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

Kayaaslan B *et al*. Adverse effects of nucleos(t)ide analogues

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**Abstract**

Oral nucleoside/nucleotide analogues (NAs) are currently the backbone in 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 the 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:** Adverse events; Adverse effects; Side effects; Safety; Nucleoside/nucleotide analogues; Lamivudine; Telbivudine; Adefovir; Entecavir; Tenofovir; Chronic hepatitis B; Hepatitis B infection; 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 making mitochondrial dysfunction. These adverse events are named as “class effect” 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[1]. Up to 15%-40% of patients with CHB are at risk of developing complications including cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC)[2]. Prevention of disease progression and disease-related complications is the main goal of treatment in CHB and achieved by suppression of viral HBV DNA replication[2]. Because CHB requires long-term treatment in the majority of patients, safety profile of drugs becomes important in addition to antiviral activity. 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)[2-4]. 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[5]. There are currently five NAs approved for the treatment of CHB. They are classified into two groups: nucleoside analogues (lamivudine, telbivudine and entecavir) and nucleotide analogues (adefovir dipivoxil and tenofovir dipivoxil fumarate)[6]. 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 current data.

All five NAs have a favorable safety profile[7]. 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[5], 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[8].

**CLASS EFFECT OF NAs**

NAs suppress viral replication by the inhibition of viral HBV polymerase enzyme. As NAs structures were similar to natural nucleosides, some of these agents can also inhibit human mitochondrial polymerase-γ and cause mitochondrial toxicity[3,5,9]. Mitochondrial toxicity was first noticed during human immunodeficiency virus (HIV) treatment with antiretroviral therapy. Nucleos(t)ide reverse transcriptase inhibitors (NRTIs) are activated by the phosphorylation in the cell, and then inhibit HIV reverse transcriptase. Additionally, these drugs also inhibit a human polymerase-γ 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 oxidatively synthesis of ATP and synthesis of DNA. The depletion of mtDNA-encoded proteins are resulted in a mitochondrial dysfunction that cause impaired oxidative phosphorylation. The other result of human mitochondrial polymerase-γ inhibition is increased reactive oxygen species that cause cellular damage **(**Figure 1**)**[5,8,10]. The close relation between NRTIs and mitochondrial toxicity have been described in many reports[5,8,11]. Because of NAs lead to a minimal mitochondrial polymerase-γ inhibition, NAs associated mitochondrial toxicity cases have been rarely reported. All NAs carry a warning of mitochondrial toxicity on prescribing information[5,8]. The clinical manifestations of mitochondrial toxicity include hematologic disorders, peripheral neuropathy, skeletal and cardiac myopathy, pancreatitis, hepatic failure, and lactic acidosis[8,11].

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 timidine kinase and accumulate in cells rich in mitochondria[5]. South Korea revoked its approval because of indirect adverse effects[12-14]. The emergence of an association between clevudine and myopathy played a role 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[15]. Xu H *et al*[16] performed muscle and nerve biopsy in the six NAs associated myopathy or neuropathy cases 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 quantitive real-time PCR in the affected muscle. Although an association between telbivudine and mitochondrial toxicity was not detected in *in-vitro* studies[12], telbivudine associated myopathy and 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 a study, three of six 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[16]. 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[10,12,15,17].

Myopathy is characterized by creatine kinase (CK) elevation alongside muscle pain and weakness. CK elevations are among the well-described adverse effects of NAs, but it is 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 was not elucidated[3,18]. Myopathy cases can be seen in every age (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 fifth year of treatment. Myopathy cases had been mostly reported from the South Korea and China, but the association between myopathy and race remains unclear[19].

**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. Active anabolite prevents HBV replication by competitively inhibiting viral reverse transcriptase and terminating proviral DNA chain extension[20]. Lamivudine has been the most experienced oral antiviral in CHB patients[8,20]. It can be used effectively in a broad range of patients with minimal adverse effects[21]. However, long-term treatment of lamivudine is associated with high rates of drug resistance which lead to virological relapse and biochemical ﬂare[1-3,8]. Therefore, lamivudine is recommended as a second-line therapy for the treatment of CHB[1,2].

Long-term lamivudine treatment was generally well-tolerated by CHB patients[21,22]. In GLOBE trial, a large, multi-center phase III study, of the 1367 CHB patients receiving telbivudine and lamivudine, adverse events were reported in 23% of lamivudine recipients, similar to those in 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) had experienced serious adverse events[23]. The primary adverse event was reported as hepatic flares due to emergence of lamivudine- resistant HBV with prolonged treatment. After four years, hepatic decompensation and other severe adverse effects increased among patients with lamivudine resistance[24]. In an Asian study by Leung *et al*[22], 12% (7) of patients treated with lamivudine experienced severe side effects. Most of these were increased transaminase and CK levels and were resolved spontaneously. Increased ALT levels were generally associated with emergence of YMDD mutant strains and had no clinical importance. In another study conducted among 998 patients with HBeAg-positive compensated liver disease who were treated with lamivudine up to 6 years, lamivudine demonstrated a good safety profile with only a 5% rate of severe adverse events[24]. 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 survival[25].

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[1]. There are limited data for experiences with the other NAs[26]. 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 in these patients[27,28]. Lamivudine has been well tolerated by patients receiving immunosuppressive treatment[8]. In a systematic review investigating the preventive effect of lamivudine on chemotherapy- induced hepatitis B–related morbidity and mortality in HBsAg-positive patients with cancer, none of the eight studies that recorded safety profile of lamivudine reported any significant adverse events[29]. Lamivudine has also been used safely in children without any serious side effects. In a study, only slight and transient increase of ALT levels were reported in 6.8% of children with CHB without any complaint or clinical findings[30].

Serious adverse events have rarely been reported with lamivudine treatment[31,32]. 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 in pathogenesis[31-33]. Clinical and laboratory findings improve generally within a few days after cessation of the drug. However, in another case, rhabdomyolysis relapsed after readministration of lamivudine for HBV infection prophylaxis and resolved completely after discontinuation of drug again[34]. 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[31]. Lamivudine-induced acute dystonic reaction was reported in two patients and acute dystonia resolved after discontinuing lamivudine therapy[35]. Lamivudine-associated ichthyosiform eruptions and pancreatitis cases had been reported in the literature[25,36-38].

**TELBIVUDINE**

Telbivudine is a timidine 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[3,39]. However, high resistance rates limit the use of telbivudine as the first line therapy[2,3]. 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[23]. CK elevations were generally self-limiting and asymptomatic. Discontinuation of telbivudine was not required in most of the cases[23,39]. Telbivudine-associated myopathy and CK elevations have been reported in several studies[12,40-42]. Zou *et al*[41] 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 three cases. None of the patients developed rhabdomyolysis. CK elevations were reported to occur in males than females and in those with HBeAg negative and aged < 45 years[41]. In another study in which 105 patients given telbivudine were evaluated for adverse reactions, five presented serious adverse events. There was nervous damage in three of the cases and cardiac arrhythmia in one. All five patients had elevated CK enzymes[42]. Therefore it is recommended that CHB patients treated with telbivudine should be monitored closely for musculoskeletal symptoms and CK enzyme levels[3].

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[43]. It results from mitochondrial dysfunction or loss due to the inhibitor activity of telbivudine on human mitochondrial DNA polymerase- γ. A few lactic acidosis cases depending on telbivudine therapy was reported in the literature. The symptoms of patients were anorexia, nausea, vomiting, muscle pain and weakness in upper and lower extremities. Their laboratory tests revealed elevated serum CK levels and hyperlactatemia[43]. One of these 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 months’ interval) lactate measurements besides 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*[42] suggested that the mechanism is associated with cell energy metabolism. Deficiency in manufacture of the energy molecule ATP and therefore the inadequate supplement 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[42].

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 in toxic adverse effects[44]. 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[8].

**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[8]. 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[45-48]. The most common adverse events were pharyngitis, asteni, headache, abdominal pain, flu-like symptoms and nausea[45]. 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[48]. Adefovir is associated with dose dependent renal toxicity. The nephrotoxic effect of adefovir was discussed in the chapter of Renal Safety of NAs.

