

## Adverse effects of oral antiviral therapy in chronic hepatitis B

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### Abstract

Oral nucleoside/nucleotide analogues (NAs) are currently the backbone of chronic hepatitis B (CHB) infection treatment. They are generally well-tolerated by patients

and safe to use. To date, a significant number of patients have been treated with NAs. Safety data has accumulated over the years. The aim of this article is to review and update the adverse effects of oral NAs. NAs can cause class adverse effects (*i.e.*, myopathy, neuropathy, lactic acidosis) and dissimilar adverse effects. All NAs carry a "Black Box" warning because of the potential risk for mitochondrial dysfunction. However, these adverse effects are rarely reported. The majority of cases are associated with lamivudine and telbivudine. Adefovir can lead to dose- and time-dependent nephrotoxicity, even at low doses. Tenofovir has significant renal and bone toxicity in patients with human immunodeficiency virus (HIV) infection. However, bone and renal toxicity in patients with CHB are not as prominent as in HIV infection. Entecavir and lamivudine are not generally associated with renal adverse events. Entecavir has been claimed to increase the risk of lactic acidosis in decompensated liver disease and high Model for End-Stage Liver Disease scores. However, current studies reported that entecavir could be safely used in decompensated cirrhosis. An increase in fetal adverse events has not been reported with lamivudine, telbivudine and tenofovir use in pregnant women, while there is no adequate data regarding entecavir and adefovir. Further long-term experience is required to highlight the adverse effects of NAs, especially in special patient populations, including pregnant women, elderly and patients with renal impairment.

**Key words:** Nucleoside/nucleotide analogues; Adverse events; Lamivudine; Chronic hepatitis B; Side effects; Safety; Telbivudine; Hepatitis B infection; Adefovir; Entecavir; Adverse effects; Tenofovir; Hepatitis B virus

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**Core tip:** Extrahepatic effects of nucleotide analogues (*i.e.*, myopathy, nephropathy, bone disorders) are more commonly indicated in current reports. Some of these adverse events can be attributed to their effect of causing mitochondrial dysfunction. These adverse events are named as "class effects" and mostly associated

with lamivudine and telbivudine treatment. Adefovir is a well-known nephrotoxic agent. Nephrotoxic and bone density loss effects of tenofovir in patients with chronic hepatitis B (CHB) are not as clear as in those with human immunodeficiency virus infection. Serum creatinine, phosphorus and creatine kinase levels should be monitored. Safety profile is a major issue that should not be ignored in the treatment of CHB.

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## INTRODUCTION

Chronic hepatitis B (CHB) infection is one of the major causes of chronic liver diseases and affects an estimated 350 to 400 million people worldwide<sup>[1]</sup>. Up to 15%-40% of patients with CHB are at risk of developing complications including cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC)<sup>[2]</sup>. Prevention of disease progression and disease-related complications is the main goal of treatment in CHB and achieved by suppression of hepatitis B virus (HBV) DNA replication<sup>[2]</sup>. Because CHB requires long-term treatment in the majority of patients, the safety profiles of drugs become important in addition to their antiviral activities. Two different groups of antiviral agents have been approved for the treatment of CHB: Conventional or pegylated interferons (IFN or Peg-IFN), and oral nucleoside/nucleotide analogues (NAs)<sup>[2-4]</sup>. IFN/Peg-IFNs have some disadvantages, including severe side effects, aggravation of decompensated cirrhosis and autoimmune diseases. NAs have become currently the backbone of CHB treatment because they have been well tolerated by patients for decades without severe side effects<sup>[5]</sup>. There are currently five NAs approved for the treatment of CHB and they are classified into two groups: Nucleoside analogues (lamivudine, telbivudine and entecavir) and nucleotide analogues (adefovir dipivoxil and tenofovir dipivoxil fumarate)<sup>[6]</sup>. To date, a significant number of patients have been treated with NAs. Therefore, experience with the efficacy, resistance and safety profile of NAs has increased over the years. The aim of this article is to provide a review of the adverse effects of oral NAs in light of the current data.

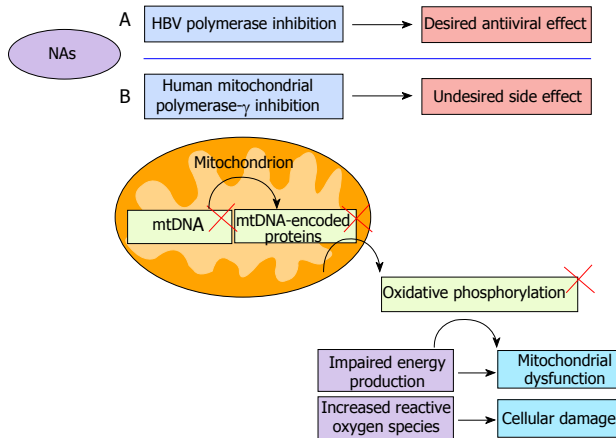
All five NAs have a favorable safety profile<sup>[7]</sup>. However, undesired extrahepatic adverse events may occur during the treatment of CHB infection. The most common extrahepatic adverse events are renal dysfunction, decreased bone mineral density and some neurological findings. Because hepatitis B infection itself may lead to extrahepatic organ involvement<sup>[5]</sup>, determining the source of extrahepatic manifestations may be difficult sometimes during the treatment of CHB. Extrahepatic adverse events may result from mitochondrial toxic effect

of NAs. These adverse effects are generally named as "class effects"<sup>[8]</sup>.

## CLASS EFFECTS OF NAs

NAs suppress viral replication by the inhibition of the HBV polymerase enzyme. As NAs structures were similar to natural nucleosides, some of these agents can also inhibit human mitochondrial polymerase- $\gamma$  and cause mitochondrial toxicity<sup>[3,5,9]</sup>. Mitochondrial toxicity was first noticed during human immunodeficiency virus (HIV) treatment with antiretroviral therapy. Nucleos(t)ide reverse transcriptase inhibitors (NRTIs) are activated by phosphorylation in the cell, and then inhibit HIV reverse transcriptase. Additionally, these drugs also inhibit a human polymerase- $\gamma$  enzyme, which is responsible for the production of mitochondrial DNA (mtDNA) content. mtDNA-encoded proteins are present in multiple copies in each mitochondrion and responsible for encoding enzyme subunits of the respiratory chain function. Respiratory chain function is required for numerous metabolic pathways, including oxidative synthesis of ATP and synthesis of DNA. The depletion of mtDNA-encoded proteins results in mitochondrial dysfunction that causes impaired oxidative phosphorylation. The other result of human mitochondrial polymerase- $\gamma$  inhibition is increased reactive oxygen species that cause cellular damage (Figure 1)<sup>[5,8,10]</sup>. The close relation between NRTIs and mitochondrial toxicity have been described in many reports<sup>[5,8,11]</sup>. Because NAs lead to a minimal mitochondrial polymerase- $\gamma$  inhibition, NA-associated mitochondrial toxicity cases have been rarely reported. All NAs carry a warning of mitochondrial toxicity as part of their prescribing information<sup>[5,8]</sup>. The clinical manifestations of mitochondrial toxicity include hematologic disorders, peripheral neuropathy, skeletal and cardiac myopathy, pancreatitis, hepatic failure and lactic acidosis<sup>[8,11]</sup>.

