



# Chronic Hepatitis B Treatment: Current Perspectives on Telbivudine

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## Abstract

Hepatitis B virus (HBV) is the primary cause of chronic viral hepatitis worldwide. Currently, there are 5 oral nucleos(t)ide analogs (NAs) approved for chronic hepatitis B (CHB) treatment and include lamivudine, adefovir, telbivudine (LTD), entecavir (ETV), and tenofovir disoproxil fumarate (TDF). ETV and TDF are those with higher anti-viral efficacy and lower resistance rates, whereas LTD shows similar efficacy but has a higher risk for viral resistance in long-term monotherapy. However, LTD carries several advantages that must be considered and are worthy of discussion. Compared to other NAs, LTD showed a potential renal protective effect particularly in patients with mild renal insufficiency. Moreover, data have suggested that LTD could be safely administered in highly viremic pregnant women for reducing the vertical transmission risk despite vaccination and HB immunoglobulin prophylaxis. In addition, reported adverse events are rare, usually transitory with patients' recovery after treatment cessation. Finally, the lower cost and the easy availability compared to ETV and TDF render LTD a valid first line alternative for CHB treatment in economically less-developed regions.

**Keywords:** Anti-viral treatment, chronic HBV infection, HBV, nucleos(t)ide analogue

## Introduction

Hepatitis B virus (HBV) is a small-enveloped DNA virus that belongs to the Hepadnaviridae family, representing the second greatest cause of chronic viral hepatitis worldwide (1). Despite decades of vaccination, HBV infection is still a major global burden, with 257 million persons chronically infected and approximately 880,000 deaths per year (2). Chronic hepatitis B (CHB) is the result of an acute, unresolved infection that induces an immune-mediated liver damage followed by fibrotic tissue deposition leading overtime to a complete alteration of the hepatic architecture toward cirrhosis and its complications, such as liver failure and hepatocellular carcinoma (HCC) (3, 4).

Remarkable advances have been made in the setting of CHB treatment (5). In particular, the development of new molecular biology techniques in association with an ever deeper understanding of the different phases of HBV infection and primarily the introduction of nucleos(t)ide analogs (NAs) are the main features that may lead to the virological cure in the near term and the functional cure in the long-term follow-up (6).

This review discusses the current available drugs and treatment guidelines for CHB therapy focusing on telbivudine (LTD), a thymidine analog that has demonstrated unique features that make the abovementioned drug still valid even in the era of new powerful anti-viral agents.

## HBV Virology and Replication Cycle

### HBV structure

Hepatitis B virus structure consists of an outer envelope made of three viral surface proteins named preS1 (large), preS2 (middle), and S (small), which correspond to the serologic HBs-antigen (HBsAg), and an inner nucleocapsid formed by core proteins, which correspond to HBcore-antigen (HBcAg) (7). Within the nucleocapsid is present the full-length HBV genome as a partially double-stranded relaxed circular (rc) DNA linked to the viral polymerase protein by a phosphotyrosine bond (8). The genome has an extremely compact organization displaying four partially overlapped major open reading frames (ORFs): the preS/S that encodes the three viral surface proteins, the pre-core/core that encodes both the nucleocapsid core protein and the non-structural core protein known as the e-antigen (HBeAg); the polymerase ORF that encodes the viral polymerase; and the X ORF that encodes the regulatory X protein that is essential for viral replication (9).

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**Table 1. Summarized indications for anti-viral treatment according to AASLD, EASL, and APASL guidelines**