Myopathy cases were reported in CHB patients given adefovir treatment, but its incidence was similar to patients receiving placebo[12]. Adefovir-related lactic acidosis may occur when combined with other NAs[49]. The development of resistance to adefovir therapy is the other undesirable event. Drug resistance was reported in 26% of CHB patients treated with adefovir after five years[8]. 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 five years[50]. To optimize therapy in lamivudine resistant patients, it is recommended not to discontinue lamivudine therapy for a while after initiating adefovir[8].

**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[3,51]. 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[3]. Entecavir is a well-tolerated antiviral agent in CHB patients with similar rates of adverse event to placebo or lamivudine therapy. In a comparative study, adverse event rate was found to be similar in patients given entecavir monotherapy to those given combination of entecavir and IFN[52]. Long-term use was reported to be associated with very low side effects. Adverse events were not dose-related; their frequencies were similar between 0.5 or 1 mg doses of entecavir[51,53]. 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 of mild or moderate severity and did not require discontinuation of the drug[51,54]. Severe adverse events were 7-10% and discontinuation of therapy was 1%-2% in patients[51]. In a randomized controlled study, severe adverse events occurred in 4.7% of pediatric patients (8), and only one of them discontinued entecavir due to headache. This adverse event was not attributed to the study drug[54]. Although preclinical data reported an association between long-term entecavir use and carcinogenicity, to date, no evidence have been detected regarding occurrence of cancer due to entecavir therapy[55].

The FDA requires all approved NAs to contain a “Black Box” warning in their product label regarding potential mitochondrial toxicity[56]. Entecavir is the most innocent antiviral agent leading to mitochondrial toxicity among effective therapies in CHB treatments. In long-term cell culture studies, ETV has been observed to have very low potential for mitochondrial toxicity *in vitro* cultures studies at the highest levels tested, 300 microM. Combination of ETV with the other NAs also did not cause an increase in the risk of other drugs[8,57]. Entecavir associated myopathy and peripheral neuropathy cases were very rarely reported in the literature[3,15,19]. Although a study reported similar CK elevation rates with both telbivudine and entecavir therapy, there were not many studies supporting this evidence[58]. 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 effect. However, entecavir group was reported to be safer than the telbivudine group in terms of adverse events[59]. In another meta-analysis comparing the effects of telbivudine and entecavir in HBe-Ag 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 the entecavir group[60].

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[61-64]. Entecavir is a good option in the treatment of CHB patients with decompensated cirrhosis because of the rapid effect on HBV decline and low resistance rates. However, it has been suggested that a high Model for End-Stage Liver Disease (MELD) score that used to detect highly impaired liver function was associated with lactic acidosis in patients recieving entecavir[49]. One retrospective study identified five cases of lactic acidosis among 16 entecavir receipient CHB patients with cirrhosis. One of them died and lactic acidosis resolved within 4-5 d after withdrawal of entecavir in the remaining four 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[49]. 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[65,66]. Entecavir has been reported to have a high safety profile in decompensated patients and recommended as one of the first-line treatment choice of CHB patient with decompansated liver disease in Asian-Pacific consensus statement[67,68]. Nevertheless, the patients should be monitored cautiously for the risk of lactic acidosis during the treatment and entecavir should be suspended in the suspicion of lactic acidosis[49,66].

Patients with severe acidosis complained of nausea, dyspnea, and weakness and showed a reduced general physical condition, impaired consciousness, and tachypnea. In addition, two of three patients with severe acidosis suffered from paresthesia and one 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 event were detected in 19% of 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 log10 decrease of HBV DNA[68]. In a multi-centric European study investigating the incidence and outcome of ALT flares during long-term entecavir in CHB, 729 patients treated with ETV 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[69]. Therefore, long-term use of entecavir is generally safe and associated with low rates of serious adverse events, and the 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 in the treatment and prophylaxis of CHB infection in the patients with renal transplant due to being an agent without signs of nephrotoxicity[2].

**TENOFOVIR**

Tenofovir disoproxil fumarate (TDF) is a prodrug of tenofovir that has been approved as a nucleotide analogue by United States FDA for use in HIV infection in 2001 and in CHB infection in 2008 at a dose of 300 mg[8]. 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[1,70]. 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 on HBV DNA decline. The nephrotoxic effect of tenofovir was diccussed in detail in the chapter of 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 headache, nasopharyngitis, back pain, nausea. Treatment-related adverse events were detected in 6% of patients, serious adverse events in 4% and adverse events required discontinuation of tenofovir in less than 1%[8,55]. A 3-year, prospective real-world data (Vireal group) reported 68 adverse events in 41 (9.3%) patients of a total 440 patients receiving tenofovir. Adverse events occurring in more than one patient were renal disorders (11), abdominal pain (8), asthenia (7), nausea (6), vomiting (5) and diarrhea (5). Nine of 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)[71].

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[55,72-74]. However, tenofovir related bone fractures were not reported in HBV monoinfection[55]. During the three-year prospective follow-up, fractures were observed in 1% of 375 HBeAg-negative and 266 HBeAg-positive patients, but none were related to tenofovir[75]. 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[72]. The exact mechanism of bone toxicity in CHB is not clear. Possibly, proximal tubular damage caused by TDF therapy leads to hypophosphatemia and indirectly inadequate mineralization of bone matrix[3]. There were case reports regarding tenofovir associated osteomalacia, but a recent study including 170 patients with CHB infection compared patients treated with tenofovir (122) and control patients (48) in terms of bone health[72]. 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[72-74]. 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[76]. 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[77]. Thus, we may conclude that BMD reduction is not a progressive event and is detected in the first years of treatment[78]. These are important findings due to CHB infection requiring a 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[79]. 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[80]. All NAs are excreted through kidneys in unchanged forms and some of them are associated with dose-dependent nephrotoxicity[3]. Nephrotoxicity results from proximal tubular damage and presents with elevated serum creatinine, proteinuria, nephrogenic diabetes insipidus, hypophosphatemia or the more severe form, Fanconi syndrome[15]. Mauss *et al*[80] reported a milder decrease in renal function with CHB therapy irrespective of medications. Co-morbidities such as diabetes, hypertension and underlying chronic renal disease may also contribute to 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[81].

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[15,45,82-84]. In the majority of studies, nephrotoxicity was defined as an increase ≥ 0.5 mg/dL from baseline in serum creatinine or a serum phosphorus value of < 1.5 mg/dL on two consecutive occasions[83]. In previous studies, including randomized controlled ones, adefovir 30 mg/d were reported to be nephrotoxic, but adefovir 10 mg/d was well tolerated and did not lead to an increase in renal dysfunction compared to placebo[45,85]. In a study including a total of 515 patients with CHB, three groups who were treated placebo (170), adefovir dipivoxil 10 mg (172) or adefovir dipivoxil 30 mg (173) were compared in terms of response to the treatment and adverse events rates[45]. Safety profile was similar in two groups given placebo and adefovir dipivoxil 10 mg per day. There was no significant change in median serum creatinin level at 48 week of the treatment in these groups. However, 8% of the 30-mg-group experienced an increase from base line of 0.5 mg per deciliter (44 µmol per liter) or greater in the serum creatinine level[45]. The prolonged use of adefovir has an extra risk of renal dysfunction. The incidence of increased creatinine level and hypophosphatemia were reported to be increased with the 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[83]. 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 knees, ankles, and ribs. The clinicians should be aware of this potential complication and monitor periodically the renal function and serum phosphate level in a patient receiving adefovir[83,86]. In a current meta-analysis, including seven randomized controlled trials (RCTs), four cohort studies and six single-arm studies, adefovir treatment was not found to be associated with increased nephrotoxicity in RCTs. However, cohort studies showed an increased nephrotoxicity risk in patients given adefovir and single-arm studies revealed a approximately 1.7-fold increased risk of renal dysfunction in patients given adefovir compared to those treated with all other NAs[82]. The authors drew attention to the differences between the risk of nephrotoxicity in RCTs and cohort studies and emphasized that since RCTs are small-sized and short observational studies, safety data may be inadequate and these studies may underestimate 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 and the secretion into urine, and accumulation of adefovir in proximal tubular cells is the primary mechanism of tubular toxicity[83].

