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A Systematic Review of Side Effects of Nucleoside and Nucleotide Drugs Used for Treatment of Chronic Hepatitis B

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Abstract Although nucleosides and nucleotides have a good safety record for the treatment of hepatitis B, there have been no systematic reviews on this topic. We searched Medline to include studies of the oral antiviral agents for hepatitis B and adverse events, with at least 48 weeks of follow-up from the initiation of treatment with the drug. Important toxicities include nephrotoxicity, myopathy, and resistance. It is often difficult to ascertain whether an adverse effect is from the study drug or the natural progression of the disease. Further safety data are needed for the newer agents and for all agents with regard to patients with decompensated liver disease, renal dysfunction, the elderly, children, and pregnant women.

Keywords Nucleosides · Nucleotides · Chronic hepatitis B virus infection · Lamivudine · Entecavir · Telbivudine · Adefovir dipivoxil · Tenofovir disoproxil fumarate

Introduction

Worldwide, 350 to 400 million people have chronic hepatitis B virus infection (CHB). Among those chronically infected, 20% to 40% develop cirrhosis, decompensated liver disease, or hepatocellular carcinoma. Treatment of CHB has evolved rapidly over the past decade as a result of improvements in antiviral treatment. Initially, interferon-α was the only available treatment, but it is effective in only 35% of patients and is poorly tolerated because of its adverse effects. The nucleoside/nucleotide medications are an important class of drugs that are changing the way CHB is treated [1]. The aim of this article is to systematically review the literature on side effects of currently approved nucleoside and nucleotide drugs in the treatment of chronic hepatitis B virus (HBV) infection in adults, focusing on adverse events, serious adverse events, resistance, and death. There are currently three nucleoside drugs (lamivudine, entecavir, and telbivudine) and two nucleotides (adefovir dipivoxil, tenofovir disoproxil fumarate) approved in the United States for the treatment of chronic HBV. Prolonged treatment with these oral agents is recommended for selected patients with HBV infection until disease remission or serologic endpoints have been achieved. Indefinite treatment is indicated for patients with HBV and advanced liver disease or in some patients on chronic immunosuppressive therapy [1, 2••, 3••].

The side effect profile for the five approved agents was generally good during registration trials, but there have been reports of serious adverse events including myopathy, neuropathy, pancreatitis and renal impairment during post marketing surveillance. As the oral agents have often been administered to patients with HIV coinfection, it is sometimes difficult to ascertain the role of HIV on reported adverse events [1, 2••]. This important population cannot be ignored, however. Every effort will be made in this article to review the side-effects of these drugs in patients with hepatitis B or for hepatitis B/HIV coinfection, and articles reporting adverse events exclusively in patients with HIV

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monoinfection will be excluded. Though there have been important narrative reviews on adverse side-effects with nucleos(t)ide drugs written previously, this article is the first systematic review on the topic to our knowledge.

Established Side Effects of Nucleoside Analogues

Information on several established side effects of the approved nucleoside and nucleotide drugs used for the treatment of CHB are described in Table 1. Information summarized in Table 1 includes year of approval, abbreviation, mechanism, clearance, dose, renal and dialysis-adjusted dose, common side effects, and pregnancy category [4••].

The five approved oral agents for CHB are analogues of nucleosides or nucleotides that pharmacologically inhibit the HBV polymerase in order to decrease viral replication and serum HBV DNA levels. Some analogues have activity against human mitochondrial DNA (mtDNA) polymerase gamma and can lead to mitochondrial dysfunction. Mitochondrial toxicity can manifest clinically as one or more of the following: myopathy, neuropathy, hepatic steatosis, pancreatitis, macrocytosis, hyperlactemia, lactic acidosis, and nephrotoxicity. All five approved agents carry a US Food and Drug Administration black box warning of potential mitochondrial toxicity [4••, 5]. Fialuridine is a nucleoside analogue which caused lactic acidosis, hepatic steatosis, pancreatitis, neuropathy, myopathy, and irreversible liver failure. It irreversibly incorporated into human mitochondrial DNA, causing mitochondrial failure, and was withdrawn from the market as a result [6].

Another important consideration is lactic acidosis, for which all five approved oral agents carry a black box warning. This black box warning originally derived from the HIV literature, though cases have been reported with nucleos(t)ide agents given at the lower doses recommended for CHB. Recently, entecavir was found to cause lactic acidosis in 5 of 16 patients (31%) in one study. All of the patients who developed lactic acidosis had highly impaired liver function, with a model for end-stage liver disease (MELD) score ≥20. Lactic acidosis occurred between 4 and 240 days after treatment initiation and was lethal in one patient, but resolved in the others with discontinuation of entecavir. In patients with a MELD score less than 18, no increased serum lactate concentrations were observed. These data indicate that entecavir should be used with caution in patients with impaired liver function [7]. All five medications also carry a black box warning for posttreatment flares of hepatitis. Adefovir dipivoxil carries a warning for potential HIV resistance in HBV treated patients with previously undiagnosed HIV [8–12].

Methods

We searched Medline for published articles up to October 2009 using a combination of search strings. The first component of the search string was the antiviral drug. For this, we searched each variation of the drug's name, including its trade names as text words, the name of the drug searched as a MeSH term, and the substance name of the drug. These variations were strung together with the "OR" function in Medline. For example, with lamivudine, the drug search was as follows: ("Lamivudine"[Text Word] OR "3TC"[Text Word] OR "Epivir"[Text Word] OR "Zeffix"[Text Word] OR "Heptovir"[Text Word] OR "Epivir-HBV"[Text Word] OR "Lamivudine"[Mesh] OR "lamivudine triphosphate "[Substance Name]). The second component of our search string was the drug side effects. For this component, we used the following string: ("complicat*"[Text Word] OR "adverse effect*"[Text Word] OR

Table 1 FDA-approved oral antivirals for CHB

	Lamivudine	Adefovir	Entecavir	Telbivudine	Tenofovir
Year of approval	1998	2002	2005	2006	2008
Abbreviation	LAM	ADV	ETV	TBV	TNV
Mechanism of action	Blocks HBV reverse transcriptase	Blocks HBV reverse transcriptase	Inhibits HBV DNA polymerase	Inhibits HBV DNA polymerase	Inhibits HBV DNA polymerase
Clearance	Renal	Renal	Renal	Renal	Renal
Dose	100 mg/d	10 mg/d	0.5 mg/d	600 mg/d	300 mg/d
Renal and dialysis-adjusted dose	50 mg/d	10 mg/d	0.25 mg/d or 0.50 mg every other day	600 mg every other day	300 mg every other day
Common side effects	Occasional myopathy, neuropathy, pancreatitis	Nephrotoxicity, pancreatitis	Negligible	Myopathy	Nephrotoxicity
Pregnancy category	C	C	C	B	B