| Guidelines   | Indication for treatment   |
|--|--|
| AASLD 2007<br>(updated in 2009)  | <ul style="list-style-type: none"> <li>• HBV DNA &gt;20,000 IU/mL+ALT=1-2xULN+LB showing moderate to severe necroinflammation and/or significant fibrosis</li> <li>• HBV DNA &gt;20,000 IU/mL+age &gt;40 years+LB showing moderate to severe necroinflammation and/or significant fibrosis</li> <li>• HBV DNA &gt;20,000 IU/mL+ALT &gt;2xULN</li> </ul>  |
| EASL 2017  | <ul style="list-style-type: none"> <li>• HBV DNA &gt;2000 IU/mL+ALT &gt;ULN+LB showing moderate necroinflammation and/or moderate fibrosis</li> <li>• HBV DNA &gt;20,000 IU/mL+ALT &gt;2xULN</li> <li>• Detectable HBV DNA+cirrhosis</li> </ul>  |
| APASL 2012   | <ul style="list-style-type: none"> <li>• HBeAg-positive+HBV DNA &gt;20,000 IU/mL+ALT &gt;2xULN+concerns for hepatic decompensation</li> <li>• HBeAg-positive+HBV DNA &gt;20,000 IU/mL+ALT &gt;5xULN</li> <li>• HBeAg-negative+HBV DNA &gt;2000 IU/mL+LB showing moderate inflammation or fibrosis</li> <li>• HBeAg-negative+HBV DNA &gt;2000 IU/mL+ALT &gt;2xULN</li> <li>• HBV DNA detectable+advanced fibrosis or cirrhosis</li> </ul> |
| <small>AASLD: American Association for the Study of Liver Disease; ALT: alanine aminotransferase; APASL: Asian Pacific Association for the Study of the Liver; EASL: European Association for the Study of the Liver; HBeAg: hepatitis B e antigen; HBV: hepatitis B virus; LB: liver biopsy; ULN: upper limit of normal</small> |  |

### HBV Replication Cycle

HB virions can bind to the hepatocytes' membrane through a non-specific interaction with cell surface glycosaminoglycans (10). Then, a high-affinity interaction between the myristoylated N-terminal region of the preS1 domain and the sodium taurocholate co-transporting polypeptide (NTCP) triggers the virus uptake likely by endocytosis or by HBV envelope fusion with the plasma membrane (11, 12).

Following virus uptake, viral nucleocapsids are released into the host cytoplasm. Through a still poorly understood process, the polymerase-bound rcDNA is released into nucleoplasm. Evidences suggest that viral nucleocapsids are transported via microtubuli to the nuclear pores where mature capsids disintegrate and release both core capsid subunits and rcDNA-polymerase complexes into the nucleoplasm (13-15). After viral polymerase removal and the completion of the positive strand by the host replicative machinery, the conversion into covalently closed circular (ccc) DNA occurs (16). Despite the mechanism of conversion from rcDNA to cccDNA is still unclear, the latter HBV form serves as a template for viral transcription and replication (17). By using cellular RNA polymerase II, cccDNA acts as template for all viral RNAs including two sub-genomic RNAs encoding for S and X proteins two pre-genomic (pg) RNAs, and pre-core RNA that encodes for pre-core protein precursor of HBeAg (16, 18). To note, cccDNA can be derived not only from the up-taken virions but also by the synthesized nucleocapsids that are transported into the nucleus without being secreted into the bloodstream. This mechanism represents the basis of the accumulation and maintenance of cccDNA pool (19, 20).

Following nuclear export, viral RNAs are translated. Non-infectious sub-viral particles are directed to the endoplasmic reticulum from where they are released via the general secretory pathway, whereas pgRNAs and polymerases undergo packaging into new nucleocapsids: a first strand DNA synthesis is followed by pgRNA degradation and a second strand DNA synthesis that leads to a new rcDNA (21, 22). Also, the final HBV assembly process is not fully understood, but after the envelopment of mature rcDNA with surface proteins, infectious viral particles are secreted through the multivesicular

bodies' pathway (23, 24). Conversely, insufficient production of surface proteins leads to mature rcDNA recycling to increase nuclear cccDNA pool (Figure 1) (25).