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 re-absorption of these solutes. Clinical manifestations in adults include polyuria, polydipsia, dehydration, and osteomalacia[88]. 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[88]. Normalization of creatinine level may require more than one year. In a retrospective case series study including 35 patients with Fanconi syndrome, hypophosphataemia, 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[88]. Fanconi syndrome was rare in CHB patients treated with tenofovir; it has been reported especially in HIV-HBV coinfection[87,89-91].

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

Tenofovir has been shown to have a potential nephrotoxic effect in patients with HIV infection who were especially treated for an extended period. However, in clinical trials, nephrotoxicity does not seem to be a major problem in HBV monoinfection[3,55,93]. 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 an increased serum creatinine levels of 0.5 mg/dL[93]. Nevertheless, renal functions and serum phosphate should be monitored regularly in patients treated with tenofovir[3].

In a study conducted by 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% (65) had a decline in GFR of ≥ 20% and 6% (26) had a decline in GFR of ≥ 30% compared to baseline. Tenofovir treatment was discontinued in 23 patients due to adverse events. Seven of them were associated with renal disorders (3 renal failures, 2 renal impairments, 2 renal tubular disorders)[71]. Patients who have an underlying renal impairment or HIV coinfection and those who receive a nephrotoxic drug are at an 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[94]. A significant number of studies reported that tenofovir did not lead to clinically relevant changes in renal function[79,95]. In a prospective open-label study, conducted by Heathcote *et al*[75], creatinine and creatinine clearance were reported to remain stable during 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 four patients a reduction in serum phosphorus < 2 mg/dL. All patients remained on the study and continued 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 (≥ 0.5 mg/dL increase in serum creatinine from baseline, phosphorus < 2 mg/dL, or CrCL < 50 mL/min) with tenofovir treatment[55]. Recently, Buti *et al*[77] reported seventh year results of tenofovir treatment for CHB. Of 585 patients, 21 (3.6%) experienced renal function impairment. Serum creatinine increase ≥ 0.5 mg/dL above baseline were confirmed in only ten patients (1.7%). The patients who did and did not develop renal insufficiency were statistically different in terms of mean age (47 *vs* 40 years; *P* = 0.003), baseline mean creatinine clearance (98.5 *vs* 117.4 mL/min; *P* = 0.003) and main serum phosphate (2.8 *vs* 3.3 mg/dL; *P* = 0.002). Despite the absence of significant evidences that tenofovir is a nephrotoxic agent, possible proximal tubular damage should still be kept in mind[3]. 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, phosphorus. The patients with impaired renal function or underlying comorbidities that increase renal failure may be monitored more frequently[96]. Dose-adjustment should be made according to renal impairment[3].

Tenofovir safety was also similar in elderly and younger patients[59]. There is little experience with tenofovir treatment in renal transplantation. One study reported 7 HBV-positive organ transplant recipients (three kidney, liver, and only three 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[97].

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[49]. In the study of Tsai *et al*[98], 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[2,99-101].

Interestingly, telbivudine improves renal functions[3,8,81]. Several real-life studies have shown that treatment with telbivudine increases GFR in CHB patients. 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[23,102]. Gane *et al*[102] indicated an improvement in renal function with telbivudine treatment by the calculation of GFR using Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), and Cockcroft–Gault (CG) 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 m2, +11.4% in 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[79]. Preemptive telbivudine use was reported to prevent renal deterioration caused by cisplatin-based chemotherapy in patients with advanced HCC[103]. Additionally, telbivudine is recommended in the prophylactic treatment of CHB in patients with renal transplant due to its renoprotective effect on transplanted patients[2]. 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[104]. 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 increase by more than 0.5 mg/dL above baseline or phosphate level decrease below 2.0 mg/dL, needed dose[8].

**SAFETY IN PREGNANCY**

Mother-to-child-transmission remains the main route of hepatitis B acquisition, especially in endemic countries[105]. Despite postnatal use of immune globulin and vaccine, mother-to-child transmission of HBV infection still occurs. Intrauterine transmission is considered the main reason of immunoprophlaxis failures[2,106]. High HBV DNA levels and HBeAg positive status are the most important risk factors for perinatal HBV transmission. Thus, reducing maternal HBV DNA level becomes the main preventive measure of perinatal mother-to-child transmission[106]. Current guidelines recommend initiating NAs in pregnant females with high HBV DNA levels (above > 106-7 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[2,105].

Two of five NAs approved for the treatment of CHB, telbivudine and tenofovir, are classified as category B by United States FDA Pregnancy Categories (means 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 (means that an adverse effect on fetus have been shown in animal studies, there are no adequate studies in humans)[107] **(**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[3]. Lamivudine is the most experienced NA in pregnancy and it has been used safely in preventing mother to child transmission of HIV infection for two decades[2]. 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 effect between lamivudine and placebo groups[108,109]. The Antiretroviral Pregnancy Registry (APR) provides an updated fetal safety data on various drugs used in pregnancy 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[110]. However, lamivudine administration, even if for short-term use such as during the pregnancy, has a risk of selecting resistant strains due to poor antiviral activity[106]. Current guidelines do not recommend lamivudine as first line therapy for the treatment of CHB infection in pregnant women[1,2].

Tenofovir is recommended in current guidelines for preventing mother-to-child transmission in pregnant women with high viremia based on their potent antiviral activity, high barrier to resistance and being safe[1,2]. Data on tenofovir safety was 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[111]. The other multi-centre prospective observational study reported tenofovir to be more effective than lamivudine in preventing vertical transmission[112]. These data is supported by other studies[113].

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[3,12]. Despite the relatively low resistance rate compared to lamivudine, telbivudine resistance may occur during therapy[105]. There are no adequate and well-controlled studies on the safety profile of entecavir and adefovir in pregnant women infected with CHB[15].

Breast-feeding is discouraged during maternal NAs treatment due to the uncertain safety on infants[1,2]. 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)[114]. Similarly, tenofovir concentrations in breast milk have been reported, but infants are exposed to a small amount because its oral bioavailability is limited[1]. There is no adequate evidence to recommend the use of entecavir and adefovir during the breast-feeding period[110,111]. Lamivudine or tenofovir is regarded as the choice in breastfeeding mothers who needed to receive treatment for HBV infection.

**CONCLUSION**

In light of 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 presented with 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, 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 an updated comprehensive data about the safety profile of NAs used in CHB.

**REFERENCES**

1 **Sarin SK**, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, Chen DS, Chen HL, Chen PJ, Chien RN, Dokmeci AK, Gane E, Hou JL, Jafri W, Jia J, Kim JH, Lai CL, Lee HC, Lim SG, Liu CJ, Locarnini S, Al Mahtab M, Mohamed R, Omata M, Park J, Piratvisuth T, Sharma BC, Sollano J, Wang FS, Wei L, Yuen MF, Zheng SS, Kao JH. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int* 2016; **10**: 1-98 [PMID: 26563120 DOI: 10.1007/s12072-015-9675-4]

2 **European Association for the Study of Liver.** EASL clinical practical guidelines: management of alcoholic liver disease. *J Hepatol* 2012; **57**: 399-420 [PMID: 22633836 DOI: 10.1016/j.jhep.2012.04.004]

3 **Fung J**, Lai CL, Seto WK, Yuen MF. Nucleoside/nucleotide analogues in the treatment of chronic hepatitis B. *J Antimicrob Chemother* 2011; **66**: 2715-2725 [PMID: 21965435 DOI: 10.1093/jac/dkr388]

4 **Newbold JE**, Xin H, Tencza M, Sherman G, Dean J, Bowden S, Locarnini S. The covalently closed duplex form of the hepadnavirus genome exists in situ as a heterogeneous population of viral minichromosomes. *J Virol* 1995; **69**: 3350-3357 [PMID: 7745682]