The most remarkable examples of mitochondrial toxicity were reported with clevudine therapy. Clevudine is a thymidine-nucleoside analogue approved in South Korea and the Philippines for the treatment of CHB. Although no mitochondrial dysfunction findings had been detected in preclinical studies, multi-center international phase III studies were terminated due to the emergence of clevudine-associated myopathy cases. Clevudine had been shown to be peripherally phosphorylated by mitochondrial thymidine kinase and to accumulate in cells rich in mitochondria<sup>[5]</sup>. South Korea revoked its approval because of indirect adverse effects<sup>[12-14]</sup>. The emergence of an association between clevudine and myopathy served as a reminder that all NAs have a potential risk for mitochondrial toxicity. Among the NAs, lamivudine and telbivudine are the agents most frequently reported to be associated with myopathy and peripheral neuropathy (Table 1). Long-peripheral neurons were more susceptible to mitochondrial toxic effect of NAs due to length-dependent effect<sup>[15]</sup>. Xu *et al*<sup>[16]</sup> performed muscle and nerve biopsy in the 6 cases



**Figure 1** Effects of nucleos(t)ide analogues. A: NAs show antiviral effect by inhibition of hepatitis B virus (HBV) polymerase; B: NAs also inhibits human mitochondrial polymerase- $\gamma$  enzyme. Thus, mitochondrial DNA (mtDNA) can not be synthesized. Oxidative phosphorylation is impaired. There are two consequences of this: Impaired energy production and increased reactive oxygen species that cause cellular damage. NAs: Nucleos(t)ide analogues.

of NAs-associated myopathy or neuropathy and revealed similar changes in all the muscle and nerve biopsy samples of the patients in light or electronic microscopy and showed the decrease of the mitochondrial DNA by the quantitative real-time PCR in the affected muscle. Although an association between telbivudine and mitochondrial toxicity was not detected *in vitro* studies<sup>[12]</sup>, telbivudine-associated myopathy and creatine kinase (CK) elevations have been reported repeatedly in real-life patients after phase studies. Myopathy may be accompanied by neuropathy in some of patients given telbivudine or lamivudine for the treatment of CHB infection. In one study, 3 of 6 patients with lamivudine or telbivudine-associated myopathy had a complaint of numbness in the distal end of limbs, suggesting peripheral neuropathy. The presence of neuropathy was confirmed by the electrophysiological studies and nerve biopsies by the study team<sup>[16]</sup>. Neuropathy cases have been reported more commonly in patients who have been treated with a combination therapy of telbivudine and Peg-IFN alfa-2a. Combination therapy provided a rapid reduction in HBV DNA level compared to telbivudine or Peg-IFN alfa-2a monotherapy. However, the risk of peripheral neuropathy has been reported to increase up to 20% in combination with Peg-IFN<sup>[10,12,15,17]</sup>.

Myopathy is characterized by CK elevation alongside muscle pain and weakness. CK elevations are among the well-described adverse effects of NAs, but they are not specific for myopathy and may be associated with strenuous exercise and many other illnesses. CK elevations may occur in patients treated with all approved NAs for CHB. However, the incidence of myopathy is very low during the treatment with adefovir, entecavir and tenofovir, and similar to comparative groups. The causal relationship has not been elucidated as of yet<sup>[3,18]</sup>. Myopathy cases can be seen in every age group (25-82 years). There is no difference between male and female

patients in terms of myopathy incidence. The mean onset time of myopathy from the initiation of NAs was reported as 6.4 mo, but it can occur even if in the 5<sup>th</sup> year of treatment. Myopathy cases had been mostly reported from the South Korea and China, but the association between myopathy and race remains unclear<sup>[19]</sup>.

## LAMIVUDINE

Lamivudine is the first oral NA approved by the United States Food and Drug Administration (FDA) for the treatment of CHB in 1998 at a dose of 100 mg/d. It is an analogue of cytidine [2',3'-dideoxy-3'thiacytidine (3TC)] and phosphorylated to its active triphosphates form by intracellular deoxycytidine kinase enzyme. The active anabolite prevents HBV replication by competitively inhibiting viral reverse transcriptase and terminating proviral DNA chain extension<sup>[20]</sup>. Lamivudine has been the most experienced oral antiviral in CHB patients<sup>[8,20]</sup>. It can be used effectively in a broad range of patients, with minimal adverse effects<sup>[21]</sup>. However, long-term treatment of lamivudine is associated with high rates of drug resistance, which lead to virological relapse and biochemical flare<sup>[1-3,8]</sup>. Therefore, lamivudine is recommended as a second-line therapy for the treatment of CHB<sup>[1,2]</sup>.

Long-term lamivudine treatment was generally well-tolerated by CHB patients<sup>[21,22]</sup>. In the GLOBE trial, a large, multi-center phase III study, of the 1367 CHB patients who received telbivudine and lamivudine, adverse events were reported in 23% of the lamivudine recipients, similar to the findings for the telbivudine recipients (29%). The most common adverse events were upper respiratory tract infection (16.2%), nasopharyngitis (13.1%), headache (13.4%) and fatigue (12.1%). Of the patients, 6% (44) experienced serious adverse events<sup>[23]</sup>. The primary adverse event was reported as hepatic flares due to emergence of lamivudine-resistant HBV with prolonged treatment. After 4 years, hepatic decompensation and other severe adverse effects increased among patients with lamivudine resistance<sup>[24]</sup>. In an Asian study by Leung *et al*<sup>[22]</sup>, 12% ( $n = 7$ ) of patients treated with lamivudine experienced severe side effects. Most of these were increased transaminase and CK levels, and resolved spontaneously. Increased alanine aminotransferase (ALT) levels were generally associated with emergence of YMDD mutant strains and had no clinical importance. In another study conducted among 998 patients with hepatitis B e antigen (HBeAg)-positive compensated liver disease who were treated with lamivudine for up to 6 years, lamivudine demonstrated a good safety profile, with only a 5% rate of severe adverse events<sup>[24]</sup>. Similarly, lamivudine has been found to be effective in HBV DNA decrease, ALT normalization and histological improvement, and it was well-tolerated by patients with cirrhosis. Lamivudine had been used in patients with acute or fulminant hepatitis without any adverse event, and led to fast recovery and increased