### Current Available Drugs

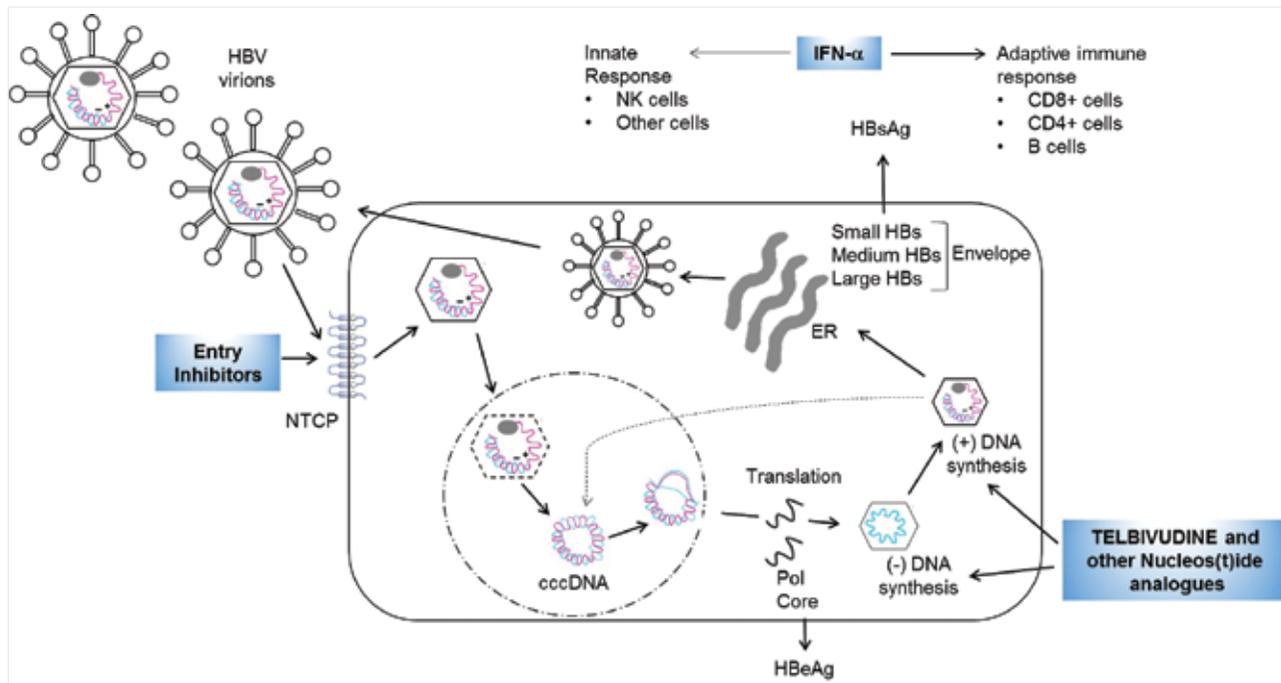
The principal goal of CHB therapy is to prevent liver disease progression by suppressing viral replication to undetectable levels and to maintain virological remission. Subsequently, a continuous suppression of HBV replication can progressively reduce fibrosis progression and in turn the risk of cirrhosis and its complications (26). Indications for treatment are mainly based on the combination of serum HBV DNA levels, alanine aminotransferase (ALT) levels, and severity of liver disease (Table 1) (26-29).

Currently, several treatment options are available due to the rapidly evolving spectrum of new drugs and strategies. Since the introduction of NAs, with lamivudine (LAM) approved in 1998 for CHB treatment, the only option was an interferon (IFN)-based therapy.

### Interferons

IFN- $\alpha$  and the pegylated formulation (peg-IFN- $\alpha$ ) are immunomodulatory agents that enhance the innate immune response and induce the anti-proliferative and anti-viral activities. Due to tolerability issues, IFN-based therapy has a finite duration, usually 6-12 months (30).

Besides finite and defined treatment course, other advantages of IFN therapy are the lack of drug resistance and a higher likelihood for HBSAg clearance. It has been reported that approximately 30% of HBeAg-positive and 40% of HBeAg-negative subjects achieve a sustained virological response (defined as HBeAg seroconversion and/or HBV DNA <20,000 copies/mL) 6 months after completion of a 48-week course of peg-IFN- $\alpha$  (31). However, due to the low rate of treatment response, the majority of patients have to be re-treated with NAs (32). Interestingly, Moucari et al retrospectively analyzed 97 patients for a median period of 14 years who previously underwent IFN therapy and found that 28 of them (29%) lost HBSAg during follow-up (33). Probably, the immunomodulatory effect of IFN can persist even after the end of therapy leading to considerable HBSAg clearance rates. In particular, patients carrying IL-