5 **Fung J**, Seto WK, Lai CL, Yuen MF. Extrahepatic effects of nucleoside and nucleotide analogues in chronic hepatitis B treatment. *J Gastroenterol Hepatol* 2014; **29**: 428-434 [PMID: 24372662 DOI: 10.1111/jgh.12499]

6 **Shan C**, Yin GQ, Wu P. Efficacy and safety of tenofovir in a kidney transplant patient with chronic hepatitis B and nucleos(t)ide multidrug resistance: a case report. *J Med Case Rep* 2014; **8**: 281 [PMID: 25146249 DOI: 10.1186/1752-1947-8-281]

7 **Petersen J**, Buti M. Considerations for the long-term treatment of chronic hepatitis B with nucleos(t)ide analogs. *Expert Rev Gastroenterol Hepatol* 2012; **6**: 683-93; quiz 694 [PMID: 23237254 DOI: 10.1586/egh.12.52]

8 **Fontana RJ**. Side effects of long-term oral antiviral therapy for hepatitis B. *Hepatology* 2009; **49**: S185-S195 [PMID: 19399802 DOI: 10.1002/hep.22885]

9 **Wolters LM**, Niesters HG, de Man RA. Nucleoside analogues for chronic hepatitis B. *Eur J Gastroenterol Hepatol* 2001; **13**: 1499-1506 [PMID: 11742201]

10 **Marcellin P**, Wursthorn K, Wedemeyer H, Chuang WL, Lau G, Avila C, Peng CY, Gane E, Lim SG, Fainboim H, Foster GR, Safadi R, Rizzetto M, Manns M, Bao W, Trylesinski A, Naoumov N. Telbivudine plus pegylated interferon alfa-2a in a randomized study in chronic hepatitis B is associated with an unexpected high rate of peripheral neuropathy. *J Hepatol* 2015; **62**: 41-47 [PMID: 25152207 DOI: 10.1016/j.jhep.2014.08.021]

11 **Martin JL**, Brown CE, Matthews-Davis N, Reardon JE. Effects of antiviral nucleoside analogs on human DNA polymerases and mitochondrial DNA synthesis. *Antimicrob Agents Chemother* 1994; **38**: 2743-2749 [PMID: 7695256]

12 **Fleischer RD**, Lok AS. Myopathy and neuropathy associated with nucleos(t)ide analog therapy for hepatitis B. *J Hepatol* 2009; **51**: 787-791 [PMID: 19665816 DOI: 10.1016/j.jhep.2009.06.011]

13 **Kim BK**, Oh J, Kwon SY, Choe WH, Ko SY, Rhee KH, Seo TH, Lim SD, Lee CH. Clevudine myopathy in patients with chronic hepatitis B. *J Hepatol* 2009; **51**: 829-834 [PMID: 19615776 DOI: 10.1016/j.jhep.2009.04.019]

14 **Tak WY**, Park SY, Cho CM, Jung MK, Jeon SW, Kweon YO, Park JY, Sohn YK. Clinical, biochemical, and pathological characteristics of clevudine-associated myopathy. *J Hepatol* 2010; **53**: 261-266 [PMID: 20466447 DOI: 10.1016/j.jhep.2010.03.006]

15 **Mak LY**, Seto WK, Lai CL, Yuen MF. DNA polymerase inhibitors for treating hepatitis B: a safety evaluation. *Expert Opin Drug Saf* 2016; **15**: 383-392 [PMID: 26752687 DOI: 10.1517/14740338.2016.1139573]

16 **Xu H**, Wang Z, Zheng L, Zhang W, Lv H, Jin S, Yuan Y. Lamivudine/telbivudine-associated neuromyopathy: neurogenic damage, mitochondrial dysfunction and mitochondrial DNA depletion. *J Clin Pathol* 2014; **67**: 999-1005 [PMID: 25190818 DOI: 10.1136/jclinpath-2013-202069]

17 **Wang M**, Da Y, Cai H, Lu Y, Wu L, Jia J. Telbivudine myopathy in a patient with chronic hepatitis B. *Int J Clin Pharm* 2012; **34**: 422-425 [PMID: 22527478 DOI: 10.1007/s11096-012-9633-3]

18 **Shin SR**, Yoo BC, Choi MS, Lee DH, Song SM, Lee JH, Koh KC, Paik SW. A comparison of 48-week treatment efficacy between clevudine and entecavir in treatment-naïve patients with chronic hepatitis B. *Hepatol Int* 2011; **5**: 664-670 [PMID: 21484144 DOI: 10.1007/s12072-010-9238-7]

19 **Yuan K**, Guochun W, Huang Z, Lin B, Zhou H, Lu X. Entecavir-associated myopathy: a case report and literature review. *Muscle Nerve* 2014; **49**: 610-614 [PMID: 24218312 DOI: 10.1002/mus.24118]

20 **Palumbo E**. Lamivudine for chronic hepatitis B: a brief review. *Braz J Infect Dis* 2008; **12**: 355-357 [PMID: 19219271]

21 **Leung N**. Treatment of chronic hepatitis B: case selection and duration of therapy. *J Gastroenterol Hepatol* 2002; **17**: 409-414 [PMID: 11982721]

22 **Leung NW**, Lai CL, Chang TT, Guan R, Lee CM, Ng KY, Lim SG, Wu PC, Dent JC, Edmundson S, Condreay LD, Chien RN; Asia Hepatitis Lamivudine Study Group. Extended lamivudine treatment in patients with chronic hepatitis B enhances hepatitis B e antigen seroconversion rates: results after 3 years of therapy. *Hepatology* 2001; **33**: 1527-1532 [PMID: 11391543]

23 **Liaw YF**, Gane E, Leung N, Zeuzem S, Wang Y, Lai CL, Heathcote EJ, Manns M, Bzowej N, Niu J, Han SH, Hwang SG, Cakaloglu Y, Tong MJ, Papatheodoridis G, Chen Y, Brown NA, Albanis E, Galil K, Naoumov NV; GLOBE Study Group. 2-Year GLOBE trial results: telbivudine Is superior to lamivudine in patients with chronic hepatitis B. *Gastroenterology* 2009; **136**: 486-495 [PMID: 19027013 DOI: 10.1053/j.gastro.2008.10.026]

24 **Lok AS**, Lai CL, Leung N, Yao GB, Cui ZY, Schiff ER, Dienstag JL, Heathcote EJ, Little NR, Griffiths DA, Gardner SD, Castiglia M. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. *Gastroenterology* 2003; **125**: 1714-1722 [PMID: 14724824]

25 **Tillmann HL**, Hadem J, Leifeld L, Zachou K, Canbay A, Eisenbach C, Graziadei I, Encke J, Schmidt H, Vogel W, Schneider A, Spengler U, Gerken G, Dalekos GN, Wedemeyer H, Manns MP. Safety and efficacy of lamivudine in patients with severe acute or fulminant hepatitis B, a multicenter experience. *J Viral Hepat* 2006; **13**: 256-263 [PMID: 16611192]

26 **Roche B**, Samuel D. The difficulties of managing severe hepatitis B virus reactivation. *Liver Int* 2011; **31 Suppl 1**: 104-110 [PMID: 21205146 DOI: 10.1111/j.1478-3231.2010.02396.x]

27 **Huprikar S**, Danziger-Isakov L, Ahn J, Naugler S, Blumberg E, Avery RK, Koval C, Lease ED, Pillai A, Doucette KE, Levitsky J, Morris MI, Lu K, McDermott JK, Mone T, Orlowski JP, Dadhania DM, Abbott K, Horslen S, Laskin BL, Mougdil A, Venkat VL, Korenblat K, Kumar V, Grossi P, Bloom RD, Brown K, Kotton CN, Kumar D. Solid organ transplantation from hepatitis B virus-positive donors: consensus guidelines for recipient management. *Am J Transplant* 2015; **15**: 1162-1172 [PMID: 25707744 DOI: 10.1111/ajt.13187]

28 **Wright AJ**, Fishman JA, Chung RT. Lamivudine compared with newer antivirals for prophylaxis of hepatitis B core antibody positive livers: a cost-effectiveness analysis. *Am J Transplant* 2014; **14**: 629-634 [PMID: 24460820 DOI: 10.1111/ajt.12598]

29 **Loomba R**, Rowley A, Wesley R, Liang TJ, Hoofnagle JH, Pucino F, Csako G. Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. *Ann Intern Med* 2008; **148**: 519-528 [PMID: 18378948]

30 **Liberek A**, Szaflarska-Popławska A, Korzon M, Łuczak G, Góra-Gebka M, Łoś-Rycharska E, Bako W, Czerwionka-Szaflarska M. Lamivudine therapy for children with chronic hepatitis B. *World J Gastroenterol* 2006; **12**: 2412-2416 [PMID: 16688835]

31 **Baharin J**, Sahari NS, Lim SM. Rhabdomyolysis due to Lamivudine administration in acute viral hepatitis B infection: a case report from Malaysia. *Electron Physician* 2014; **6**: 863-867 [PMID: 25763159 DOI: 10.14661/2014.863-86].]