CHB chronic hepatitis B virus infection, *FDA* US Food and Drug Administration, *HBV* hepatitis B virus

"adverse event*"[Text Word] OR "safe*"[Text Word] OR "drug monitor*"[Text Word] OR "toxic*"[Text Word] OR "poison*"[Text Word] OR etiol*[text word] OR aeitol*[text word] OR causation[text word] OR causal*[text word] OR "complications "[Subheading] OR "adverse effects "[Subheading] OR "Safety"[Mesh] OR "Biomarkers, Pharmacological"[Mesh] OR "Drug Toxicity"[Mesh] OR "Causality"[Mesh] OR "etiology "[Subheading] OR "prevention and control "[Subheading] OR "chemically induced "[Subheading]). The final component of our search string was hepatitis B. We searched the following: ("Hepatitis B"[Mesh] OR "Hepatitis B virus"[Mesh] OR "hepatitis B"[Text Word]). Included under the broader category of "Hepatitis B" in Medline is "Chronic Hepatitis B," obviating the need to explode the MeSH term. Because MeSH subject headings are hierarchical, in order to retrieve a term and its narrower terms, a subject heading must be exploded. PubMed automatically explodes MeSH subject headings to include all narrower terms unless "Do not explode" is selected. Finally, the three components (drug, side effect, and hepatitis B) were combined using the AND function of Ovid Medline. We constructed a publication type hedge in Medline to include the following types of studies: randomized controlled trials, controlled clinical trials, cohort studies, and case-control studies. We did not restrict this review to randomized controlled trials due to lack of randomized controlled trials devoted to reporting harm. We chose our search strategy based on the Cochrane Handbook's Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity and precision maximizing version with the addition of cohort studies and case-control studies.

In the final review, we included all English-language articles if they were 1) original research articles; 2) reported side effects or adverse events of one of the nucleoside or nucleotide drugs; 3) reported results for a population with CHB (either with or without HIV); 4) involved only human subjects; and 5) had at least 48 weeks of follow-up. If a phase 3 trial was available, we included the phase 1 or 2 trial only if they contained data not reported in the phase 3 trial. If a trial was reported in two journals, we chose one of the articles.

Results

Description of Study Characteristics

Table 2 provides the descriptive characteristics in terms of author, country, study design, number of patients, participant characteristics, length of follow-up, outcomes assessed, and primary purpose of the study for each article included.

Lamivudine

Lamivudine (LAM) was the first oral nucleoside analogue approved for the treatment of CHB, at a dose of 100 mg daily. It is the negative enantiomer of 2′-3′ dideoxy-3′-thiacytidine. Incorporation of 3TC-TP into growing DNA results in premature chain termination inhibiting HBV DNA synthesis. Lamivudine has been studied extensively and has the well-documented adverse event of liver disease flares due to the emergence of lamivudine-resistant HBV. For the purpose of this review, lamivudine will be discussed in narrative form as hundreds of studies fit the inclusion criteria for this review. Lamivudine was approved for the treatment of CHB in 1998 for adults and in 2001 for children. It was thought to have a side effect profile similar to placebo in registration trials [13]. With prolonged use in postmarketing surveillance, it was noted that genotypic resistance can be detected in 14% to 32% after 1 year of lamivudine treatment and up to 70% after 5 years of treatment [2••]. Virologic breakthrough in those with LAM-resistant virus was usually followed by biochemical breakthrough, with increase in serum alanine transaminase (ALT), followed by acute exacerbations of liver disease and even hepatic decompensation and death. Mutations in the tyrosine-methionine-aspartate-aspartate (YMDD) motif occur frequently and confer genotypic resistance to LAM. Lamivudine is now considered second-line therapy for treatment naïve patients due to this resistance pattern. Rare cases of neuropathy, pancreatitis, Fanconi syndrome, and reversible myopathy have been reported in patients coinfected with HBV and HIV [13].

Adefovir

Adefovir dipivoxil is the orally bioavailable pro-drug of adefovir (ADV), a nucleotide analogue that inhibits reverse transcriptase and DNA polymerase and causes HBV chain termination. ADV was developed as an antiretroviral for HIV infection but due to nephrotoxicity at high doses, it was not developed for this indication. For CHB, it was approved at a dose of 10 mg daily in 2002. It was approved for children 12 to 17 years of age in 2008. The two most common side effects observed with adefovir therapy are dose-dependent but reversible nephrotoxicity and antiviral resistance [2••].

Grade 1 nephrotoxicity, defined as serum creatinine ≥0.5 mg/dL above baseline values, was not observed to be an issue in the registration trials for ADV. Postmarketing surveillance revealed a different picture, with 7% of patients in a cohort of 29 patients coinfected with HIV and LAM-resistant HBV demonstrating grade 1 nephrotoxicity [14]. In a cohort of 185 patients with chronic hepatitis B e antigen (HBeAg)-negative hepatitis B treated with