**Figure 1.** Schematic HBV replication cycle and anti-viral sites of action. Following hepatocyte infection, HBV nucleocapsid is released into the cytoplasm and rcDNA is transferred to the nucleus of the cell. After removal of viral polymerase, rcDNA is converted into cccDNA. Viral RNAs necessary for HBV proteins production and viral replication are transferred into the cytoplasm where nucleocapsid and negative and positive strand HBV DNA synthesis occurs. Mature nucleocapsid can be either re-transported into the nucleus to maintain cccDNA pool or can be enveloped with S proteins and released into the bloodstream. Two classes of drugs are available for CHB treatment: IFN and NAs. In contrast to IFN immunomodulatory effect, NAs act by inhibiting HBV polymerase leading to termination of HBV DNA synthesis. In particular, LtD is a potent inhibitor of both HBV first strand ( $EC_{50}$  value= $1.3 \pm 1.6 \mu\text{M}$ ) and second strand synthesis ( $EC_{50}$  value= $0.2 \pm 0.2 \mu\text{M}$ ). Entry inhibitors target NTCP inhibiting receptor transport function, thus interfering with hepatocyte infection.

cccDNA: covalently closed circular DNA; CHB: chronic hepatitis B;  $EC_{50}$ : concentration with 50% of the maximum response; ER: endoplasmic reticulum; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B s antigen; HBV: hepatitis B virus; IFN: interferon; LtD: telbivudine; NA: nucleos(t)ide analog; NK: natural killer; NTCP: sodium taurocholate co-transporting polypeptide; rcDNA: relaxed circular DNA.

28b rs12979860 CC genotype appear more likely to achieve HBsAg seroclearance compared to those carrying either CT or TT genotype (34). However, these findings are still a subject of debate, since other studies reported no association between treatment outcome or spontaneous HBsAg seroclearance with rs12979860 polymorphism in both HBeAg-positive and -negative CHB patients (35, 36).

### Nucleos(t)ide Analogs

The mechanism of action of NAs is based on HBV replication inhibition by competing with the natural substrate deoxyadenosine triphosphate (dATP) leading to the termination of HBV DNA synthesis. Long-term treatment with NAs is recommended to prevent virological relapse, particularly in HBeAg-positive patients who do not develop anti-HBe seroconversion and in patients with cirrhosis irrespective of the HBeAg status (26). An effective long-term control of HBV replication has been associated with a significant reduction of inflammation, fibrosis, as well as a partial reversion of cirrhosis (37-40). Moreover, patients with cirrhosis under NAs treatment showed lower HCC incidence rates in comparison to untreated patients (41).

Currently, there are five approved NAs for CHB treatment: L-nucleosides, such as LAM and LtD; acyclic diphosphonates, such as adefovir dipivoxil (ADV) and tenofovir disoproxil fumarate (TDF); and entecavir (ETV).

### Novel Therapies

Beyond IFN and NAs, major efforts have been made to investigate possible new targets for anti-viral intervention to increase

functional cure (i.e., undetectable HBV DNA and HBsAg loss with or without anti-HBs seroconversion) rate and desirable complete cure (i.e., elimination of cccDNA). In particular, the identification of NTCP as an essential hepatocyte receptor for HBV-specific binding provided a novel promising strategy for the development of viral entry inhibitors blocking receptor function. Among these, Myrcludex B is a highly selective peptide targeting hepatocytes NTCP that has already passed phase I safety trials and is currently under evaluation in phase II trials to assess the efficacy in chronic HBV-infected patients (42). The use of a combined strategy with NAs may represent a novel effective approach for a simultaneous suppression of viral replication and inhibition of naïve hepatocytes infection.

### Telbivudine

LtD (Sebivo<sup>®</sup>, Tyzeka<sup>®</sup>; Novartis, Basel, Switzerland) is a synthetic thymidine analog licensed in October 2006, which when phosphorylated into the active form LtD-5'-triphosphate competitively inhibits HBV DNA polymerase by preventing HBV DNA chain prolongation (Figure 1) (43).