**Table 1 Characteristics of approved oral antiviral drugs for chronic hepatitis B treatment**

NAs (approval year)	Class effect	Renal effect	Most common adverse events	Laboratory monitoring	Rare severe adverse reactions	Pregnancy category	Detection in breastfeeding
Lamivudine (1998)	Myopathy and neuropathy cases were reported	No significant effect	Upper respiratory tract infection, nasopharyngitis, headache and fatigue ALT flairs CK elevation may occur (usually not requiring cessation of drug)	Serum ALT and bilirubin	Rhabdomyolysis, acute dystonia, pancreatitis Rare lactic acidosis	C	Yes
Telbivudine (2006)	Myopathy and neuropathy cases were reported (especially in combination with Peg- IFN)	Nephroprotective effect Increase in GFR	Upper respiratory tract infection, nasopharyngitis, headache and fatigue Increased incidence of CK elevation (usually asymptomatic and self-limiting, not required cessation of drug)	CK level Serum lactate	Lactic acidosis	B	Yes
Adefovir (2002)	Very rare, No increased incidence of myopathy compared to placebo	Clinically significant nephrotoxicity Decrease in GFR	Pharyngitis, asteni, headache, abdominal pain, flu-like symptoms and nausea	Serum creatinine and phosphate level	Hypophosphatemia Fanconi syndrome	C	Unknown, not recommend for use
Entecavir (2005)	Very rare, No increased incidence of mitochondrial toxicity in combination of entecavir with other NAs and IFN	No decrease in GFR	Headache, upper respiratory tract infection, cough, nasopharyngitis, fatigue, dizziness, upper abdominal pain and nausea	Serum lactate	Lactic acidosis	C	Unknown, not recommend for use
Tenofovir (2008)	Very rare, No increased incidence of myopathy compared to placebo	May decrease GFR, clinically insignificant Nephrotoxic in HIV patients Hypophosphatemia	Headache, nasopharyngitis, back pain, nausea Bone mineral density loss (more prominent in HIV patients)	Serum creatinine and phosphate level BMD		B	Yes

NAs: Nucleos(t)ide analogues; ALT: Alanine aminotransferase; CK: Creatine kinase; IFN: Interferon; GFR: Glomerular filtration rate; HIV: Human immunodeficiency virus; BMD: Bone mineral density.

survival<sup>[25]</sup>.

Lamivudine has a good safety profile in different patient populations having some comorbid diseases. It is the most experienced drug for preemptive treatment of hepatitis B infection in solid-organ recipient and immunosuppressive patients<sup>[1]</sup>. There are limited data for experiences with the other NAs<sup>[26]</sup>. Although highly potent oral NAs with high genetic barriers to antiviral resistance, such as entecavir and tenofovir, have become the current preferred regimen, lamivudine remains a therapeutic option for hepatitis B prophylaxis since it is the most cost-effective choice for these patients<sup>[27,28]</sup>. Lamivudine has been well tolerated by patients receiving immunosuppressive treatment. In a systematic review investigating the preventive effect of lamivudine on chemotherapy - induced hepatitis B-related morbidity and mortality in hepatitis B surface antigen (HBsAg)-positive patients with cancer, none of the eight studies that recorded safety profile of lamivudine reported any significant adverse events<sup>[29]</sup>. Lamivudine has also been

used safely in children without any serious side effects. In one study, only slight and transient increase of ALT levels were reported in 6.8% of children with CHB, without any complaint or clinical findings<sup>[30]</sup>.

Serious adverse events have rarely been reported with lamivudine treatment<sup>[31,32]</sup>. Lamivudine-induced rhabdomyolysis is one of them and characterized by a triad of muscle weakness, myalgia and abnormal laboratory findings including CK elevation, increased urine and blood myoglobin level, and acute renal injury. Tubular damage and obstruction is considered the main reason underlying pathogenesis<sup>[31-33]</sup>. Clinical and laboratory findings improve generally within a few days after cessation of the drug. However, in one case, rhabdomyolysis relapsed after readministration of lamivudine for HBV infection prophylaxis and resolved completely after discontinuation of the drug again<sup>[34]</sup>. The mortality rate was reported to be high in patients who developed rhabdomyolysis and may be reduced by the early recognition of the disease and fluid resuscitations<sup>[31]</sup>.

Lamivudine-induced acute dystonic reaction was reported in 2 patients, and the acute dystonia resolved after discontinuing the lamivudine therapy<sup>[35]</sup>. Lamivudine-associated ichthyosiform eruptions and pancreatitis cases have been reported in the literature<sup>[25,36-38]</sup>.

## TELBIVUDINE

Telbivudine is a thymidine nucleoside analogue which selectively inhibits HBV DNA synthesis. It was approved in 2006 for the treatment of CHB patients at a dose of 600 mg/d. Telbivudine is a more potent NA against HBV compared to lamivudine and adefovir<sup>[3,39]</sup>. However, high resistance rates limit the use of telbivudine as the firstline therapy<sup>[2,3]</sup>. Upper respiratory tract infection, nasopharyngitis, fatigue and headache were reported as the most frequent adverse events associated with telbivudine use. Adverse events' frequencies were found to be similar in lamivudine and telbivudine groups. However, Grade 3/4 increase in CK level occurred more commonly in patients given telbivudine (12.9% vs 4.1%), but these were not associated with musculoskeletal adverse events and no rhabdomyolysis cases were detected during the study period<sup>[23]</sup>. CK elevations were generally self-limiting and asymptomatic. Discontinuation of telbivudine was not required in most of the cases. Telbivudine-associated myopathy and CK elevations have been reported in several studies<sup>[12,40-42]</sup>. Zou *et al.*<sup>[41]</sup> conducted a prospective study to investigate clinical features and risk factors of telbivudine-associated myopathy and CK elevations. The serum CK levels of 200 patients treated with telbivudine were analyzed. The 3-year cumulative incidence of CK elevations was considerably high (84.3%). Nine patients (5%) experienced myopathy and were required to discontinue telbivudine therapy in 3 of those. None of the patients developed rhabdomyolysis. CK elevations were reported to occur in males more often than in females and in those with HBeAg negativit and aged < 45 years. In another study in which 105 patients given telbivudine were evaluated for adverse reactions, 5 presented serious adverse events. There was nervous system damage in 3 of the cases and cardiac arrhythmia in 1 case. All 5 patients had elevated CK enzymes. Therefore, it is recommended that CHB patients treated with telbivudine should be monitored closely for musculoskeletal symptoms and CK enzyme levels<sup>[3]</sup>.

Some infrequent but serious side effects were reported in previous studies. Lactic acidosis is one of them and it was reported also in patients treated with all the other nucleos(t)ide analogues<sup>[43]</sup>. It results from mitochondrial dysfunction or loss due to the inhibitor activity of telbivudine on human mitochondrial DNA polymerase- $\gamma$ . A few lactic acidosis cases depending on telbivudine therapy were reported in the literature. The symptoms of patients were anorexia, nausea, vomiting, muscle pain and weakness in upper and lower extremities. The laboratory tests revealed elevated serum CK levels and hyperlactatemia<sup>[43]</sup>. One patient's complaints

continued even after the withdrawal of telbivudine treatment, and the patient recovered after venovenous hemodiafiltration. To diagnose hyperlactatemia, the patients should be monitored by periodic (3-6 mo interval) lactate measurements, in addition to the CK monitoring.