Table 2 Description of study characteristics

Author, country	Design description	Subject characteristics	Adverse events
Adefovir			
Benhamou et al. [14], France	Prospective open-label pilot study of ADV 10 mg daily to determine safety and efficacy, 144-wk follow up.	*N*=29. LAM-resistant HBV/HIV coinfected patients	No grade 3 or 4 AEs, increase in creatinine ≥0.5 mg/dL in 2 patients (7%), no change in phosphorus, 1 resolved with continued treatment, 1 stopped treatment. Asthenia=most frequent AE. 2 patients with baseline cirrhosis developed HCC, 1insomnia, 2 IDDM. No mitochondrial toxicity or HIV or HBV resistance seen.
Hadziyannis et al. [15], multinational	International, multicenter, prospective double-blind, placebo-controlled trial of ADV vs placebo for 48 wk, then possible crossover for 48 wk, followed by open-label 144-wk follow-up.	*N*=185 HBeAg-negative patients with chronic hepatitis B.	6 patients (3%) developed resistance at 144 wk. Adverse events in wk 1-48 similar to 49–96. Drug was discontinued in 5 patients (1 with≥0.5 mg/dL increase in creatinine, 1 with HCC, 3 patients became jaundiced, developed elevated ALT, and skin disorders). 73% in continued ADV group, 68% in placebo-ADV group, and 80% in ADV-placebo group had one AE. All SAEs considered unrelated to ADV. 3% had confirmed increases in serum creatinine ≥0.5 mg/dL.
Ha et al. [17], United States	Retrospective matched cohort study in a community setting to evaluate renal dysfunction that may be underestimated in a clinical trial, exposed time measured in patient years, 100 patient years recorded.	*N*=290 chronic hepatitis B patients, 145 treated with 10 mg daily ADV and 145 unexposed to ADV, matched for age, sex, and baseline eGFR.	Incidence density for renal dysfunction defined by treatment termination and/or development of eGFR ≤50 mL/min was 5 cases/100 patient years in ADV group compared to 1.36 cases/100 patient years in the unexposed group. Relative risk of exposed to unexposed was 3.68 (1.1, 19.3). ADV is an independent predictor for significant deterioration of renal function, particularly with older patients, baseline renal insufficiency, and/or DM.
Izzedine et al. [18], France	Two double-blind, placebo controlled trials to investigate the safety and tolerability of two dosing regimens of ADV (10 mg daily or 30 mg daily), 48-wk follow-up.	*N*=515 in the 10-mg study and 185 in the 30-mg study, chronic hepatitis B patients with compensated liver disease not undergoing treatment with evidence of viral replication.	No overall median change from baseline in serum creatinine or phosphorus levels in 10 mg group. In 30 mg group, increase of 0.2 mg/dL in serum creatinine levels, decrease of 0.1 mg/dL in serum phosphorus, suggesting dose response relationship to renal toxicity. No grade 4 proteinuria, hematuria, or glycosuria.
Schiff et al. [16], multinational	Prospective open-label compassionate use study of ADV for wait-listed and post-liver transplantation patients with LAM-resistant hepatitis B, 144-wk follow up.	*N*=226 wait-listed patients, 241 post-liver transplant patients, and 61 on-study transplant with LAM-resistant hepatitis B.	Treatment-related AEs in 19% of wait-listed and 46% of posttransplant patients. 60 patients terminated study participation for AEs. 88% of these patients died within 30 d. 3 deaths were considered related to ADV, with progression of lung cancer, multiorgan failure, and hepatorenal syndrome. 400 patients survived and of those only 7 had AEs. Elevations in serum creatinine were common in posttransplant patients, less common in patients awaiting

			transplant (all transplant patients were also receiving nephrotoxic immunosuppressants).
Zeng et al. [21], China	Multicenter, double-blind, randomized, placebo-controlled study of ADV 10 mg once daily. Patients received adefovir (A) or placebo (P) in one of the following combinations AAA, AAP, or PAA for 12, then 28, then 12 wk, followed by every patient on open-label ADV for 208 wk.	*N*=120 PAA, 240 AAA, 120 AAP, in total 480 Chinese patients with hepatitis B e antigen (HBeAg)-positive chronic hepatitis B	6 subjects discontinued the drug prematurely (3 with AEs–1 with IgA nephritis, but baseline proteinuria, 1 with back pain, and 1 with alopecia). 5% of patients had one AE. SAEs consisted of 1 nasopharyngeal cancer, 2 increases in ALT, 1 spontaneous abortion, 1 fracture, 8 exacerbations of hepatitis B, 1 bronchial pneumonia. There were no deaths. Increased serum ALT was the most common lab finding of toxicity.
Sung et al. [35], multinational	Multicenter, double-blind, randomized study comparing LAM+ADV to LAM in HBeAg-positive patients, 104-wk follow-up.	*N*=115 patients with HBeAg-positive chronic hepatitis B from 22 centers around the world	93% of those on monotherapy with LAM and 90% in the combination group had at least one AE. Headache, fatigue, nausea, pharyngeal pain, abdominal pain, and pharyngitis were more common in monotherapy and arthralgias more common in combination. 1 in each group withdrew due to AEs. No nephrotoxicity was seen. 11 in the monotherapy and 5 in the combination group had grade 3 or 4 increase in serum ALT during treatment. 11 in monotherapy and 4 in combination had SAEs. A flare of reactivation HBV after completion of the study was the most common SAE, others unrelated to study medication or disease state.
Hannon et al. [36], France	Prospective open-label trial of ADV for LAM-resistant individuals with frequent monitoring for renal parameters including serum creatinine, urea, electrolytes, calcium, phosphate, and bicarbonate. The Cockcroft Gault formula was used for creatinine clearance, follow-up for 52 wk.	*N*=35 patients coinfected with HIV and lamivudine-resistant HBV.	Serum ALT increased transiently and decreased to below baseline by wk 48. No dysuria was reported. No significant change in serum sodium, chloride, potassium, bicarbonate, or phosphate were noted. There was a statistically significant increase in serum calcium, but this was still within normal range. There was no associated increase in albumin. No significant change in serum creatinine noted overall, but 2 patients had increases, one attributed to acyclovir that resolved with discontinuation of acyclovir and the other attributed to ADV.
Pellicelli et al. [37], Italy	Retrospective, multicenter, nonrandomized, open-label study of ADV and LAM compared with ADV monotherapy for HBeAg-negative chronic HBV, 24–32 mo follow-up.	*N*=36 patients with ADV+LAM, 34 with ADV monotherapy, all HBeAg-negative chronic hepatitis B.	No AEs reported, no changes in serum creatinine or any other laboratory parameter compared to baseline. No patients with dose reduction or ADV treatment discontinuation. Child-Turcotte-Pugh scores remained unchanged. No patients who achieved a virologic response had a serum HBV-DNA rebound > 1 log copies/mL compared with on treatment.
Jonas et al. [38], multinational	Randomized, double-blind, placebo-controlled trial of ADV for the treatment of CHB in children 2–17 y old, 48-wk follow-up.	*N*=173 children ages 2–17 y with CHB randomized in a 2:1 ratio to receive treatment or placebo	3 subjects discontinued treatment prematurely, one for an AE, two because of noncompliance. 83% of patients in the ADV and placebo groups

Table 2 (continued)