### Anti-viral Activity

LtD efficacy was initially compared to LAM in a 1-year phase II trial (44). At week 52, LtD showed a significantly greater mean reduction in HBV DNA levels ( $6.01$  vs.  $4.57 \log_{10}$  copies/mL), significant HBV DNA reduction to undetectable levels (61% vs. 32%), and normalization of ALT levels (86% vs. 63%) compared with LAM. Furthermore, in a 1-year extension study, higher HBeAg seroconver-

sion rates (38% vs. 21%) and lower virological breakthrough rates (4.5% vs. 21.1%) were found (45).

The superiority of LtD over LAM was definitively showed by the GLOBE trial results in both HBeAg-positive and -negative CHB patients (46, 47). Subsequently, in an open-label trial, 44 patients were randomized to receive LtD or ETV for 12 weeks (48). The two treatment groups achieved similar reductions in HBV DNA ( $6.6 \pm 1.6$  and  $6.5 \pm 1.5 \log_{10}$  copies/mL, respectively for LtD and ETV) and ALT levels. In addition, Kim and colleagues showed that treatment-naïve patients with HBV-related cirrhosis showed improvement in the Child-Turcotte-Pugh score after 24 months of therapy irrespective of LtD or ETV treatment (49).

Recently, Lu et al. (50) compared two rescue strategies (LtD+ADV vs. ETV) for HBeAg-positive CHB patients with resistance to ADV. Authors found that after 48 weeks of treatment, there were no differences in serum HBV DNA decrease ( $<3 \log_{10}$  copies/mL, 73.3% vs. 57.1%,  $p=0.195$ ), whereas LtD+ADV-treated patients showed a significantly higher rate of HBeAg seroconversion compared to those treated with ETV (20% vs. 0%,  $p=0.039$ ) (50).

Finally, LtD has been shown to restore HBV-caused abnormal expression and histone modification (i.e., methylation of histone H3 lysines 4) at multiple genomic loci involved in different functions of the HBV life cycle, such as HBV-entry, viral replication, and pathogenesis of liver cells promoting inflammation, fibrosis, and carcinogenesis (51).

### Resistance Rate

In the course of NAs treatment, due to the competitive mechanism of HBV DNA polymerase inhibition, HBV variants harboring mutations in the polymerase gene can be positively selected leading to viral breakthrough and subsequent treatment failure (52).

Low resistance rates have been reported in treatment-naïve patients who receive NAs, such as TDF and ETV with strong anti-viral activity and high genetic barrier to resistance, whereas higher rates have been described in patients under LtD, ADV, and particularly LAM (53). Among all, LAM has a lower genetic barrier to resistance, showing an annual resistance rate between 15% and 25% and  $>80\%$  after a 5-year treatment (54). ADV resistance rate is approximately 30% after a 5-year treatment, with even higher rates in NAs experienced patients (55). ETV and TDF are the drugs with a higher genetic barrier to resistance, reporting 1.2% of resistant mutation after 5 years of treatment for ETV, while no resistance has been previously been reported after 6 years of treatment for TDF (56, 57).

LtD is associated with a medium genetic barrier to resistance. The second year of the GLOBE trial reported viral breakthrough-associated resistance rates of 25% and 11% in HBeAg-positive and HBeAg-negative patients, respectively (47). In 2008, Hou et al. (58) compared LtD efficacy with LAM in CHB HBeAg-positive Chinese patients and reported 7.5% and 14.7% 1-year resistance rates in LtD- and LAM-treated groups, respectively. Recently, comparing ETV and LtD anti-viral efficacy in 151 treatment-naïve patients with HBV-related cirrhosis, a significantly higher rate of resistance was found after 2 years of treatment in patients treated with LtD compared to those treated with ETV (27.3% vs. 0%;  $p=0.0001$ ) (49). However, according to the Roadmap concept, early on treatment

virologic response could be used as a good predictor of treatment efficacy to reduce long-term resistance (59). In particular, patients with undetectable HBV DNA at 24 weeks of treatment are those showing not only the highest rates of sustained virologic response ( $>90\%$ ) and ALT normalization ( $\sim 80\%$ ) after 2 years of treatment but also the lowest rates of viral breakthrough ( $<5\%$ ) due to the development of anti-viral resistance (59).