The mechanism of adverse events associated with telbivudine use has not yet been defined. Because adverse events may occur in multiple organs including muscles, nervous and cardiac systems, Zhang *et al.*<sup>[42]</sup> suggested that the mechanism is associated with cell energy metabolism. Deficiency in manufacture of the energy molecule ATP and, therefore, inadequate supplementation of substrate for oxidative phosphorylation causes mitochondrial damage. Highly energy-dependent organs such as nerves, heart and muscles are the most susceptible to mitochondrial dysfunction. Telbivudine leads to adverse events in these organs. However, to establish a link between adverse events and mitochondrial disease, muscle biopsy and DNA studies should be done<sup>[42]</sup>.

Synergistic effect can occur in case of simultaneous use of two drugs. A study comparing telbivudine and lamivudine combination and lamivudine monotherapy reported that the addition of telbivudine to lamivudine treatment did not increase the toxic adverse effects<sup>[44]</sup>. However, the combination of telbivudine with Peg-IFN caused peripheral neuropathy in 17.0% of patients. For this reason, telbivudine should not be recommended in combination with Peg-IFN<sup>[8]</sup>.

## ADEFOVIR DIPIVOXIL

Adefovir dipivoxil is an oral prodrug of the nucleotide analogue adefovir, approved for CHB treatment at 10 mg/d dose in 2002. It was used initially in patients with HIV infection, but its use was abandoned due to the fact that higher doses of adefovir led to nephrotoxicity<sup>[8]</sup>. Adefovir improves histological, biochemical and virological outcomes in CHB patients with lamivudine resistance. The rates of adverse events in patients given adefovir are similar to those given placebo<sup>[45-48]</sup>. The most common adverse events were pharyngitis, asteni, headache, abdominal pain, flu-like symptoms and nausea<sup>[45]</sup>. In a randomized controlled study, adverse events were similar in two groups, but headache and abdominal pain occurred more frequently in the adefovir group than in the placebo group. However, these adverse events did not lead to discontinuation of the study drug<sup>[48]</sup>. Adefovir is associated with dose-dependent renal toxicity. The nephrotoxic effect of adefovir was discussed in the section below on "Renal Safety of NAs".

Myopathy cases were reported in CHB patients given adefovir treatment, but its incidence was similar to patients receiving placebo<sup>[12]</sup>. Adefovir-related lactic acidosis may occur when combined with other NAs<sup>[49]</sup>. The development of resistance to adefovir therapy is another undesirable event. Drug resistance was reported in 26% of CHB patients treated with adefovir, after

5 years<sup>[8]</sup>. The resistance rate of adefovir in patients with lamivudine resistance who were given adefovir add-on lamivudine rescue therapy was 6% at the end of 5 years<sup>[50]</sup>. To optimize therapy in lamivudine-resistant patients, it is recommended not to discontinue lamivudine therapy for a while after initiating adefovir<sup>[8]</sup>.

## ENTECAVIR

Entecavir is a highly selective guanosine nucleoside analogue, approved by the FDA at a dose 0.5 mg in treatment naive and 1 mg/d in lamivudine-resistant CHB patients in 2005<sup>[3,51]</sup>. It inhibits three steps of viral replication, which involves HBV polymerase priming, reverse transcription of the pre-genomic messenger RNA and synthesis of the positive-stranded HBV DNA<sup>[3]</sup>. Entecavir is a well-tolerated antiviral agent in CHB patients, with rates of adverse events similar to placebo or lamivudine therapy. In a comparative study, the adverse event rate was found to be similar in patients given entecavir monotherapy to those given combination of entecavir and IFN<sup>[52]</sup>. Long-term use was reported to be associated with a very low rate of side effects. Adverse events were not dose-related; their frequencies were similar between 0.5 or 1 mg doses of entecavir<sup>[51,53]</sup>. The most frequent adverse events in clinical trials were headache (17%-23%), upper respiratory tract infection (18%-20%), cough (12%-15%), nasopharyngitis (9%-5%), fatigue (10%-13%), dizziness (9%), upper abdominal pain (9%) and nausea (6%-8%). Most of these adverse effects were mild or moderate severity and did not require discontinuation of the drug<sup>[51,54]</sup>. Severe adverse events accounted for 7%-10% and discontinuation of therapy accounted for 1%-2% of patients<sup>[51]</sup>. In a randomized controlled study, severe adverse events occurred in 4.7% of pediatric patients ( $n = 8$ ), and only one of them discontinued entecavir due to headache. This adverse event was not attributed to the study drug<sup>[54]</sup>. Although preclinical data reported an association between long-term entecavir use and carcinogenicity, to date, no evidence has been detected regarding occurrence of cancer due to entecavir therapy<sup>[55]</sup>.

The FDA requires all approved NAs to include a "Black Box" warning in their product label regarding potential mitochondrial toxicity<sup>[56]</sup>. Entecavir is the most innocent antiviral agent leading to mitochondrial toxicity among the effective therapies in CHB treatments. In long-term cell culture studies, entecavir has been observed to have very low potential for mitochondrial toxicity in *in vitro* cultures studies at the highest levels tested, 300  $\mu\text{mol/L}$ . Combination of entecavir with the other NAs also did not cause an increase in the risk of other drugs<sup>[8,57]</sup>. Entecavir-associated myopathy and peripheral neuropathy cases were very rarely reported in the literature<sup>[3,15,19]</sup>. Although a study reported similar CK elevation rates with both telbivudine and entecavir therapy, there were not many studies supporting this<sup>[58]</sup>. In a meta-analysis, six randomized controlled trials involving

555 patients treated with telbivudine and entecavir for 24 or 52 wk were evaluated. Both drugs had similar antiviral and biochemical effects. However, the entecavir group was reported have greater safety than the telbivudine group, in terms of adverse events<sup>[59]</sup>. In another meta-analysis comparing the effects of telbivudine and entecavir in HBeAg-positive CHB patients, thirteen trials (3925 patients in total) were evaluated. Adverse effects were reported in 10 trials and CK elevations in 5 trials. The rates of increased CK were found to be statistically higher in the telbivudine group than in the entecavir group<sup>[60]</sup>.