Author, country	Design description	Subject characteristics	Adverse events
			reported AEs, most of which were mild to moderate (grade 1 or 2), all thought to be unrelated to treatment. No renal AEs, no hepatic decompensation noted. Treatment-related AEs were seen in 14% of ADV treated and 10% of placebo treated. 6% of ADV treated and 9% of placebo treated subjects had one SAE. The only treatment-related SAE was a grade 3 increase in hepatic enzymes that resolved with continuing treatment.
Marcellin et al. [20], France	Randomized, double-blind, placebo controlled, parallel group for 2 y, then open-label LTSES for y 3–5 with ADV 10 mg daily.	*N*=65 patients who agreed to participate in the LTSES, with e antigen-positive CHB	16 patients reported SAEs, most commonly elevated ALT. 65% of patients reported AEs that were considered to be possibly or probably treatment related, most commonly lack of drug effect, asthenia, increased ALT, headache, and abdominal pain. These effects were similar between the first 48 wk and 5 y of the study, with more patients reporting lack of drug effect at 5 y. No deaths noted during the study. ADV not discontinued due to SAE in any patients. Five patients had permanent discontinuation of drug due to AEs in the LTSES period. 5 patients had grade 3 serum amylase abnormalities, all spontaneously resolved. Six patients had increases of 0.5 mg/dL in serum creatinine. Abnormalities in LFTs were seen with misallocation of dosing and off-treatment periods. On-treatment ALT flares (greater than 10×ULN and greater than twice patient's baseline) in 15 patients not accounting for misallocation patients. These patients developed ADV-resistant mutations.
Lee et al. [19], Korea	Open-label trial to study mutations in LAM-resistant patients switched to ADV and to compare this mutation rate to treatment-naïve patients on ADV, 48 wk follow-up.	*N*=57 LAM-resistant patients with chronic hepatitis B and 38 treatment naïve patients with chronic hepatitis B	18% of the LAM-resistant patients developed ADV-resistant mutations, while none of the 38 treatment naïve patients developed mutations to ADV. Among LAM-resistant patients, reduction in serum HBV DNA levels was significantly lower in patients with ADV-resistant mutations than in those without such mutations. The rates of ALT normalization and HBeAg loss were not significantly different between the two groups.
Entecavir			
Gish et al. [22]; Han et al.[23] multinational	Double-blind, double-dummy, randomized, controlled trial comparing the safety and efficacy of ETV 0.5 mg once daily and LAM 100 mg	*N*=709 HBeAg-positive CHB patients randomized to receive ETV or lamivudine	Through 96 wk, no patient had virologic breakthrough due to ETV resistance. 87% had on treatment AEs with ETV, 84% with LAM.

	once daily in HBeAg-positive CHB. 52 wk blinded treatment phase, extended blinded treatment phase (96 wk total).		SAEs in 8% in both groups. Fatigue, increased ALT levels, and headache were the most common and very similar in the two groups. One patient discontinued ETV due to AEs, 9 discontinued LAM due to AEs. On treatment ALT flares in 3% of ETV and 7% of LAM group (no increase in HBV DNA in ETV group). In LAM-refractory patients, genotypic resistance to ETV was 51%. In naïve patients, resistance is 1.2%.
Chang et al. [39], multinational	Randomized (1:1:1:1), double-blind, multicenter, multinational study comparing 1.0, 0.5, and 0.1 mg of ETV with continued LAM 100 mg daily in patients with continued viremia on LAM. 76 wk follow-up.	*N*=182 patients with CHB persistently viremic on LAM	AEs were evenly distributed among treatment groups. Most AEs were mild to moderate and considered unrelated to the study drug. 13 patients discontinued drug use due to an AE or protocol-specific lab abnormality: 8 with liver enzyme elevations, 1 with enzyme elevations and chromaturia, 1 with hypoglycemia, 1 with chest pain, 1 with hepatic failure, and 1 with hepatocellular carcinoma. Flares of ALT on blinded treatment were seen in 4% of patients in the ETV group and 11% in the LAM group. Flares in the 0.1-mg ETV and LAM groups were due to increasing HBV DNA levels. In the 0.1- and 1-mg ETV groups, ALT levels normalized with continued treatment.
Sherman et al. [40], multinational	Double-blind, double-dummy, randomized controlled trial comparing the safety and efficacy of ETV 1 mg once daily to continued LAM 100 mg daily in HBeAg-positive CHB patients refractory to LAM. 52-wk blinded treatment phase, extended blinded treatment phase (96 wk total follow-up).	*N*=286 patients with CHB refractory to LAM	In ETV arm, 7 patients (5%) had preexisting ETV-resistance substitutions in addition to LAM-resistance substitutions. Through 2 y of treatment, 23 patients (16%) in the ETV arm had ETV-resistance substitutions and 9 (6%) experienced virologic breakthrough. AEs were 83% in the ETV group and 80% in the LAM group. SAEs were 11% in the ETV group and 7% in the LAM group. ALT flare during treatment observed in < 1% ETV treated and 11% LAM-treated patients. Entecavir ALT flare was associated with decline in HBV DNA while all LAM flares were seen with stable or rising HBV DNA levels. 1% discontinued the drug due to AEs in the ETV group and 7% in the LAM group. 5 deaths, 2 in the ETV group (liver failure and lymphoma), 3 in the LAM group (liver failure in 2 and septic shock in 1). No deaths were thought to be attributable to the drugs.
Tenney et al. [24], multinational	Patients from 6 phase 2 and 3 clinical studies of safety and efficacy of ETV were monitored for resistance through wk 240 (year 5).	*N*=663 nucleoside-naïve CHB patients (345 HBeAg Positive, 318 HBeAg Negative)	In nucleoside-naïve patients, cumulative probability of genotypic ETVr and genotypic ETVr associated with virologic breakthrough was 1.2% and 0.8%, respectively. In LAM-refractory patients, a 5 year cumulative probability of genotypic ETVr and

Table 2 (continued)