The main mutation conferring primary resistance to LtD is the substitution of methionine to isoleucine at position 204 of reverse transcriptase gene of HBV (rtM204I). Moreover, the association of methionine to valine substitution at position 204 (rtM204V) and leucine to methionine at position 180 (rtL180M) confer LtD resistance (26, 60).

### Tolerability

LtD treatment is generally well tolerated. However, it has been reported to be associated with creatine kinase (CK) elevations and myopathy as well as neurological side effects (61).

CK elevations and myopathy was firstly observed in the GLOBE trial (47). A significant CK increase was reported in patients receiving LtD compared with LAM recipients (12.9% vs. 4.1%,  $p<0.001$ ), whereas 2 patients developed myopathy (47). However, the majority of on-treatment CK elevations resolved spontaneously and the two patients with myopathy recovered after cessation of LtD. Recently, Zou et al. (62) investigated risk factors of CK elevations and myopathy associated with LtD treatment and found that CK elevations occurred in 84.3% of patients taking LtD for 3 years. Interestingly, following a multivariate analysis, male gender, age of  $<45$  years, and HBeAg negativity were considered independent predictors of CK elevations. Regarding myopathy, authors reported a 3-year cumulative incidence of 5% (62).

Sporadic cases of peripheral neuropathy (PN) have been reported in patients undergoing LtD monotherapy ( $<1\%$ ) (63-65). However, significantly higher rates have been reported in patients who received a combination therapy of peg-IFN and LtD (from 14% to 18.8%) (64, 65). Currently, the mechanism leading to PN following LtD and peg-IFN combined therapy is still unclear. Despite the improved anti-viral efficacy in terms of HBV DNA and HBsAg reduction (65), concomitant use of such drugs in clinical practice is not recommended.

### Telbivudine and Renal Function

All approved NAs undergo renal clearance and some degree of renal toxicity has been reported for all of them, except for LtD. Renal impairment seems particularly frequent after not only long-term treatment with ADV but also with TDF and ETV (66). Besides, LtD in comparison with other NAs showed a potential renal protective effect. In a double-blind randomized trial involving 232 treatment-naïve patients with decompensated CHB, LtD treatment was associated with a significant improvement in estimated glomerular filtration rate (eGFR) compared to LAM after 52 weeks of treatment (67). More importantly, Gane et al. (66) gathered data of CHB patients who participated in the GLOBE trial for 2 years and in the long-term extension studies (4-6 years) as well as patients with decompensated cirrhosis (A2303 trial; a 2-year study) to assess renal function in CHB patients receiving LtD treatment. Interestingly, authors reported an improved renal function in terms of eGFR in LtD-treated patients during the 2-year GLOBE study (8.5%

increase in mean eGFR). Moreover, such improvement was maintained for 4-6 years (66). Increased eGFR with LtD treatment was also observed in patients at increased risk for renal impairment. Indeed, patients with baseline eGFRs from 60 to 89 mL/min/1.73 m<sup>2</sup>, older than 50 years, and with liver fibrosis/cirrhosis achieved an eGFR improvement of 17.2%, 11.4%, and 7.2%, respectively (66). In decompensated patients with a high renal risk, eGFR declined during LAM treatment (-4.6%), whereas it improved in LtD-treated patients (+2.0%;  $p=0.023$ ) (67).

A similar eGFR increase has also been reported in CHB patients with underlying comorbidities, such as type II diabetes and hypertension (68). In addition, comparing eGFR during LtD and ETV treatment in those patients, authors found that at month 18, mean eGFR increased by 7.6% in LtD patients, while it decreased by 4.1% in the ETV-treated group (68).

Also, the addition of ADV to LtD does not seem to affect eGFR improvement. In fact, in a multicenter, open-label, controlled study involving 606 HBeAg-positive NA-naïve patients randomized in LtD monotherapy and LtD+ADV in case of suboptimal response after 24 weeks (HBV DNA  $\geq 300$  copies/mL), it has been shown that both treatment strategies were associated with a consistent eGFR increase (+12.4 and +13.2 mL/min/1.73 m<sup>2</sup> in patients receiving either LtD or LtD+ADV, respectively) (69). Similar results were found in a retrospective study including patients treated with LAM+ADV, LtD+ADV, and ETV+ADV (70). A significant decrease in eGFR after a combination treatment of 24 months was found in LAM+ADV (-18.3 mL/min/1.73 m<sup>2</sup>) and ETV+ADV (-10.0 mL/min/1.73 m<sup>2</sup>), while an eGFR increase was observed in LtD+ADV group (+2.1 mL/min/1.73 m<sup>2</sup>) (70).