Lactic acidosis can also occur during treatment with NAs as a result of mitochondrial toxicity. US prescribing information for entecavir and the other NAs carries a warning regarding the risk of lactic acidosis in CHB patients treated with NAs<sup>[61-64]</sup>. Entecavir is a good option for the treatment of CHB patients with decompensated cirrhosis because of the rapid effect on HBV decline and low resistance rates. However, it was suggested that a high Model for End-Stage Liver Disease (MELD) score that is used to detect highly impaired liver function can be associated with lactic acidosis in patients receiving entecavir<sup>[49]</sup>. One retrospective study identified 5 cases of lactic acidosis among 16 entecavir-recipient CHB patients with cirrhosis. One of them died, and the lactic acidosis resolved within 4-5 d after withdrawal of entecavir in the remaining 4 cases. All patients who developed lactic acidosis had a MELD score of at least 20 (22-38), whereas the patients who did not develop lactic acidosis had a MELD score below 18. A significant ( $P = 0.002$ ) correlation was seen between the MELD score and the development of lactic acidosis<sup>[49]</sup>. However, a small retrospective study did not find an increased risk of lactic acidosis in the CHB patients with decompensated liver disease and high MELD scores during entecavir treatment, compared to those who have non-HBV-related decompensated liver disease and similar clinical features<sup>[65,66]</sup>. Entecavir has been reported to have a high safety profile in decompensated patients and recommended as one of the first-line treatment choices of CHB patients with decompensated liver disease in an Asian-Pacific consensus statement<sup>[67,68]</sup>. Nevertheless, the patients should be monitored cautiously for the risk of lactic acidosis during the treatment and entecavir should be suspended in the case of suspected lactic acidosis<sup>[49,66]</sup>.

Patients with severe acidosis complained of nausea, dyspnea and weakness, and showed a reduced general physical condition, impaired consciousness and tachypnea. In addition, 2 of 3 patients with severe acidosis suffered from paresthesia and the remaining 1 patient developed hepatic steatosis typical for mitochondrial toxicity. ALT flares, potentially leading to decompensated hepatic disease, can be another serious health problem in a patient given entecavir for CHB. In clinical trials, ALT flare had been reported to occur in a small percentage of patients treated with entecavir and to resolve even if the treatment continued. In an open-label study evaluating

the safety and tolerability of entecavir, Grade 3 and 4 adverse events were detected in 19% of the patients, with only 4% of them possibly related to entecavir. These Grade 3 and 4 adverse events were myalgia, neuropathy, increased lipase, increased creatinine and lactate, CK elevation, decreased bicarbonate and pancreatitis. Entecavir treatment was discontinued in only 1% of cases due to adverse events. ALT flares were reported in 3% of the patients during the treatment, and were associated with inhibition of viral replication, at least 2 log<sub>10</sub> decrease of HBV DNA<sup>[68]</sup>. In a multicenter European study investigating the incidence and outcome of ALT flares during long-term entecavir in CHB, 729 patients treated with entecavir for a median of 3.5 years were evaluated. Flares were classified as host-induced (preceded by HBV DNA decline), virus-induced (HBV DNA increase) or indeterminate (stable HBV DNA). A total cumulative incidence of ALT flare was 6.3% (30) at year 5. Of them, 12 were host-induced and associated with biochemical remission. HBeAg and HBsAg seroconversion was observed in only these host-induced flares. Virus-induced flares were reported to be associated with entecavir resistance and non-compliance to the therapy<sup>[69]</sup>. Therefore, long-term use of entecavir is generally safe and associated with low rates of serious adverse events, and discontinuation of the treatment is rarely required. ALT flares were low in patients receiving entecavir and generally associated with the improvement of liver disease. In current guidelines, entecavir is also recommended as treatment and prophylaxis of CHB infection in patients with renal transplant due to being an agent without signs of nephrotoxicity<sup>[2]</sup>.

## TENOFOVIR

Tenofovir disoproxil fumarate (TDF) is a prodrug of tenofovir that has been approved as a nucleotide analogue by the United States FDA for use in HIV infection in 2001 and in CHB infection in 2008 at a dose of 300 mg<sup>[8]</sup>. TDF is converted to tenofovir by hydrolysis and then phosphorylated by cellular enzymes to tenofovir diphosphate. It inhibits (potentially) HBV DNA polymerase and reverse transcriptase. Tenofovir, one of the main components in antiretroviral regimens, plays a key role in HIV treatment. It is also a highly potent inhibitor of HBV DNA replication and recommended as a first-line treatment choice in CHB by the current clinical guidelines due to the absence of resistance to the drug<sup>[1,70]</sup>. The molecular structure and general safety profile of tenofovir is similar to adefovir, but nephrotoxicity has not been a major problem with tenofovir at therapeutic doses. Therefore, it can be used at higher doses compared to adefovir and leads to more effective responses in HBV DNA decline. The nephrotoxic effect of tenofovir is discussed in detail in the below section on "Renal Safety of NAs".

In phase III studies of tenofovir, the adverse event profiles were similar to those in the comparative arm of adefovir. The most frequent adverse events were head-

ache, nasopharyngitis, back pain and nausea. Treatment-related adverse events were detected in 6% of patients, serious adverse events in 4% and adverse events that required discontinuation of tenofovir in less than 1%<sup>[8,55]</sup>. A 3-year, prospective real-world study (Vireal group) reported 68 adverse events in 41 (9.3%) patients among a total of 440 patients receiving tenofovir. Adverse events occurring in more than one patient were renal disorders ( $n = 11$ ), abdominal pain ( $n = 8$ ), asthenia ( $n = 7$ ), nausea ( $n = 6$ ), vomiting ( $n = 5$ ) and diarrhea ( $n = 5$ ). Nine of the 16 serious side effects were reported to be tenofovir-related (visual impairment, nausea, asthenia gait disturbance, weight loss, depression, muscular weakness, muscular pain and psoriasis)<sup>[71]</sup>.

Osteomalacia can occur during long-term tenofovir treatment. In randomized clinical trials, a great loss of bone mineral density (BMD) had been well-described in patients with HIV infection treated with tenofovir<sup>[55,72-74]</sup>. However, tenofovir-related bone fractures were not reported in patients with HBV mono-infection<sup>[55]</sup>. During the 3-year prospective follow-up, fractures were observed in 1% of 375 HBeAg-negative and 266 HBeAg-positive patients, but none were related to tenofovir<sup>[75]</sup>. The primary responsible mechanism for bone density loss is believed to be related with inhibitory effects of HIV proteins or immune status in osteoblasts and an increased osteoclastic activity. Modifying effects of tenofovir on osteoblast gene expression and function was the other mechanism defined in recent reports<sup>[72]</sup>. The exact mechanism of bone toxicity in CHB is not clear. Possibly, proximal tubular damage caused by TDF therapy leads to hypophosphatemia and, indirectly, to inadequate mineralization of bone matrix<sup>[3]</sup>. There have been case reports regarding tenofovir-associated osteomalacia. A recent study including 170 patients with CHB infection compared patients treated with tenofovir ( $n = 122$ ) and control patients ( $n = 48$ ) in terms of bone health<sup>[72]</sup>. The prevalence of BMD loss in patients receiving tenofovir was similar to those who were not exposed to tenofovir. Tenofovir was reported to be associated with a lower T score only in the hips. Additionally, in the study, there was no significant correlation between duration of exposure to tenofovir and reduction in BMD at any side. The risk factors for reduction in BMD other than tenofovir exposure were the known classical factors including advancing age, lower body mass index and smoking<sup>[72-74]</sup>. A large retrospective study including 53500 subjects in Hong Kong (46454 untreated and 7046 treated) investigated renal and bone events in CHB patients with and without NAs. The patients treated with NAs had similar risk of hip fracture, spine fracture and all fracture, compared to untreated CHB patients. Treatment with nucleotide analogues, compared to nucleoside analogues, was found to increase only the risk of hip fracture but not the other side fracture, and the overall fracture rate was low<sup>[76]</sup>. Additionally, BMD reduction was demonstrated to remain constant on a plateau from year 4 through year 7 of tenofovir treatment, for both hip and lumbar spine<sup>[77]</sup>. Thus, we may conclude that