Author, country	Design description	Subject characteristics	Adverse events
			genotypic ETVr associated with breakthrough was 51% and 43%, respectively. Only 4 patients who achieved <300 copies/mL HBV DNA subsequently developed ETVr.
Suzuki et al. [41], Japan	Subgroup analysis of a multicenter randomized controlled trial done at a single center. Biologic and virologic responses to ETV examined among 19 patients who developed hepatitis breakthrough during long-term lamivudine therapy. 144 wk follow-up.	*N*=19 patients with LAM resistance mutations who were then switched to ETV, either 0.5 mg daily (10 patients) or 1.0 mg daily (9 patients) for 52 wk, then all were given 1.0 mg daily for an additional 68–92 wk.	No difference in biochemical and virologic response between the two study groups. HBV mutants resistant to ETV emerged in 5/19 (26%) of patients and hepatitis flare occurred in two of these patients (40%).
Kobashi et al. [42], Japan	Randomized, double-blind, multicenter trial of 0.1 mg ETV once daily and 0.5 mg ETV once daily for 52 wk in nucleoside-naïve patients with HBeAg-positive or negative chronic hepatitis B.	*N*=66 nucleoside naïve Japanese patients with CHB	2 patients developed amino acid substitutions associated with LAM resistance, but ETV was efficacious and neither patient had virological breakthrough or elevation of ALT. 2 patients had virological breakthrough, but neither had resistance mutations. Both achieved undetectable HBV DNA. AEs were mild and not related to the dug for the most part. Grade 3–4 AEs were seen in 2 patients (6%) in each study group, none related to the study drug. Grade 3–4 lab adverse events occurred in 5 (16%) and 6 (18%) of patients in the 0.1 mg and 0.5 mg groups (AST/ALT elevations, lipase elevations, glucose elevations). There were no deaths in the study.
Leung et al. [43], multinational	Open-label phase 3b study in which eligible patients were randomized (1:1) to open-label treatment with oral ETV 0.5 mg daily or oral ADV 10 mg daily for 52 wk.	*N*=69 nucleoside-naïve CHB patients with baseline HBV DNA of 10^8 copies/mL or more.	78% of the ETV group and 82% of the ADV group experienced any adverse event, most frequently headache, URI, nasopharyngitis, pyrexia, and influenza. 6% of the ETV group and 15% of the ADV group had grade 3 or 4 adverse events, 3% of the ETV group and 9% of the ADV group had SAEs. There was 1 discontinuation due to an SAE (ALT flare) in the ADV group thought to be due to the drug that resolved on discontinuation.
Pessoa et al. [44], multinational	Prospective, randomized, double-blind, placebo-controlled phase 2 study. Patients were randomized to either ETV 1 mg once daily or placebo in a 2:1 ratio in addition to continuing lamivudine. Treated for 24 wk blinded and then open-label ETV for another 24 wk.	*N*=68 patients coinfected with HIV/HBV already receiving LAM as a part of antiretroviral therapy	AEs were seen in 86% of the ETV group and 82% of the placebo group. Elevations of AST and ALT > 2×ULN were seen in both groups, likely due to concomitant HIV treatment. ALT elevations > 10×ULN were seen in 2 patients on ETV and did not change treatment. 1 patient in the ETV group had an SAE during the blinded phase (hepatic encephalopathy and bleeding esophageal varices in the same patient) and 4 patients had SAEs during the open label phase (myocardial infarction, pneumonia, testicular neoplasm, and esophageal

			varices/hemorrhage), all thought not to be due to the drug. No deaths were reported. 2 patients in the ETV group discontinued treatment due to lab abnormalities, which existed prior to treatment. No changes in CD4 or HIV RNA were seen.
Schiff et al. [26], multinational	Post-hoc analysis of 3 prospective, randomized, multi-center, double-blind trial, patients randomized to receive a minimum of 48 wk of ETV or LAM. Nucleoside-naïve patients received ETV, 0.5 mg daily. LAM-refractory patients received ETV, 1 mg daily or continued LAM, 100 mg daily.	*N*=1,633 patients, 245 with advanced liver fibrosis/cirrhosis (120 ETV, 125 LAM)	The frequency of on-treatment adverse events was comparable among those with advanced liver fibrosis/cirrhosis and the overall study population (between 81–85%). 3 LAM-treated patients with advanced liver fibrosis/cirrhosis discontinued the treatment due to AEs. No ETV-treated patients discontinued therapy due to AEs. ALT flares were lower in the fibrosis/cirrhosis population that the larger study group. All deaths (3 ETV group, 4 LAM group) occurred in patients with advanced liver fibrosis/ cirrhosis. No deaths thought to be due to study drug.
Sherman et al. [45], multinational	Randomized, phase III, double-blind, double-dummy trial to study the effect of ETV on LAM refractory, HBeAg-Positive CHB. Patients randomized to switch to ETV 1 mg daily or continue LAM 100 mg daily for a minimum of 52 wk.	*N*=141 ETV, 145 LAM patients, all with LAM-refractory, HBeAg-positive CHB.	The frequencies of AEs were 85% and 81% in the ETV and LAM groups respectively. The frequencies of SAEs were 10% and 8% in the ETV and LAM groups, respectively. 7% of LAM patients compared to 1% of ETV patients discontinued the drug due to adverse events. 11% of LAM patients had ALT flares compared to < 1% of ETV patients. 3 deaths occurred, none was judged related to the study medication.
Chang et al. [46], multinational	Double-blind, double-dummy randomized controlled trial. Patients from 137 centers received ETV 0.5 mg daily or LAM 100 mg daily for a minimum of 52 wk.	*N*=354 patients in the ETV group, 355 in the LAM group. All patients had HBeAg-Positive CHB and were nucleoside naïve.	86% of the ETV group and 84% of the LAM group reported any AE, 8% of both groups reported a SAE. 3% of the LAM and < 1% of the ETV group discontinued the drug due to an AE. 6% of the LAM group and 3% of the ETV group had an ALT flare during treatment, while 7% of the LAM and 1% of the ETV group had a post treatment ALT flare. Two deaths, considered unrelated to the study therapy occurred in the LAM group.
Chang et al. [47], multinational	Double-blind, double-dummy randomized controlled trial. Patients from 146 centers received ETV 0.5 mg daily or LAM 100 mg daily for a minimum of 52 wk.	*N*=296 patients in the ETV group, 287 patients in the LAM group. All patients had HBeAg-Negative CHB and were nucleoside naïve.	76% of the ETV group and 79% of the LAM group reported any AE, 6% of the ETV group and 8% of the LAM group reported an SAE. 2% of the ETV and 3% of the LAM group discontinued the drug due to an AE. < 1% of the ETV group and 2% of the LAM group experienced an ALT flare during treatment, 8% of the ETV group and 11% of the LAM group experienced an ALT flare in post-treatment follow-up. Two deaths, considered unrelated to the study therapy occurred in the ETV group.
Telbivudine			
Lai et al. [27], multinational	International, multicenter, double-blind, randomized phase 2b trial investigating 5 antiviral treatment regimens for CHB for 52 wk. Patients	*N*=104 patients with hepatitis B e antigen-positive CHB from 16 clinical centers in 5 countries	AEs occurred with similar overall frequency across the 5 treatment groups. Most AEs were not attributed to study drugs and no patterns could be found with