32 **Yahagi K**, Ueno Y, Mano Y, Shimosegawa T. Rhabdomyolytic syndrome during the lamivudine therapy for acute exacerbation of chronic type B hepatitis. *Liver Transpl* 2002; **8**: 1198-1199 [PMID: 12474162]

33 **Holt SG**, Moore KP. Pathogenesis and treatment of renal dysfunction in rhabdomyolysis. *Intensive Care Med* 2001; **27**: 803-811 [PMID: 11430535]

34 **Adani GL**, Baccarani U, Risaliti A, Bresadola F, Della Rocca G, Viale P. Rhabdomyolysis due to Lamivudine administration in a liver transplant recipient. *Am J Transplant* 2005; **5**: 634 [PMID: 15707423]

35 **Song X**, Hu Z, Zhang H. Acute dystonia induced by lamivudine. *Clin Neuropharmacol* 2005; **28**: 193-194 [PMID: 16062101]

36 **Kaptanoglu AF**, Kutluay L. Ichthyosiform eruption associated with lamivudine in a patient with chronic hepatitis-B infection. *Int J Clin Pract* 2005; **59**: 1237-1238 [PMID: 16178993]

37 **Tuon FF**, Guastini CM, Boulos MI. Acute pancreatitis associated with lamivudine therapy for chronic B hepatitis. *Braz J Infect Dis* 2008; **12**: 263 [PMID: 19030723]

38 **Soylu AR**, Dökmeci G, Tezel A, Cakir B, Umit H, Karahan N, Amuca H. Lamivudine-induced acute pancreatitis in a patient with decompensated Hbv-related chronic liver disease. *J Clin Gastroenterol* 2004; **38**: 134 [PMID: 14745288]

39 **Matthews SJ**. Telbivudine for the management of chronic hepatitis B virus infection. *Clin Ther* 2007; **29**: 2635-2653 [PMID: 18201580 DOI: 10.1016/j.clinthera.2007.12.032]

40 **Wang YH**, Wu BQ, Liu H. Continuous venovenous hemodiafiltration for hyperlactatemia caused by telbivudine in a patient with chronic hepatitis B: a case report and update review. *J Dig Dis* 2015; **16**: 164-167 [PMID: 25043654 DOI: 10.1111/1751-2980.12173]

41 **Zou XJ**, Jiang XQ, Tian DY. Clinical features and risk factors of creatine kinase elevations and myopathy associated with telbivudine. *J Viral Hepat* 2011; **18**: 892-896 [PMID: 22093034 DOI: 10.1111/j.1365-2893.2010.01412.x]

42 **Zhang XS**, Jin R, Zhang SB, Tao ML. Clinical features of adverse reactions associated with telbivudine. *World J Gastroenterol* 2008; **14**: 3549-3553 [PMID: 18567085]

43 **Jin JL**, Hu P, Lu JH, Luo SS, Huang XY, Weng XH, Zhang JM. Lactic acidosis during telbivudine treatment for HBV: a case report and literature review. *World J Gastroenterol* 2013; **19**: 5575-5580 [PMID: 24023503 DOI: 10.3748/wjg.v19.i33.5575]

44 **Lai CL**, Leung N, Teo EK, Tong M, Wong F, Hann HW, Han S, Poynard T, Myers M, Chao G, Lloyd D, Brown NA; Telbivudine Phase II Investigator Group. A 1-year trial of telbivudine, lamivudine, and the combination in patients with hepatitis B e antigen-positive chronic hepatitis B. *Gastroenterology* 2005; **129**: 528-536 [PMID: 16083710]

45 **Marcellin P**, Chang TT, Lim SG, Tong MJ, Sievert W, Shiffman ML, Jeffers L, Goodman Z, Wulfsohn MS, Xiong S, Fry J, Brosgart CL; [Adefovir Dipivoxil 437 Study Group](http://www.ncbi.nlm.nih.gov/pubmed/?term=Adefovir%2520Dipivoxil%2520437%2520Study%2520Group%255BCorporate%2520Author%255D). Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *N Engl J Med* 2003; **348**: 808-816 [PMID: 12606735]

46 **Dando T**, Plosker G. Adefovir dipivoxil: a review of its use in chronic hepatitis B. *Drugs* 2003; **63**: 2215-2234 [PMID: 14498759]

47 **Sokal EM**, Kelly D, Wirth S, Mizerski J, Dhawan A, Frederick D. The pharmacokinetics and safety of adefovir dipivoxil in children and adolescents with chronic hepatitis B virus infection. *J Clin Pharmacol* 2008; **48**: 512-517 [PMID: 18276803 DOI: 10.1177/0091270007313325]

48 **Hadziyannis SJ**, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, Marcellin P, Lim SG, Goodman Z, Wulfsohn MS, Xiong S, Fry J, Brosgart CL; Adefovir Dipivoxil 438 Study Group. Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. *N Engl J Med* 2003; **348**: 800-807 [PMID: 12606734]

49 **Lange CM**, Bojunga J, Hofmann WP, Wunder K, Mihm U, Zeuzem S, Sarrazin C. Severe lactic acidosis during treatment of chronic hepatitis B with entecavir in patients with impaired liver function. *Hepatology* 2009; **50**: 2001-2006 [PMID: 19937695 DOI: 10.1002/hep.23346]

50 **Kim SB**, Kim SU, Kim BK, Park JY, Kim do Y, Ahn SH, Han KH. Outcome of adefovir add-on lamivudine rescue therapy of up to 5 years in patients with lamivudine-resistant chronic hepatitis B. *J Gastroenterol Hepatol* 2016; **31**: 241-247 [PMID: 26204913 DOI: 10.1111/jgh.13046]

51 **Matthews SJ**. Entecavir for the treatment of chronic hepatitis B virus infection. *Clin Ther* 2006; **28**: 184-203 [PMID: 16678641]

52 **Tangkijvanich P**, Chittmittraprap S, Poovorawan K, Limothai U, Khlaiphuengsin A, Chuaypen N, Wisedopas N, Poovorawan Y. A randomized clinical trial of peginterferon alpha-2b with or without entecavir in patients with HBeAg-negative chronic hepatitis B: Role of host and viral factors associated with treatment response. *J Viral Hepat* 2016; **23**: 427-438 [PMID: 26387494 DOI: 10.1111/jvh.12467]

53 **Suzuki F**, Toyoda J, Katano Y, Sata M, Moriyama M, Imazeki F, Kage M, Seriu T, Omata M, Kumada H. Efficacy and safety of entecavir in lamivudine-refractory patients with chronic hepatitis B: randomized controlled trial in Japanese patients. *J Gastroenterol Hepatol* 2008; **23**: 1320-1326 [PMID: 18554238 DOI: 10.1111/j.1440-1746.2008.05455.x]

54 **Jonas MM**, Chang MH, Sokal E, Schwarz KB, Kelly D, Kim KM, Ling SC, Rosenthal P, Oraseanu D, Reynolds L, Thiry A, Ackerman P. Randomized, controlled trial of entecavir versus placebo in children with hepatitis B envelope antigen-positive chronic hepatitis B. *Hepatology* 2016; **63**: 377-387 [PMID: 26223345 DOI: 10.1002/hep.28015]