BMD reduction is not a progressive event and is detected in the first years of treatment<sup>[78]</sup>. These are important findings due to CHB infection requiring lifelong treatment in the majority of patients because the discontinuation of NAs after sustained viral response have a high risk of relapse. Tenofovir can be preferred and used safely in CHB patients in the long-term. Nevertheless, BMD should be periodically performed in patients with CHB infection treated with tenofovir<sup>[79]</sup>. Osteoporotic patients, especially with advanced age and smoking history, should be monitored more closely and, if required, consulted with a physical rehabilitation specialist.

## RENAL SAFETY OF NAs

The adverse effect of NAs on renal function is an important issue that should be carefully evaluated, since HBV infection alone carries an increased risk of renal impairment<sup>[80]</sup>. All NAs are excreted through kidneys in unchanged forms and some of them are associated with dose-dependent nephrotoxicity<sup>[3]</sup>. Nephrotoxicity results from proximal tubular damage and presents with elevated serum creatinine, proteinuria, nephrogenic diabetes insipidus, hypophosphatemia or the more severe form, Fanconi syndrome<sup>[15]</sup>. Mauss *et al.*<sup>[81]</sup> reported a milder decrease in renal function with CHB therapy irrespective of medications. Comorbidities such as diabetes, hypertension and underlying chronic renal disease may also contribute to the nephrotoxic effect of NAs and aggravate renal dysfunction. In a study analyzing effects of NAs and comorbidities on renal function in 4178 CHB patients, age, diabetes, chronic renal disease, renal transplantation and simultaneous administration of diuretics were found to be independent risk factors for the rapid progression of renal disease<sup>[81]</sup>.

Renal toxicity is the most noticeable side effect of adefovir. It is generally dose- and time-dependent, and reversible with dose-adjustment or discontinuation of the drug<sup>[15,45,82-84]</sup>. In the majority of studies, nephrotoxicity was defined as an increase  $\geq 0.5$  mg/dL from baseline in serum creatinine or a serum phosphorus value of  $< 1.5$  mg/dL on two consecutive occasions<sup>[83]</sup>. In previous studies, including randomized controlled ones, adefovir at 30 mg/d was reported to be nephrotoxic, but adefovir at 10 mg/d was well tolerated and did not lead to an increase in renal dysfunction compared to placebo<sup>[45,85]</sup>. In a study including a total of 515 patients with CHB, three groups who were treated placebo ( $n = 170$ ), adefovir dipivoxil at 10 mg ( $n = 172$ ) or adefovir dipivoxil at 30 mg ( $n = 173$ ) were compared in terms of response to the treatment and adverse events rates<sup>[45]</sup>. The safety profile was similar in two groups, the placebo group and the adefovir dipivoxil at 10 mg per day group. There was no significant change in median serum creatinine level at wk 48 of the treatment in these groups. However, 8% of the 30-mg group experienced an increase from baseline of 0.5 mg/dL (44  $\mu$ mol/L) or greater in the serum creatinine level. The prolonged use of adefovir carries an extra risk of renal dysfunction. The incidences

of increased creatinine level and hypophosphatemia were reported to be increased with longer usage of adefovir, even in patients receiving standard low-dose drug.

In recent years, Fanconi syndrome cases due to long-term use of adefovir have been increasingly reported, especially in East Asian populations<sup>[83]</sup>. Fanconi syndrome is defined as hypophosphatemia and a slight increase in serum creatinine, resulting in proximal renal tubular dysfunction. Additionally, osteomalacia may develop secondary to hypophosphatemia. The patient's main symptoms can be muscular weakness and bone pain involving the knees, ankles and ribs. Clinicians should be aware of this potential complication and monitor periodically the renal function and serum phosphate level in any patient receiving adefovir<sup>[83,86]</sup>. In a current meta-analysis, including seven randomized controlled trials, four cohort studies and six single-arm studies, adefovir treatment was not found to be associated with increased nephrotoxicity in the randomized controlled trials. However, the cohort studies showed an increased nephrotoxicity risk in patients given adefovir, and the single-arm studies revealed an approximately 1.7-fold increased risk of renal dysfunction in patients given adefovir compared to those treated with all other NAs<sup>[82]</sup>. The authors drew attention to the differences between the risk of nephrotoxicity in randomized controlled trials and cohort studies and emphasized that since the randomized controlled trials were small-sized and short observational studies, the safety data may be inadequate and that these studies may have underestimated the adverse events. Current evidence indicated an increased risk of nephrotoxicity in CHB patients treated with adefovir.

The mechanism of adefovir nephrotoxicity was poorly understood. Nephrotoxicity may result from the apoptotic or mitochondrial toxic effect of adefovir in the renal tubular epithelium. The deterioration of the balance between the active adefovir uptake from blood into proximal tubular cells, the secretion into urine, and accumulation in proximal tubular cells represent the primary mechanism of tubular toxicity.

Fanconi syndrome is a rare but serious adverse effect of adefovir treatment. Fanconi syndrome is characterized by proximal renal tubular toxicity and leads to increased urinary excretion of amino acids, uric acid, bicarbonate, glucose and phosphate, and impaired reabsorption of these solutes. Clinical manifestations in adults include polyuria, polydipsia, dehydration and osteomalacia<sup>[87]</sup>. There are a significant number of cases of adefovir-associated Fanconi syndrome in the literature. Most cases occurred after prolonged use of the drug and resolved after cessation of adefovir or switching to another NA. The lowest dose of adefovir (10 mg) can also lead to Fanconi syndrome<sup>[88]</sup>. Normalization of creatinine level may require more than 1 year. In a retrospective case series study including 35 patients with Fanconi syndrome, hypophosphatemia, increased urinary phosphate excretion and elevated alkaline phosphatase were detected in all patients.



Although serum phosphate levels rapidly increased, especially within the 4 wk after adefovir discontinuation, serum creatinine levels did not decrease to normal range even 1 year after discontinuation of therapy<sup>[88]</sup>. Fanconi syndrome was rare in CHB patients treated with tenofovir; it has been reported especially in cases of HIV-HBV coinfection<sup>[87,89-91]</sup>.

