeks post therapy, only 21% of the patients had undetectable HDV viral levels[40]. A retrospective study of 50 patients suggests that HDV RNA levels at 24 weeks of treatment for HDV (with or without adefovir) can help predict treatment response and should help guide a provider's clinical judgment on prolonged IFN therapies[41]. From a patient perspective, interferon therapies are often difficult to tolerate

due to major side effects such as flu-like symptoms, myalgias, and arthralgias[37,40].

Other therapies such as Bulevirtide[37], an HBV and HDV entry inhibitor, and Lonafarnib[42], an inhibitor that disrupts the interaction of HDV and HBV, are currently being explored. Bulevirtide is currently undergoing randomized, multicenter studies and has been shown to decrease HDV RNA in a dose dependent manner and to normalize ALT in about 50% of patients[43,44]. However, HDV RNA relapse did occur in follow-up in up to 80% of the subjects who initially responded[44]. Lonafarnib is also currently being investigated in randomized, placebo-controlled studies of HDV patients and has shown promising dose-dependent HDV RNA decline when used in addition to peg-IFN, which seems to have synergistic effects[45,46]. However, since these newer medications currently remain under investigation, recommendations for their use cannot be made at this time, and standard of care remains peg-IFN.

Human Immunodeficiency Virus and Hepatitis B Coinfected Patients

Within the United States and Europe, it is estimated that approximately 7-10% of the patients with human immunodeficiency virus (HIV) infection have chronic HBV coinfection, and HIV-HBV coinfection is more common in men who have sex with men and individuals who inject drugs[47,48]. HBV-HIV coinfection is not only associated with a fivefold decrease in HBeAg clearance, but also associated with an elevated risk of developing chronic HBV after acute infection (up to sixfold risk), accelerated fibrosis/increased risk of cirrhosis, development of HCC, and liver-related deaths[49–52].

Current guidelines recommend all patients with HIV be started on antiretroviral therapy (ART) irrespective of CD4 count[34]. When initiating HBV-HIV therapy, the primary regimens should include nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) with coverage of both HBV and HIV to prevent viral resistance development; these formulations include tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF), with emtricitabine (FTC) or Lamivudine (LAM). There are 3 fixed dose combinations (1)elvitegravir /cobicistat/emtricitabine/TAF, (2) emtricitabine/ rilpivirine/TAF and (3) emtricitabine/TAF[34]. First line therapies for HBV-HIV should include tenofovir given resistance mutations to tenofovir are rare[53] even in patients with prior LAM exposure or resistance[54].

Prior to starting antiviral therapy, baseline renal function should be assessed and for patients with creatinine clearance less than 30 ml/min, ETV can be an option[55]. A large, multicenter randomized control trial showed similar efficacy of TAF to TDF, but improved bone mineral density (through assessment of T scores of hips and spine) and renal function in the TAF group[56]. Another study looking into TAF co-formulated with elvitegravir, cobicistat and emtricitabine in 72 HIV-HBV coinfected individuals showed, at 48 weeks, 91.7% achieved and maintained both HIV and HBV viral suppression[57]. Of the 70 patients who were HBsAg positive and HBsAb negative prior to initiation of therapy, 1.4% (1/70) had HBsAg to HbSAb seroconversion at week 24, and 2.9% (2/70) lost HBsAg at week 48[57]. Finally, a retrospective study of 1419 HBV-HIV patients was conducted in France and patients were categorized into three groups: (1) LAM or FTC (N = 150), (2) TDF with or without LAM or FTC (N = 489), or (3) LAM or FTC followed by adding or switching to TDF (N = 780) and followed for 89 months[58]. Overall, 97 patients cleared HBsAg. High CD4 count, short delay between HBV diagnosis and treatment, longer duration of HBV therapy, African origin, and TDF-based therapy were independent predictors of HBsAg clearance[58].

After initiating antiviral therapy, monitoring of HBV DNA and ALT should be performed every 3 months[34]. Goals of antiviral therapy include preventing disease progression (i.e., development of cirrhosis, HCC), durable HBV viral suppression ALT normalization, HBeAg seroconversion, and ultimately loss of HBsAg[59]. Primary treatment endpoint is usually sustained HBV DNA suppression, which is achieved in most patients in 1-3 years[60,61].

Patients with Immunosuppression-Associated Hepatitis B Reactivation

It is recommended that patients undergoing immunosuppressive therapies (IST) should first be tested for HBV serologies (i.e., HBsAg, anti-HBc and anti-HBs)[34]. The prevalence of HBV reactivation following immunosuppressive therapy is unclear, but studies have estimated that it ranges between 20-50%[62,63]. Previous studies have suggested that reactivation of HBV is most associated with concomitant use of steroids, diagnosis of lymphoma or breast cancer, and the presence of detectable HBV DNA prior to initiation of therapy[64]. For patients who are HBsAg negative and anti HBcAb positive, they have a lower risk of HBV reactivation[65]. B-cell depleting therapies like rituximab, ofatumumab or hematopoietic stem cell

transplants are most highly associated with risk of reactivation[66]. Per the American Gastroenterology Association (AGA), anti-TNF drugs, cytokine or integrin inhibitors, tyrosine kinase inhibitors, low dose (<10mg) prednisone daily for ≥4 weeks, and anthracycline derivatives are classified as moderate risk (1-10%) of HBV reactivation, whereas Azathioprine, Methotrexate, and 6-mercaptopurine are classified as low risk (<1%)[34].