The reported LtD treatment benefit on renal function has also been investigated in special populations, such as long-term liver transplant (LT) recipients that are at high risk of renal impairment. In 2014, Perrella et al. (71) compared 12 CHB patients with end-stage liver disease receiving LtD before and after LT with 12 patients on LAM prophylaxis. Patients receiving LtD had a significant improvement in renal function throughout 18 months of follow-up compared to those receiving LAM (71). Similarly, Turan et al. (72) reported increased eGFR in 76% of LT recipients who switched from LAM to LtD. However, the study terminated early due to increased rates of PN. Despite the improvement in renal function, careful monitoring is suggested in such patients for the risk of adverse events on neuromuscular function associated with LtD prophylaxis.

### Telbivudine and Pregnancy

In CHB endemic regions, HBV vertical transmission from HBsAg-positive mothers at the time of delivery or in early infancy occurs with a rate of 70%-90% (73). Despite that the prevention of perinatal transmission is based on the combination of hepatitis B immunoglobulin (HBIG) and HBsAg immunization, there is a significant residual risk of HBV transmission particularly in women with increased viral load (74). Based on the risk of teratogenicity in preclinical evaluation, LAM, ADV, and ETV are listed by the Food and Drug Administration as pregnancy category C drugs, whereas LtD and TDF are listed as category B (26).

In an open-label study, LtD efficacy and safety was evaluated on 135 HBeAg-positive highly viremic (HBV DNA  $>1 \times 10^7$  copies/mL)

mothers who received 600 mg/day of LtD from week 20 to 32 of gestation in comparison to a group of 94 untreated mothers with same virologic characteristics (75). After 7 months from delivery, no case of HBV perinatal transmission was reported in infants born from LtD-treated mothers, while vertical transmission occurred in 8% of those born from women treated only with HBIG and HBV vaccination ( $p=0.002$ ) (75). Moreover, no serious adverse events were observed in LtD-treated mothers or their infants (75).

A prospective study including 160 highly viremic mothers showed that HBsAg positivity rates were significantly lower in infants born from LtD-treated women from either the second or third trimester of gestation (0% and 3.1%, respectively) in comparison to untreated controls (24.4%) (76). Also, in this study, LtD was well tolerated with no safety concerns. Similarly, Tan et al. (77) reported no mother to child transmission of HBV infection in HBsAg-positive pregnant women who began LtD treatment before or between 14 and 28 weeks of gestation. In addition, no differences in neonatal outcomes at birth or 7 months after birth was observed compared to untreated pregnant women (77). Therefore, LtD could be recommended in pregnant women with HBV DNA  $>10^{6-7}$  IU/mL who carry a significant risk of vertical HBV transmission, although HBIG prophylaxis and HBV vaccine was administered.

### Conclusion

Since the introduction of new anti-viral agents, such as ETV and TDF with high efficacy in viral suppression and high genetic barrier to resistance, the success of CHB therapy is remarkable. However, ETV and TDF are not widely used, particularly in economically less-developed regions due to the high daily cost or limited availability. As reported in a recent pharmaco-economic evaluation, LtD treatment demonstrated better cost-effectiveness compared to other NAs for CHB in Chinese healthcare settings (78). Therefore, it represents a valid alternative drug with potent anti-viral activity and medium genetic barrier to resistance, particularly for the treatment of low viremic NA-naïve patients. Moreover, LtD treatment is generally well tolerated and only a minority of patients experienced serious adverse events when administered in monotherapy. In addition, in special populations, such as LT recipients, patients with renal insufficiency, and highly viremic pregnant women, LtD treatment could be cautiously considered as first-line anti-viral therapy.

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