Despite tenofovir being a higher dose preparation (300 mg/d) that has similar molecular structure with adefovir, renal toxicity has been less commonly detected<sup>[3]</sup>. In animal studies, tenofovir was reported to be associated with renal dysfunction<sup>[3,84]</sup>. The mechanism of nephrotoxicity is poorly understood, but it may involve proximal tubular damage, mitochondrial toxicity and apoptosis<sup>[8,92]</sup>.

Tenofovir has been shown to have a potential nephrotoxic effect in patients with HIV infection who were treated for an especially extended period. However, in clinical trials, nephrotoxicity does not seem to be a major problem in HBV mono-infection<sup>[3,55,93]</sup>. Increases in serum creatinine of > 0.5 mg/dL were reported to be detected in 1% of patients and remained stable over 4 years in less than 1% of patients, with increased serum creatinine levels of 0.5 mg/dL<sup>[93]</sup>. Nevertheless, renal functions and serum phosphate should be monitored regularly in patients treated with tenofovir<sup>[3]</sup>.

In a study conducted by the Vireal group, a slight decrease of mean glomerular filtration rate (GFR) was reported during tenofovir therapy. Median change in creatinine clearance and serum creatinine level remained stable over time. Of the patients, 15% ( $n = 65$ ) had a decline in GFR of  $\geq 20\%$  and 6% ( $n = 26$ ) had a decline in GFR of  $\geq 30\%$  compared to baseline. Tenofovir treatment was discontinued in 23 patients due to adverse events. Seven of them were associated with renal disorders ( $n = 3$ , renal failures;  $n = 2$ , renal impairments;  $n = 2$ , renal tubular disorders)<sup>[71]</sup>. Patients who have an underlying renal impairment or HIV coinfection and those who receive a nephrotoxic drug are at increased risk of nephrotoxicity. In a study comparing tenofovir and entecavir in the same number of patients, diabetes and transplantation but not tenofovir treatment were found to be associated with increased risk of renal impairment<sup>[94]</sup>. A significant number of studies reported that tenofovir did not lead to clinically relevant changes in renal function<sup>[79,95]</sup>.

In a prospective open-label study, conducted by Heathcote *et al.*<sup>[75]</sup>, creatinine and creatinine clearance were reported to remain stable during a 3-year period, with a change in creatinine of 0.02 mg/dL at week 144. Two patients experienced a 0.5 mg/dL increase in creatinine and 4 patients a reduction in serum phosphorus < 2 mg/dL. All patients remained in the study and continued the tenofovir therapy. The long-term follow-up results of tenofovir therapy support the previous data. At year 6, less than 1.5% experienced impairment in renal function ( $\geq 0.5$  mg/dL increase in serum creatinine from baseline, phosphorus < 2 mg/dL, or CrCL < 50 mL/min) with tenofovir treatment<sup>[55]</sup>. Recently, Buti

*et al.*<sup>[77]</sup> reported 7<sup>th</sup> year results of tenofovir treatment for CHB. Of 585 patients, 21 (3.6%) experienced renal function impairment. A serum creatinine increase  $\geq 0.5$  mg/dL above baseline were confirmed in only 10 patients (1.7%). The patients who did and did not develop renal insufficiency were statistically different in terms of mean age (47 years vs 40 years;  $P = 0.003$ ), baseline mean creatinine clearance (98.5 mL/min vs 117.4 mL/min;  $P = 0.003$ ) and main serum phosphate (2.8 mg/dL vs 3.3 mg/dL;  $P = 0.002$ ). Despite the absence of significant evidence that tenofovir is a nephrotoxic agent, possible proximal tubular damage should still be kept in mind<sup>[3]</sup>. The patients with normal renal function or mild renal impairment who have no increased risk for renal toxicity should be monitored every 6 mo for serum creatinine and phosphorus. The patients with impaired renal function or underlying comorbidities that show increased renal failure may be monitored more frequently<sup>[96]</sup>. Dose-adjustment should be made according to the renal impairment<sup>[3]</sup>.

Tenofovir safety was also similar in elderly and younger patients<sup>[59]</sup>. There is little experience with tenofovir treatment in renal transplantation. One study reported 7 HBV-positive organ transplant recipients ( $n = 3$ , kidney;  $n = 1$ , liver;  $n = 3$ , hearts) who were safely and effectively treated with tenofovir. No adverse events or kidney rejection were observed. There were no statistically significant changes in renal functions<sup>[97]</sup>.

In contrast to the nucleotide analogues, nucleoside analogues are not generally associated with renal adverse events. Increase in serum creatinine was reported in less than 1% of patients treated with entecavir<sup>[49]</sup>. In the study of Tsai *et al.*<sup>[98]</sup>, entecavir and telbivudine were found to be associated with GFR improvement. Despite the absence of strong evidence, the current guidelines recommend entecavir as the best option in renal transplant recipients due to lack of data demonstrating a major renal toxicity with entecavir<sup>[2,99-101]</sup>.

Interestingly, telbivudine improves renal functions<sup>[3,8,81]</sup>. Several real-life studies have shown that treatment with telbivudine increases GFR in CHB patients. The GLOBE study and long-term extension studies had revealed that long-term telbivudine treatment was associated with a sustained improvement in renal function in patients with compensated and decompensated cirrhosis who had an increased risk of renal impairment<sup>[23,102]</sup>. Gane *et al.*<sup>[102]</sup> indicated an improvement in renal function with telbivudine treatment by the calculation of GFR using the Modification of Diet in Renal Disease, Chronic Kidney Disease Epidemiology Collaboration, and Cockcroft-Gault methods. The increment of GFR was also shown in patients at increased risk for renal impairment: +17.2% in patients with baseline GFR of 60-89 mL/min per 1.73 m<sup>2</sup>, +11.4% in patients older than 50 years and +7.2% in cirrhotic patients. Additionally, improved renal function has been reported to be maintained for 4-6 years. In a study investigating the renoprotective effect of telbivudine on patients receiving adefovir-based combination therapy, combination of adefovir

and telbivudine was found to have a more protective effect on renal functions than the combination of adefovir and entecavir, combination of adefovir and lamivudine, adefovir alone or entecavir alone<sup>[79]</sup>. Preemptive telbivudine use was reported to prevent renal deterioration caused by cisplatin-based chemotherapy in patients with advanced HCC<sup>[103]</sup>. Additionally, telbivudine is recommended in the prophylactic treatment of CHB in patients with renal transplant due to its renoprotective effect on transplanted patients<sup>[2]</sup>. Telbivudine is a good option, especially in patients with renal impairment or in those with risk factors for renal disease.

All NAs are cleared by kidneys and their dosage should be adjusted in patients with creatinine clearance below 50 mL/min<sup>[104]</sup>. To minimize the risk of nephrotoxicity, simultaneous administration of the other nephrotoxic drugs should be avoided. Secondly, all patients with CHB infection who are treated with adefovir or tenofovir should be regularly monitored for serum creatinine and phosphate levels and drug dose should be modified if creatinine increases by more than 0.5 mg/dL above baseline or phosphate level decreases below 2.0 mg/dL, to the needed dose<sup>[8]</sup>.