Table 2 (continued)

Author, country	Design description	Subject characteristics	Adverse events
	were randomized (1:1:1:1) to the following 5 daily oral treatment regimens: telbivudine 400 mg, telbivudine 600 mg, telbivudine 400 mg plus lamivudine 100 mg (Comb400), telbivudine 600 plus LAM 100 mg (Comb600), or LAM 100 mg.		treatment type, dose, or time after start of therapy. The most common AEs were influenza, headache, cough, and fatigue. Two SAEs were reported (1 mediastinal tumor, 1 papillary thyroid carcinoma). 9 patients experienced grade 3 or 4 lab abnormalities by wk 52, 1 patient (telbivudine 600 mg) elevation of ALT level, 5 patients elevation of creatine kinase levels (one telbivudine 400 mg, 2 telbivudine 600 mg, one Comb600), 1 patient with elevation of lipase (Comb600), and 2 patients (Comb600) with neutropenia. All continued treatment except for one with elevated CK level, the rest resolved spontaneously. 10 patients experienced viral breakthrough, 15.8% LAM, 4.5% telbivudine, and 12.2% combination, most of which were due to resistance.
Hou et al. [48], China	Multicenter, double-blind, randomized phase III trial to assess 2 y (104 wk) of treatment with telbivudine vs lamivudine in Chinese adults with compensated hepatitis B. The patients were randomized to 600 mg of telbivudine or 100 mg of lamivudine.	*N*=332 Chinese patients with compensated CHB	In HBeAg-positive patients, viral breakthrough was significantly more common in the LAM arm at wk 48 compared with telbivudine (17.5% vs 7.5%, *P*=0.009). Resistance was more common with HBeAg-positive LAM recipients. 5 of 11 patients (45%) with telbivudine resistance and 10 of 21 patients (48%) with LAM resistance were genotype B. AEs were reported in about half of patients in both arms, most not attributed to the study drug. Nasopharyngitis was the most common complaint in both groups. Myalgia and other muscle-related AEs were equivalent in both groups. 1 telbivudine patient developed a polymyositis not attributed to study drug. Grade 3 or 4 serum ALT and AST elevations were more common in the LAM group (9.1% vs 5.4% and 6.7% vs 5.4%). Grade 3 or 4 elevations of CK were more common in the telbivudine group but did not reach statistical significance (8.4% vs 3.0%, *P*=0.06).
Chan et al. [49], multinational	Open-label, randomized trial (1:1:1) of 52 wk of telbivudine or ADV, or 24 wk of ADV and then telbivudine for the remaining 28 wk. 52 wk follow-up.	*N*=131 patients with HBeA-Positive CHB	Viral breakthrough (confirmed increase in serum HBV DNA levels of > 1 log above nadir value) occurred in 4 ADV and 3 telbivudine recipients and in no combination group recipients. No resistance mutations were noted in the ADV recipients, but all 3 telbivudine recipients had resistance mutations. No drug-attributed SAEs occurred, no discontinuations of the drug due to AEs occurred, no deaths occurred. Two cases of grade 1 myopathy and persistent

			myalgia with creatine kinase elevations were reported in telbivudine recipients at 52 and 41 wk, treatment was continued without dose modification. Serum creatinine was elevated in 1 ADV recipient, and returned to normal on switching to telbivudine.
Lai et al. [28], multinational	Randomized, double-blind, active agent-controlled trial at 112 academic centers in 20 countries. Subjects randomly assigned in a 1:1 ratio to receive 600 mg telbivudine or 100 mg lamivudine orally once daily.	*N*=1,370 patients with CHB	AEs through wk 52 were similar between the two groups (73% telbivudine, 69% LAM). SAEs were seen in 2.6% in the telbivudine group and 4.8% in the LAM group. Grade 3 or 4 elevations in CK levels (at least 7 times ULN) were more common in recipients of telbivudine (7.5%) than LAM (3.1%). These levels decreased spontaneously to grade 2 or lower in 66.7% of telbivudine patients and 73.9% of LAM patients. Muscle related symptoms correlated poorly with elevations in CK levels. CK levels returned to normal when telbivudine was discontinued within 1 month. Grade 3 or 4 e×levations in ALT and AST in 13.1% of LAM patients and 12.5% of telbivudine patients who had viral breakthrough. 1 patients with LAM resistance had liver failure and required a transplant. ALT levels of at least 500 IU per liter were more common with LAM (2.2%) than telbivudine (0.4%).
Zhang et al. [30], China	Retrospective review of 105 patients treated with telbivudine from January 2007 to January 2008	*N*=105 patients treated with telbivudine for CHB	5 male patients aged 25–45 had SAEs 0.5 to 5 months after treatment, associated with telbivudine, including myalgia and general weakness, one with cardiac arrhythmia, and nervous symptoms in 3. CK levels were between 191 IU/L and 900 IU/L and there was no correlation between severity of symptoms and CK elevation. The myalgia was noted to be dose dependent.
Liaw et al. [29], multinational	Prospective, randomized, double-blind phase 3 trial comparing telbivudine to lamivudine for CHB. 104 wk follow-up.	*N*=921 HBeAg-positive and 446 HBeAg-negative patients	Patients with one AE were 81% and 77% in the telbivudine and LAM groups, respectively. AES considered to be possibly related to study treated were reported in 197 telbivudine patients (29%) and 159 LAM recipients (23%). SAEs were reported in 33 telbivudine recipients (5%) and 44 LAM recipients (6%). 5 drug-related SAEs were reported in the study: 3 telbivudine recipients (myopathy, liver failure, and elevated CK level) and 2 LAM recipients (urticarial rash, hepatitis flare). 116 patients developed grade 3 or 4 CK elevations (7 times ULN), 12.9% in telbivudine compared with 4.1% of LAM ($P<0.001$). The mean time to first elevation was 56.9 wk for telbivudine treated patients and 42.1 wk for LAM-treated patients, no increase in MB fraction of CK. Grade 3 or 4 ALT or ASAT elevations were less frequent with telbivudine compared with LAM

Table 2 (continued)