55 **Ridruejo E.** Treatment of chronic hepatitis B in clinical practice with entecavir or tenofovir. *World J Gastroenterol* 2014; **20:** 7169-80 [PMID: 24966587 DOI: 10.3748/wjg.v20.i23.7169]

56 **Mao H**, Kang T. Lactic Acidosis during Entecavir Antiviral Treatment in a Patient with Hepatitis B Virus-related Decompensated Cirrhosis. *West Indian Med J* 2015; **64**: 165-166 [PMID: 26360694 DOI: 10.7727/wimj.2013.198]

57 **Mazzucco CE**, Hamatake RK, Colonno RJ, Tenney DJ. Entecavir for treatment of hepatitis B virus displays no in vitro mitochondrial toxicity or DNA polymerase gamma inhibition. *Antimicrob Agents Chemother* 2008; **52**: 598-605 [PMID: 18056280]

58 **Zhang Y**, Hu P, Qi X, Ren H, Mao RC, Zhang JM. A comparison of telbivudine and entecavir in the treatment of hepatitis B e antigen-positive patients: a prospective cohort study in China. *Clin Microbiol Infect* 2016; **22**: 287.e1-287.e9 [PMID: 26548508 DOI: 10.1016/j.cmi.2015.10.024]

59 **Liang J**, Jiang MJ, Deng X, Xiao Zhou X. Efficacy and Safety of Telbivudine Compared to Entecavir Among HBeAg+ Chronic Hepatitis B Patients: a Meta-Analysis Study. *Hepat Mon* 2013; **13**: e7862 [PMID: 24032045 DOI: 10.5812/hepatmon.7862]

60 **Su QM**, Ye XG. Effects of telbivudine and entecavir for HBeAg-positive chronic hepatitis B: a meta-analysis. *World J Gastroenterol* 2012; **18**: 6290-6301 [PMID: 23180951 DOI: 10.3748/wjg.v18.i43.6290]

61 Bristol-Myers Squibb. Baraclude® (entecavir): US prescribing information [online]. Available from URL:<http://packageinserts.bms.com/pi/pi_baraclude.pdf> [Accessed 2016 Sept 16]

62 Gilead Sciences, Inc. Viread® (tenofovir disoproxil fumarate) tablets: US prescribing information [online]. Available from URL:<http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021356s035lbl.pdf>[Accessed 2016 Sept 16]

63 Novartis. Tyzeka (telbivudine): US prescribing information [online]. Available from URL: http: //www.pharma.us.novartis.com/product/pi/pdf/tyzeka.pdf [Accessed 2016 Sept 16]

64 Gilead Sciences, Inc. Hepsera (adefovir dipivoxil) tablets: US prescribing information [online]. Available from URL: http: //www.accessdata.fda.gov/drugsatfda\_docs/label/2009/021449s016lbl.pdf[Accessed 2016 Sept 16]

65 **Marzano A**, Marengo A, Marietti M, Rizzetto M. Lactic acidosis during Entecavir treatment in decompensated hepatitis B virus-related cirrhosis. *Dig Liver Dis* 2011; **43**: 1027-1028 [PMID: 21782535 DOI: 10.1016/j.dld.2011.06.013]

66 **Keating GM**. Entecavir: a review of its use in the treatment of chronic hepatitis B in patients with decompensated liver disease. *Drugs* 2011; **71**: 2511-2529 [PMID: 22141390 DOI: 10.2165/11208510-000000000-00000]

67 **Liaw YF**, Leung N, Kao JH, Piratvisuth T, Gane E, Han KH, Guan R, Lau GK, Locarnini S; Chronic Hepatitis B Guideline Working Party of the Asian-Pacific Association for the Study of the Liver. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update. *Hepatol Int* 2008; **2**: 263-283 [PMID: 19669255 DOI: 10.1007/s12072-008-9080-3]

68 **Manns MP**, Akarca US, Chang TT, Sievert W, Yoon SK, Tsai N, Min A, Pangerl A, Beebe S, Yu M, Wongcharatrawee S. Long-term safety and tolerability of entecavir in patients with chronic hepatitis B in the rollover study ETV-901. *Expert Opin Drug Saf* 2012; **11**: 361-368 [PMID: 22233350 DOI: 10.1517/14740338.2012.653340]

69 **Chi H**, Arends P, Reijnders JG, Carey I, Brown A, Fasano M, Mutimer D, Deterding K, Oo YH, Petersen J, van Bommel F, de Knegt RJ, Santantonio TA, Berg T, Welzel TM, Wedemeyer H, Buti M, Pradat P, Zoulim F, Hansen BE, Janssen HL. Flares during long-term entecavir therapy in chronic hepatitis B. *J Gastroenterol Hepatol* 2016; **31**: 1882-1887 [PMID: 27008918 DOI: 10.1111/jgh.13377]

70 **Lok AS**, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology* 2009; **50**: 661-662 [PMID: 19714720 DOI: 10.1002/hep.23190]

71 **Marcellin P**, Zoulim F, Hézode C, Causse X, Roche B, Truchi R, Pauwels A, Ouzan D, Dumortier J, Pageaux GP, Bourlière M, Riachi G, Zarski JP, Cadranel JF, Tilliet V, Stern C, Pétour P, Libert O, Consoli SM, Larrey D. Effectiveness and Safety of Tenofovir Disoproxil Fumarate in Chronic Hepatitis B: A 3-Year, Prospective, Real-World Study in France. *Dig Dis Sci* 2016; **61**: 3072-3083 [PMID: 26821154]

72 **Gill US**, Zissimopoulos A, Al-Shamma S, Burke K, McPhail MJ, Barr DA, Kallis YN, Marley RT, Kooner P, Foster GR, Kennedy PT. Assessment of bone mineral density in tenofovir-treated patients with chronic hepatitis B: can the fracture risk assessment tool identify those at greatest risk? *J Infect Dis* 2015; **211**: 374-382 [PMID: 25156561 DOI: 10.1093/infdis/jiu471]

73 **Perrot S**, Aslangul E, Szwebel T, Caillat-Vigneron N, Le Jeunne C. Bone pain due to fractures revealing osteomalacia related to tenofovir-induced proximal renal tubular dysfunction in a human immunodeficiency virus-infected patient. *J Clin Rheumatol* 2009; **15**: 72-74 [PMID: 19265350 DOI: 10.1097/RHU.0b013e31819c20d8]

74 **Bedimo R**, Maalouf NM, Zhang S, Drechsler H, Tebas P. Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents. *AIDS* 2012; **26**: 825-831 [PMID: 22301411 DOI: 10.1097/QAD.0b013e32835192ae]

75 **Heathcote EJ**, Marcellin P, Buti M, Gane E, De Man RA, Krastev Z, Germanidis G, Lee SS, Flisiak R, Kaita K, Manns M, Kotzev I, Tchernev K, Buggisch P, Weilert F, Kurdas OO, Shiffman ML, Trinh H, Gurel S, Snow-Lampart A, Borroto-Esoda K, Mondou E, Anderson J, Sorbel J, Rousseau F. Three-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B. *Gastroenterology* 2011; **140**: 132-143 [PMID: 20955704 DOI: 10.1053/j.gastro.2010.10.011]

76 **Wong GL**, Tse YK, Wong VW, Yip TC, Tsoi KK, Chan HL. Long-term safety of oral nucleos(t)ide analogs for patients with chronic hepatitis B: A cohort study of 53,500 subjects. *Hepatology* 2015; **62**: 684-693 [PMID: 25973979 DOI: 10.1002/hep.27894]

77 **Buti M**, Tsai N, Petersen J, Flisiak R, Gurel S, Krastev Z, Schall RA, Flaherty JF, Martins EB, Charuworn P, Kitrinos KM, Subramanian GM, Gane E, Marcellin P. Seven-year efficacy and safety of treatment with tenofovir disoproxil fumarate for chronic hepatitis B virus infection. *Dig Dis Sci* 2015; **60**: 1457-1464 [PMID: 25532501 DOI: 10.1007/s10620-014-3486-7]