## SAFETY IN PREGNANCY

Mother-to-child-transmission remains the main route of hepatitis B acquisition, especially in endemic countries<sup>[105]</sup>. Despite postnatal use of immune globulin and vaccine, mother-to-child transmission of HBV infection still occurs. Intrauterine transmission is considered the main reason underlying immunoprophylaxis failures<sup>[2,106]</sup>. High HBV DNA levels and HBeAg-positive status are the most important risk factors for perinatal HBV transmission. Thus, reducing maternal HBV DNA level has become the main preventive measure of perinatal mother-to-child transmission<sup>[106]</sup>. Current guidelines recommend initiating NAs in pregnant females with high HBV DNA levels (above  $> 10^{6-7}$  IU/mL) at 28-32 wk of gestation and cessation of NAs after delivery or 4-12 wk after delivery in females who do not have a risk for ALT flares and pre-existing advanced liver fibrosis/cirrhosis<sup>[2,105]</sup>.

Two of five NAs approved for the treatment of CHB, telbivudine and tenofovir, are classified as category B in the United States FDA Pregnancy Categories (meaning that no risk was observed in animal studies; however, there are no adequate and well-controlled studies performed in pregnant women). The other three NAs, lamivudine, entecavir and adefovir, are classified as category C (meaning that an adverse effect on the fetus have been shown in animal studies, but there are no adequate studies in humans)<sup>[107]</sup> (Table 1). Prospective studies have revealed that fetal abnormality rates in mothers treated with NAs is low, and similar to those in the general population<sup>[3]</sup>. Lamivudine is the most experienced NA in pregnancy and it has been used safely in preventing mother-to-child transmission of HIV infection for 2 decades<sup>[2]</sup>. In randomized controlled studies, lamivudine has been shown to be effective in

preventing mother-to-child-transmission when used in the third trimester of pregnancy and early postnatal period. There was no significant difference in the incidence of fetal adverse effects between lamivudine and placebo groups<sup>[108,109]</sup>. The Antiretroviral Pregnancy Registry (APR) provides updated fetal safety data on various drugs used in pregnancy, and includes data from January 1989 to date. Up to 31 July 2015, APR reported newborn defect rates as 3.1% during the first trimester of 4566 pregnant women and 2.9% during the second/third trimester of 7263 pregnant women who were exposed to lamivudine. These rates were not different from those reported in the general population<sup>[110]</sup>. However, lamivudine administration, even if for short-term use such as during pregnancy, has a risk of selecting resistant strains due to poor antiviral activity<sup>[106]</sup>. Current guidelines do not recommend lamivudine as first-line therapy for the treatment of CHB infection in pregnant women<sup>[1,2]</sup>.

Tenofovir is recommended in current guidelines for preventing mother-to-child transmission in pregnant women with high viremia based on its potent antiviral activity, high barrier to resistance and being safe<sup>[1,2]</sup>. Data on tenofovir safety has been usually obtained from patients with HIV infection. It has been safely used in pregnant women with HIV infection for a relatively long time. APR reported newborn defect rates as 2.3% during the first trimester of 2608 pregnant women and 2.1% during the second/third trimester of 1258 pregnant women, which is similar to the rates in the general population. In a retrospective study, conducted in 45 HBeAg-positive pregnant women with high HBV DNA levels, tenofovir was found to be effective in preventing vertical transmission and no significant fetal adverse events were observed<sup>[111]</sup>. The other multi-center prospective observational study reported tenofovir to be more effective than lamivudine in preventing vertical transmission<sup>[112]</sup>. These data are supported by other studies<sup>[113]</sup>.

Telbivudine has greater potency than lamivudine in decreasing HBV DNA level and it is recommended by current guidelines in the prevention of mother-to-child transmission of HBV infection. Use of telbivudine during the second/third trimester of pregnancy was reported to be effective and safe. Compared to placebo, no serious adverse events were found in telbivudine-treated mothers and their infants<sup>[3,12]</sup>. Despite the relatively low resistance rate compared to lamivudine, telbivudine resistance may occur during therapy<sup>[105]</sup>. There are no adequate and well-controlled studies on the safety profile of entecavir and adefovir in pregnant women infected with CHB<sup>[15]</sup>.

Breast-feeding is discouraged during maternal NAs treatment due to the uncertain safety on infants<sup>[1,2]</sup>. Lamivudine is concentrated in breast milk. However, its amount in infants exposed to lamivudine during breast-feeding is accepted to be insignificant (approximately 2% of the recommended daily treatment dose)<sup>[114]</sup>. Similarly, tenofovir concentrations in breast milk have

been reported, but infants are exposed to a small amount because its oral bioavailability is limited<sup>[1]</sup>. There is no adequate evidence to recommend the use of entecavir and adefovir during the breast-feeding period<sup>[110,111]</sup>. Lamivudine or tenofovir is regarded as the choice in breastfeeding mothers who needed to receive treatment for HBV infection.

## CONCLUSION

In light of the current data, the treatment of CHB seems to be a life-long therapy. Thus, the long-term safety of the drugs is one of the main factors that influence treatment decision. To date, five oral NAs have been approved for the treatment of CHB. All NAs are generally safe and well-tolerated by CHB patients. All NAs carry a "Black Box" warning about mitochondrial dysfunction. The majority of mitochondrial toxicity cases are associated with lamivudine and telbivudine and generally present as myopathy, neuropathy or lactic acidosis. No increased incidence of myopathy was reported with adefovir, tenofovir and entecavir treatment, compared to placebo. Adefovir is a well-known nephrotoxic agent and may cause renal proximal tubular dysfunction. Fanconi syndrome cases have been increasingly reported in long-term adefovir therapy. Tenofovir has potential nephrotoxic and bone density loss effects, especially in patients with HIV coinfection. Entecavir and lamivudine are not generally associated with renal adverse events. Interestingly, telbivudine has the effect of improving renal function. Serum creatinine, phosphorus and CK levels should be monitored, especially in patients treated with adefovir and tenofovir. Since BMD reduction may occur during tenofovir treatment, BMD measurements should be periodically performed. Although entecavir is suggested to be associated with lactic acidosis in CHB patients with high MELD scores, its use in compensated and decompensated cirrhotic patients were reported to be safe. Safety profile is a major issue that should not be ignored in the treatment of CHB. Further studies should be done to clarify the adverse effects of NAs and determine follow-up timing and frequency, especially in selected patient populations including those with HIV-coinfection or renal impairment, and pregnant or breastfeeding women.

Prolonged treatment experience can still reveal some unknown adverse effects of drugs. Clinical trial data in different patient populations continue to accumulate in the literature. This review contains updated comprehensive data about the safety profile of NAs used in CHB.

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