Zhou et. al. recommends either (1) to initiate antiviral prophylactically during IST and for 6-12 months post IST with routine monitoring of HBV DNA levels or (2) to initiate antiviral therapy if HBV DNA becomes detectable or if HBsAg becomes positive during IST[34]. A randomized control study compared ETV vs. LAM (taken 1 week before to 6 months after initiation of IST) in 121 HBsAg positive patients with diffuse large B-cell lymphoma who were undergoing Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone therapy (R-CHOP) therapy. Compared to LAM, the ETV group had both lower rates of HBV related hepatitis (0% vs 13.3%, p=0.003) and lower rates of HBV reactivation (6.6% vs 30%, p=0.001)[67]. It is important to note in this study that all patients included in the study had no prior exposure to HBV antiviral therapy. Another randomized control study compared ETV and TDF in 120 HBsAg and/or anti-HBc positive patients undergoing IST for various oncologic comorbidities and found similar efficacy of both medications in preventing HBV reactivation when taken during IST therapy and 6-12 months after completion of IST[68]. No HBV reactivation was observed in either the ETV group or the TDF group while on antiviral therapy, but at 1 year after stopping HBV antiviral therapy, 10.8% in the ETV group and 14.3% in the TDF group experienced HBV reactivation[68].

Given the current data, the preferred HBV antiviral drugs include ETV, TDF or TAF and should be started along with initiation of IST and continued for 6-12 months post IST[34]. Based on the specific risk level of IST, it is recommended that patients receiving moderate risk IST should remain on HBV antiviral therapy and have HBV DNA monitoring for at least 6 months post completion of IST and for patients receiving high-risk IST, the antiviral treatment duration and monitoring extended to 12 months[66]. The duration of antiviral therapy should consider other factors such as stage of fibrosis, HBeAg status, ALT levels and other potential co-infections such as HIV, HCV, or HDV[34].

Hepatitis B in Liver Transplant Patients

Prior data in HBV reactivation for organ transplant patients was primarily in renal and heart transplants[69] because HBV was initially a contraindication for liver transplant given recurrence of HBV post-transplant and its association with rapid disease progression, high risk of cirrhosis, and only about 50% graft survival at 5 years post-transplant[70,71]. A study showed that prior to adopting HBV antiviral prophylaxis as standard of care, about 5-10% of patients undergoing liver transplant for HBV-related disease would develop fibrosing cholestatic hepatitis, which is associated with accelerated graft failure and extremely high mortality[71]. However, after the advent of combination therapy with HBV immunoglobulin (HBIG) and HBV antivirals post-liver transplant, the risk of HBV recurrence and graft failure has decreased significantly, and more liver transplants are being performed in patients with chronic HBV[72].

Combination HBIG and HBV antiviral therapy was shown to be effective in preventing HBV graft re-infection in up to 95% of patients transplanted for HBV-related liver disease[73]. Subsequently, therapy with HBV antiviral therapy was also shown to be effective without long-term HBIG. A prospective study of 20 chronic HBV patients undergoing liver transplant showed that LAM along with Adefovir dipivoxil (ADV) is effective prophylaxis against HBV recurrence without long-term HBIG[74]. In this study, HBIG was given after liver transplantation for 7 days, and then stopped. At a median follow-up of 57-months post transplantation, all patients were alive and without HBV recurrence on LAM + ADV alone[74]. Another retrospective study was conducted of 265 HBV post-liver transplant patients treated with ETV monotherapy. ETV was shown to be highly effective in preventing HBV reactivation and was associated with a HBsAg sero-clearance of 92%, undetectable HBV DNA in 100% at 8 years, and survival rate of 85% at 9 years[75]. Finally, a randomized controlled trial of 40 chronic HBV patients undergoing liver transplant suggests withdrawing HBIG at 6 months while continuing HBV antiviral therapy (FTC or TDF) can be effective in preventing chronic HBV recurrence. In this study, all 40 patients received FTC/TDF and HBIG for 24 weeks post-transplant and then were randomized to continue FTC/TDF plus HBIG or FTC/TDF alone for an additional 72 weeks. No patients during follow up in either arm experienced HBV recurrence and no major adverse events were reported[76].

Since the emergence of effective HBV antiviral therapy, patients with chronic HBV can safely receive liver transplants, and with appropriate regimens, can achieve successful long-term outcomes. For patients with LAM resistance, ETV and TDF are the preferred agents given their high barrier to genetic resistance[34], and in cases where avoiding renal toxicity is a factor, TAF can be the preferred agent[77]. For patients with prior antiviral drug exposure or other viral co-infections (i.e., HDV, HIV, etc.), they can be considered for the HBIG and HBV antiviral combination method[34]. For patients requiring long-term HBIG and antiviral therapy, the goal anti-HBs trough level is unclear, but some reports suggest trough titers >100 IU/L[78,79].

Conclusion

Since the introduction of effective antiviral HBV therapy, management of HBV in special patient populations have been possible and have been shown to safe and efficacious. Patients with ACLF should be initiated on HBV therapy immediately and new experimental therapies have shown promising data that improves outcomes further. For HBV-HCV coinfection, it is imperative to identify the predominant disease and treat the dominant virus as monotherapy with close monitoring of the non-dominant virus. HBV-HDV patients continue to have interferon-based therapies as mainstay, but newer antivirals and HDV therapies are showing promising results. In HBV-HIV coinfected individuals, it is important to have dual treatment of both viruses given overlapping mechanisms of antivirals for both diseases. HBV reactivation must be very closely monitored for patients undergoing immunosuppressive therapies and based on their risk profile as classified by the AGA, antiviral treatment durations should be tailored accordingly. Lastly, now that chronic HBV is not perceived as a major contraindication for liver transplant as compared to the early transplant era, it is of monumental importance to provide prophylactic antiviral HBV therapy with consideration of HBIG only for higher risk individuals.

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