78 **Fung S**, Kwan P, Fabri M, Horban A, Pelemis M, Hann HW, Gurel S, Caruntu FA, Flaherty JF, Massetto B, Dinh P, Corsa A, Subramanian GM, McHutchison JG, Husa P, Gane E. Randomized comparison of tenofovir disoproxil fumarate vs emtricitabine and tenofovir disoproxil fumarate in patients with lamivudine-resistant chronic hepatitis B. *Gastroenterology* 2014; **146**: 980-988 [PMID: 24368224 DOI: 10.1053/j.gastro.2013.12.028]

79 **Ridruejo E**, Silva MO. Safety of long-term nucleos(t)ide treatment in chronic hepatitis B. *Expert Opin Drug Saf* 2012; **11**: 357-360 [PMID: 22417072 DOI: 10.1517/14740338.2012.672972]

80 **Shin JH**, Kwon HJ, Jang HR, Lee JE, Gwak GY, Huh W, Jung SH, Lee JH, Kim YG, Kim DJ, Oh HY. Risk Factors for Renal Functional Decline in Chronic Hepatitis B Patients Receiving Oral Antiviral Agents. *Medicine (Baltimore)* 2016; **95**: e2400 [PMID: 26735542 DOI: 10.1097/MD.0000000000002400]

81 **Mauss S**, Berger F, Filmann N, Hueppe D, Henke J, Hegener P, Athmann C, Schmutz G, Herrmann E. Effect of HBV polymerase inhibitors on renal function in patients with chronic hepatitis B. *J Hepatol* 2011; **55**: 1235-1240 [PMID: 21703180 DOI: 10.1016/j.jhep.2011.03.030]

82 **Yang Q**, Shi YU, Yang Y, Lou G, Lv F. Association between adefovir dipivoxil treatment and the risk of renal insufficiency in patients with chronic hepatitis B: A meta-analysis. *Biomed Rep* 2015; **3**: 269-275 [PMID: 25798251]

83 **Eguchi H**, Tsuruta M, Tani J, Kuwahara R, Hiromatsu Y. Hypophosphatemic osteomalacia due to drug-induced Fanconi's syndrome associated with adefovir dipivoxil treatment for hepatitis B. *Intern Med* 2014; **53**: 233-237 [PMID: 24492692]

84 **Chen G**, Lin W, Shen F, Iloeje UH, London WT, Evans AA. Past HBV viral load as predictor of mortality and morbidity from HCC and chronic liver disease in a prospective study. *Am J Gastroenterol* 2006; **101**: 1797-1803 [PMID: 16817842]

85 **Izzedine H**, Hulot JS, Launay-Vacher V, Marcellini P, Hadziyannis SJ, Currie G, Brosgart CL, Westland C, Arterbrun S, Deray G; Adefovir Dipivoxil International 437 Study Group; Adefovir Dipivoxil International 438 Study Group. Renal safety of adefovir dipivoxil in patients with chronic hepatitis B: two double-blind, randomized, placebo-controlled studies. *Kidney Int* 2004; **66**: 1153-1158 [PMID: 15327411]

86 **Girgis CM**, Wong T, Ngu MC, Emmett L, Archer KA, Chen RC, Seibel MJ. Hypophosphataemic osteomalacia in patients on adefovir dipivoxil. *J Clin Gastroenterol* 2011; **45**: 468-473 [PMID: 20661153 DOI: 10.1097/MCG.0b013e3181e12ed3]

87 **Samarkos M**, Theofanis V, Eliadi I, Vlachogiannakos J, Polyzos A. Tenofovir-associated Fanconi syndrome in a patient with chronic hepatitis B. *J Gastrointestin Liver Dis* 2014; **23**: 342 [PMID: 25267967]

88 **Xu LJ**, Jiang Y, Liao RX, Zhang HB, Mao JF, Chi Y, Li M, Wang O, Liu XQ, Liu ZY, Xing XP, Yu W, Xia WB. Low-dose adefovir dipivoxil may induce Fanconi syndrome: clinical characteristics and long-term follow-up for Chinese patients. *Antivir Ther* 2015; **20**: 603-611 [PMID: 25814481 DOI: 10.3851/IMP2954]

89 **Viganò M**, Brocchieri A, Spinetti A, Zaltron S, Mangia G, Facchetti F, Fugazza A, Castelli F, Colombo M, Lampertico P. Tenofovir-induced Fanconi syndrome in chronic hepatitis B monoinfected patients that reverted after tenofovir withdrawal. *J Clin Virol* 2014; **61**: 600-603 [PMID: 25453573 DOI: 10.1016/j.jcv.2014.09.016]

90 **Gracey DM**, Snelling P, McKenzie P, Strasser SI. Tenofovir-associated Fanconi syndrome in patients with chronic hepatitis B monoinfection. *Antivir Ther* 2013; **18**: 945-948 [PMID: 23839869 DOI: 10.3851/IMP2649]

91 **Gómez Martinez MV**, Gallardo FG, Pirogova T, García-Samaniego J. Bone scintigraphy and secondary osteomalacia due to nephrotoxicity in a chronic hepatitis B patient treated with tenofovir. *Rev Esp Med Nucl Imagen Mol* 2014; **33**: 103-105 [PMID: 23920225 DOI: 10.1016/j.remn.2013.05.011]

92 **Karras A**, Lafaurie M, Furco A, Bourgarit A, Droz D, Sereni D, Legendre C, Martinez F, Molina JM. Tenofovir-related nephrotoxicity in human immunodeficiency virus-infected patients: three cases of renal failure, Fanconi syndrome, and nephrogenic diabetes insipidus. *Clin Infect Dis* 2003; **36**: 1070-1073 [PMID: 12684922]

93 **Pol S**, Lampertico P. First-line treatment of chronic hepatitis B with entecavir or tenofovir in 'real-life' settings: from clinical trials to clinical practice. *J Viral Hepat* 2012; **19**: 377-386 [PMID: 22571899 DOI: 10.1111/j.1365-2893.2012.01602.x]

94 **Gish RG**, Clark MD, Kane SD, Shaw RE, Mangahas MF, Baqai S. Similar risk of renal events among patients treated with tenofovir or entecavir for chronic hepatitis B. *Clin Gastroenterol Hepatol* 2012; **10**: 941-96; quiz e68 [PMID: 22507876 DOI: 10.1016/j.cgh.2012.04.008]

95 **Kim JH**, Jung SW, Byun SS, Shin JW, Park BR, Kim MH, Kim CJ, Park NH. Efficacy and safety of tenofovir in nucleos(t)ide-naïve patients with genotype C chronic hepatitis B in real-life practice. *Int J Clin Pharm* 2015; **37**: 1228-1234 [PMID: 26364195 DOI: 10.1007/s11096-015-0193-1]

96 **Lok AS**. Drug therapy: tenofovir. *Hepatology* 2010; **52**: 743-747 [PMID: 20597070 DOI: 10.1002/hep.23788]

97 **Daudé M**, Rostaing L, Sauné K, Lavayssière L, Basse G, Esposito L, Guitard J, Izopet J, Alric L, Kamar N. Tenofovir therapy in hepatitis B virus-positive solid-organ transplant recipients. *Transplantation* 2011; **91**: 916-920 [PMID: 21325995 DOI: 10.1097/TP.0b013e3182100f59]

98 **Tsai MC**, Chen CH, Hung CH, Lee CM, Chiu KW, Wang JH, Lu SN, Tseng PL, Chang KC, Yen YH, Hu TH. A comparison of efficacy and safety of 2-year telbivudine and entecavir treatment in patients with chronic hepatitis B: a match-control study. *Clin Microbiol Infect* 2014; **20**: O90-O100 [PMID: 23659493 DOI: 10.1111/1469-0691.12220]

99 **Ridruejo E**. Antiviral treatment for chronic hepatitis B in renal transplant patients. *World J Hepatol* 2015; **7**: 189-203 [PMID: 25729474 DOI: 10.4254/wjh.v7.i2.189]