Author, country	Design description	Subject characteristics	Adverse events
			(ALT 6.3% vs 11.6% and AST 6% vs 8.9%, respectively).
Tenofovir			
Peters et al. [50]	Prospective randomized, double blind, placebo-controlled trial evaluating whether TDF was not inferior to ADV for treatment of HBV in patients coinfected with HIV and HBV. Subjects randomized to 10 mg ADV plus TDF placebo daily or 300 mg of TDF plus ADV placebo daily with stratification by Child-Pugh Turcotte score	*N*=52 patients (25 ADV, 27 TDF) coinfected with HIV and HBV	Two subjects died, one on ADV at wk 48 from hepatocellular carcinoma, and another on TDF at wk 57 while hospitalized for an unknown cause. 18 subjects in each arm showed laboratory toxicities (3 on ADV had hypophosphatemia, 3 on TDF had hypophosphatemia, no elevation in serum creatinine). 3 subjects developed pancreatitis, 2 of whom received concomitant ddI.
Bommel et al. [51]	Retrospective cohort study of patients who had a virological breakthrough on LAM, then insufficient virological response on ADV, switched from ADV to TDF	*N*=20 patients with CHB, treated with LAM, then ADV, then switched to TDF	No side effects were reported.
Santos et al. [52]	Prospective study of 7 patients with CHB on ADV monotherapy or ADV containing regimen changed to tenofovir 300 mg daily and emtricitabine 200 mg daily. 14–28 month follow-up.	*N*=7 patients with CHB, who failed to achieve undetectable HBV DNA on ADV.	No rise in serum creatinine or significant adverse events were reported during the tenofovir and emtricitabine therapy.
Leeman et al. [32]	Retrospective cohort study of patients with LAM resistant CHB switched from LAM+ tenofovir to ADV monotherapy. 78 wk follow-up.	*N*=10 patients with LAM resistant CHB	Two patients had an increase of > 1 log copies/mL during tenofovir treatment.
Marcellin et al. [33]	Two double-blind phase 3 studies of tenofovir 300 mg daily and ADV 10 mg daily in CHB patients, 48 wk follow-up.	*N*=382 HBeAg-negative and 272 HBeAg-positive CHB patients	No genotypic substitutions with decreased sensitivity to tenofovir were detected. Nausea occurred more frequently in the tenofovir group than the ADV group. One hepatocellular carcinoma was reported. There was no evidence of compromised renal function or renal tubular dysfunction in any patient taking tenofovir. AEs were similar in the two groups, 74% in the tenofovir group and 73% in the ADV group. SAEs were 6% in the tenofovir group and 7% in the ADV group. ALT flares were 1% of the tenofovir group and 2% of the ADV group.
Tan et al. [34]	Retrospective cohort study of HIV/HBV coinfected patients to determine renal function in patients treated with long-term tenofovir. 260- wk follow-up.	*N*=39 patients (38 male, 1 female) with HIV/HBV HBeAg-positive.	No patients developed TDF resistance mutations. The eGFR as calculated by the MDRD equation declined by 22.19 mL/min/1.73 mm from baseline (P=0.023) over this period, with controlling for protease inhibitor use, baseline CD4 count, ALT or HBV DNA level. 3 patients discontinued TDF due to renal dysfunction.

ADV adefovir, *AE* adverse event, *ALT* alanine transaminase, *CHB* chronic hepatitis B virus infection, *CK* creatine kinase, *ETV* entecavir, *ETVr* entecavir resistance, *HBeAg* hepatitis B e antigen; *HBV* hepatitis B virus, *HCC* hepatocellular carcinoma, *IDDM* insulin-dependent diabetes mellitus, *LAM* lamivudine, *LTSES* long-term safety and efficacy study, *SAE* serious adverse event, *TDF* telbivudine, *TNV* tenofovir, *URI* upper respiratory infection

ADV for 5 years, grade 1 nephrotoxicity was seen in 3% of patients with compensated liver disease [15]. In another study, 6% on the transplant waiting list, and 47% of those who underwent liver transplant during the study experienced grade 1 nephrotoxicity [16]. Patients in the latter two groups may have had alternate explanations for renal dysfunction such as use of other nephrotoxic medications, hepatorenal syndrome, or may have had a magnified effect of ADV due to advanced liver disease.

A retrospective matched cohort study carried out in a community setting by university investigators revealed that over 100 patient years, ADV is an independent predictor for significant deterioration of renal function, particularly with older patients, baseline renal insufficiency, and/or diabetes mellitus. In this study, incidence density for renal dysfunction was defined by treatment termination and/or development of eGFR ≤50 mL/minute, with 5 cases/100 patient years in the ADV treatment group compared to 1.36 cases/100 patient years in the unexposed group. A relative risk of the exposed to unexposed was 3.68 with 95% confidence intervals of 1.1 and 19.3. The authors stated that this may be a more realistic picture of the renal dysfunction in the community as opposed to a clinical trial [17]. Other studies have detected no change in serum creatinine at a dose of 10 mg daily, including two double-blind, placebo-controlled trials to investigate the safety and tolerability of two dosing regimens for ADV, 10 mg daily and 30 mg daily. At the higher dose, patients had an increase of 0.2 mg/dL in creatinine when treated for more than 6 months [18].

The mechanism of nephrotoxicity with ADV is not elucidated; however, there is likely proximal tubular injury and a Fanconi-like renal tubular acidosis or alterations in multidrug resistance protein 4 expression in renal tubular epithelium. Dose reductions or increased dosing intervals in those with renal insufficiency and monitoring of renal function every 3 months for those with comorbidities that predispose to renal insufficiency or in patients on the drug for more than 1 year are recommended. Clinically, nephrotoxicity will manifest as slight increases in serum creatinine and decreases in serum phosphate levels occurring 4 to 12 months after starting ADV.

Resistance is a major concern emerging with use of ADV. ADV resistance may be more frequent in patients who already have LAM resistance. In an open-label trial to study mutations in LAM resistant patients, 18% of the LAM-resistant patients developed ADV resistant mutations, while none of the treatment naïve patients developed mutations to ADV [19]. In a long term safety and efficacy study following patients for 5 years on treatment, ALT flares were seen in 15 of 65 patients. These patients had ADV mutations [20]. Rare serious adverse events include nasopharyngeal cancer, spontaneous abortion, fracture, and bronchial pneumonia [21]; however, it is not certain that these are attributable to ADV. Further long term follow-up in patients to determine adverse events associated with adefovir is needed.