100 **Koklu S**, Gulsen MT, Tuna Y, Koklu H, Yuksel O, Demir M, Guner R, Dogan Z, Kucukazman M, Poyrazoglu OK, Biyik M, Ozturk NA, Aydogan T, Coban S, Kocaman O, Sapmaz F, Gokturk SH, Karaca C, Demirezer A, Tanoglu A, Yildirim B, Altinbas A, Atak BM, Cosar AM, Alkan E. Differences in nephrotoxicity risk and renal effects among anti-viral therapies against hepatitis B. *Aliment Pharmacol Ther* 2015; **41**: 310-319 [PMID: 25982037 DOI: 10.1111/apt.13036]

101 **Levitsky J**, Doucette K; AST Infectious Diseases Community of Practice. Viral hepatitis in solid organ transplantation. *Am J Transplant* 2013; **13 Suppl 4**: 147-168 [PMID: 23465008 DOI: 10.1111/ajt.12108]

102 **Gane EJ**, Deray G, Liaw YF, Lim SG, Lai CL, Rasenack J, Wang Y, Papatheodoridis G, Di Bisceglie A, Buti M, Samuel D, Uddin A, Bosset S, Trylesinski A. Telbivudine improves renal function in patients with chronic hepatitis B. *Gastroenterology* 2014; **146**: 138-146.e5 [PMID: 24067879 DOI: 10.1053/j.gastro.2013.09.031]

103 **Lin CL**, Chien RN, Yeh C, Hsu CW, Chang ML, Chen YC, Yeh CT. Significant renoprotective effect of telbivudine during preemptive antiviral therapy in advanced liver cancer patients receiving cisplatin-based chemotherapy: a case-control study. *Scand J Gastroenterol* 2014; **49**: 1456-1464 [PMID: 25283499 DOI: 10.3109/00365521.2014.962604]

104 **Pipili C**, Cholongitas E, Papatheodoridis G. Review article: nucleos(t)ide analogues in patients with chronic hepatitis B virus infection and chronic kidney disease. *Aliment Pharmacol Ther* 2014; **39**: 35-46 [PMID: 24299322 DOI: 10.1111/apt.12538]

105 **Wong F**, Pai R, Van Schalkwyk J, Yoshida EM. Hepatitis B in pregnancy: a concise review of neonatal vertical transmission and antiviral prophylaxis. *Ann Hepatol* 2014; **13**: 187-195 [PMID: 24552860]

106 **Yi P**, Chen R, Huang Y, Zhou RR, Fan XG. Management of mother-to-child transmission of hepatitis B virus: Propositions and challenges. *J Clin Virol* 2016; **77**: 32-39 [PMID: 26895227 DOI: 10.1016/j.jcv.2016.02.003]

107 FDA Pregnancy Categories. [Updated Mar 30th, 2016]. Available from: http: //www.drugs.com/pregnancy-categories.html (Access date: Apr 24th, 2016)

108 **Yu M**, Jiang Q, Ji Y, Jiang H, Wu K, Ju L, Tang X, Wu M. The efficacy and safety of antiviral therapy with lamivudine to stop the vertical transmission of hepatitis B virus. *Eur J Clin Microbiol Infect Dis* 2012; **31**: 2211-2218 [PMID: 22314409]

109 **Xu WM**, Cui YT, Wang L, Yang H, Liang ZQ, Li XM, Zhang SL, Qiao FY, Campbell F, Chang CN, Gardner S, Atkins M. Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection: a multicentre, randomized, double-blind, placebo-controlled study. *J Viral Hepat* 2009; **16**: 94-103 [PMID: 19175878 DOI: 10.1111/j.1365-2893.2008.01056.x]

110 Antiretroviral Pregnancy Registry [Internet]. WHO. [Updated 2015 Dec 17]. Available from: URL: http: //www.apregistry.com/InterimReport.aspx (Access date: 20.03.2016)

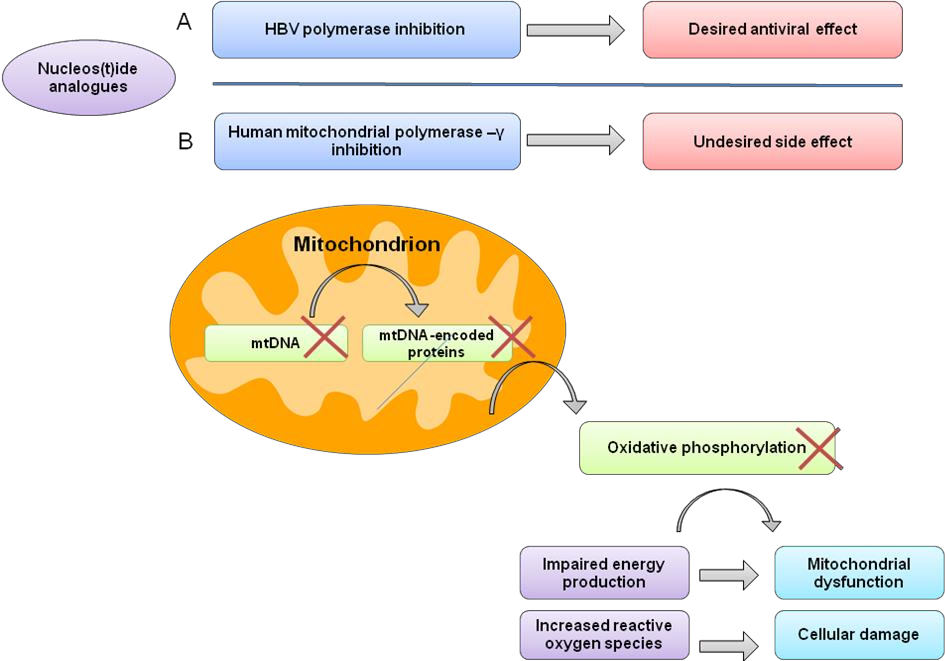
111 **Celen MK**, Mert D, Ay M, Dal T, Kaya S, Yildirim N, Gulsun S, Barcin T, Kalkanli S, Dal MS, Ayaz C. Efficacy and safety of tenofovir disoproxil fumarate in pregnancy for the prevention of vertical transmission of HBV infection. *World J Gastroenterol* 2013; **19**: 9377-9382 [PMID: 24409065 DOI: 10.3748/wjg.v19.i48.9377]

112 **Greenup AJ**, Tan PK, Nguyen V, Glass A, Davison S, Chatterjee U, Holdaway S, Samarasinghe D, Jackson K, Locarnini SA, Levy MT. Efficacy and safety of tenofovir disoproxil fumarate in pregnancy to prevent perinatal transmission of hepatitis B virus. *J Hepatol* 2014; **61**: 502-507 [PMID: 24801414 DOI: 10.1016/j.jhep.2014.04.038]

113 **Hu YH**, Liu M, Yi W, Cao YJ, Cai HD. Tenofovir rescue therapy in pregnant females with chronic hepatitis B. *World J Gastroenterol* 2015; **21**: 2504-2509 [PMID: 25741161 DOI: 10.3748/wjg.v21.i8.2504]

114 **Mirochnick M**, Thomas T, Capparelli E, Zeh C, Holland D, Masaba R, Odhiambo P, Fowler MG, Weidle PJ, Thigpen MC. Antiretroviral concentrations in breast-feeding infants of mothers receiving highly active antiretroviral therapy. *Antimicrob Agents Chemother* 2009; **53**: 1170-1176 [PMID: 19114673 DOI: 10.1128/AAC.01117-08]

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**Figure 1 The effects of Nucleos(t)ide analogues (NAs).** A: NAs show antiviral effect by inhibition of HBV polymerase; B: NAs also inhibits human mitochondrial polymerase-γ enzyme. Thus, mitochondrial DNA (mtDNA) can not be synthesized. Oxidative phosphorilation 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; HBV: Hepatitis B virus.

**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 required 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 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 acdosis | 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 | Hypophosphatmi Fanconi syndrome | C | Unknown. Not  recommend for use |
| **Entecavir**  **(2005)** | Very rare. No increased incidence of mytochondiral 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.