Entecavir

Entecavir (ETV) is a nucleoside analogue of 2′deoxyguanosine and inhibits HBV replication at three different steps: priming of HBV DNA polymerase, reverse transcription of the negative-strand HBV DNA, and synthesis of the positive-strand HBV DNA [2]. It was approved in 2005 at a dose of 0.5 mg/d for treatment-naïve CHB patients and 1.0 mg/d for LAM-resistant patients. In animal studies, there has been a higher incidence of solid tumors; long-term human studies are underway.

Resistance is rare with entecavir in nucleoside treatment naïve patients and when it does occur, it tends to happen in those patients who already have LAM resistance. In a double-blind, placebo-controlled study comparing the efficacy of entecavir, 0.5 mg once daily, and lamivudine, 100 mg once daily, in HBeAg-positive CHB, there was no virologic breakthrough due to entecavir resistance at 96 weeks. In lamivudine refractory patients, genotypic resistance to entecavir was 51% [22, 23]. In 5 years of follow-up of nucleoside-naïve patients from six phase 2 and 3 clinical studies of safety and efficacy of ETV, the cumulative probability of genotypic entecavir resistance (ETVr) and genotypic ETVr associated with virologic breakthrough was 1.2% and 0.8%, respectively. In LAM-refractory patients, the 5-year cumulative probability of genotypic ETVr and genotypic ETVr associated with breakthrough was 51% and 43%, respectively. Only four patients who achieved less than 300 copies/mL HBV DNA subsequently developed ETVr [24]. The 6-year resistance data for entecavir reveal a cumulative probability of genotypic resistance of 1.2% in nucleoside-naïve patients and 57% in LAM-resistant patients. A total of 74 of 187 LAM-refractory patients (40%) achieved HBV DNA less than 300 c/mL while on treatment with entecavir and of those 74 patients, only 5 (7%) developed genotypic resistance. The 6-year resistance data support the conclusion that ETV has a high genetic barrier to resistance in nucleoside-naïve patients. Even in the lamivudine-refractory patients, favorable prognostic subgroups can be identified by response to treatment with entecavir [25].

ETV is generally well tolerated even in patients with advanced fibrosis and cirrhosis. In a post-hoc analysis of three prospective, randomized, multicenter, double-blind trials, patients with CHB and advanced hepatic fibrosis or cirrhosis were randomly assigned to receive a minimum of 48 weeks of ETV or LAM. Nucleoside-naïve patients received ETV, 0.5 mg daily. LAM-refractory patients received entecavir, 1 mg daily, or continued LAM at 100 mg daily. The frequency of on-treatment adverse events was comparable

among those with advanced liver fibrosis/cirrhosis and the overall study population. No entecavir-treated patients discontinued therapy due to adverse events [26]. Entecavir has been proven effective against CHB, but continued surveillance is necessary to determine its long-term safety.

Telbivudine

Telbivudine is a potent L-nucleoside analogue approved for the treatment of CHB in 2006 at a dose of 600 mg/d. It is more potent than lamivudine in suppressing HBV replication, but it is associated with a high rate of viral resistance, reflecting mutations cross-resistant with lamivudine, so monotherapy is limited [2••]. The safety profile of telbivudine looked similar to that of lamivudine in registration trials, but at 2 years, significant adverse effects were noted [27, 28]. Creatine phosphokinase (CPK) elevations greater than 7 times the upper limit of normal were noted more frequently in patients on telbivudine at 2 years as compared to patients on lamivudine (12.9% with telbivudine compared to 4.1% with lamivudine treated patients, $P<0.001$) [29]. Although CPK levels were elevated to be between 191 IU/L and 900 IU/L, there was no correlation with severity of muscle symptoms and absolute CPK elevations. On the other hand, subjective myalgia was noted to be dose dependent [30]. Two patients developed myopathy that resolved with drug discontinuation. Given these reports, it is recommended that patients taking telbivudine undergo monitoring for musculoskeletal symptoms and CPK levels before commencing therapy and then every 3 months during therapy.

Reports exist of moderately severe peripheral neuropathy in 17% of patients treated with telbivudine and peginterferon alfa-2a [31]. Accordingly, telbivudine is not recommended for use in combination with peginterferon at this time. Telbivudine in combination with adefovir and tenofovir is currently being studied.

Tenofovir

Tenofovir disoproxil fumarate is a nucleotide analogue that was approved for HIV infection as Viread (tenofovir alone) or Truvada (tenofovir plus emtricitabine as a single pill) (both, Gilead Sciences, Foster City, CA). It was approved for CHB at a dose of 300 mg/d in 2008. It is structurally similar to adefovir, but is less nephrotoxic, so higher doses can be used, conferring better antiviral activity in clinical studies [2••, 32, 33]. Tenofovir is currently recommended as part of the nucleos[t]ide reverse transcriptase inhibitor (NRTI) backbone in combination with a non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor as first line highly active antiretroviral therapy, which makes it an excellent choice for therapy in coinfected individuals [34]. To date, neither phenotypic nor genotypic resistance to CHB has been identified with tenofovir. It is effective against lamivudine-resistant strains of CHB.

A 4% rate of nephrotoxicity is reported in HIV patients taking tenofovir, but most were able to continue tenofovir at reduced doses. Accordingly, it is recommended that serum creatinine, phosphate levels, and urinalysis be monitored every 3 months in patients taking tenofovir, because the nephrotoxicity from this drug is thought to be reversible with dose reduction or discontinuation. Decreased bone density and osteomalacia have also been described in HIV patients taking tenofovir. Bone density measurements and calcium and vitamin D supplementation are recommended in patients taking tenofovir for HIV. The experience with tenofovir in CHB is still in its early stages, and long-term data regarding nephrotoxicity, decreased bone density, and osteomalacia in patients with CHB has not been determined.

Conclusions

The five approved nucleoside/nucleotide drugs for CHB carry much promise for the treatment of this disease. The side effects associated with these medications are clinically significant, and close monitoring of patients while on therapy is indicated. Future studies to address the long-term safety profile of these nucleoside/nucleotide analogues given for CHB are needed or currently underway. These include studies assessing nephrotoxicity, myopathy, mitochondrial toxicity, bone mineral density, and drug resistance. Additionally, further studies are needed to assess the safety of nucleoside/nucleotide analogues in special patient populations including pregnant women, children, the elderly, and patients with decompensated liver disease.

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