Tenofovir and adefovir for the treatment of chronic HBV infection

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INTRODUCTION

Tenofovir disoproxil fumarate, tenofovir alafenamide, and adefovir are nucleotide reverse transcriptase inhibitors (NRTIs) that are used for the treatment of chronic hepatitis B virus (HBV) infection. Tenofovir has generally replaced adefovir because it is more potent and has a better safety profile.

This topic will focus on the efficacy and safety of NRTIs for the treatment of patients infected with HBV alone. Topic reviews that provide additional information on the treatment of HBV, as well as the use of tenofovir for the treatment of HIV, are presented elsewhere. (See "Hepatitis B virus: Overview of management" and "Treatment of chronic hepatitis B in patients with HIV" and "Overview of antiretroviral agents used to treat HIV" and "Overview of antiretroviral agents used to treat HIV", section on 'Tenofovir' and "Management of hepatitis B virus infection in children and adolescents".)

TENOFOVIR

Formulations — Tenofovir is an acyclic nucleotide diester analog of adenosine monophosphate, which is administered orally as the prodrug tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF). The intracellular, pharmacologically active moiety is tenofovir-diphosphate. TDF (300 mg daily) has been used extensively for the treatment of HIV

and chronic hepatitis B virus (HBV) infection. The newer formulation of tenofovir, TAF (25 mg daily), is also effective for the treatment of HIV and HBV and has fewer adverse effects on renal function and bone density [1,2]. (See 'Safety' below.)

Effect of tenofovir disoproxil fumarate on virologic outcomes — There is extensive experience demonstrating the virologic efficacy of TDF for the treatment of chronic HBV. TDF is effective regardless of the patient's hepatitis B e antigen (HBeAg) status, the presence or absence or cirrhosis, or prior use of nucleos(t)ide analogues. Tenofovir has also been used in patients with severe spontaneous exacerbations of chronic HBV.

A positive response to treatment is characterized by suppression of HBV DNA and loss of HBeAg (in patients who were initially HBeAg positive). This is followed by loss of hepatitis B surface antigen (HBsAg) in a small percentage of patients during the course of follow-up.

Patients with HBeAg-positive chronic hepatitis B — TDF is effective for the treatment of chronic HBV in patients who are HBeAg-positive. However, patients in the immune-tolerant phase of infection (ie, a high viral load, and a normal alanine aminotransferase [ALT]) should generally not be treated because efficacy is lower in this setting. Indications for the treatment of chronic HBV are discussed elsewhere. (See "Hepatitis B virus: Overview of management", section on 'Indications for antiviral therapy'.)

- The largest study in nucleoside-naïve patients included 266 patients with HBeAg-positive chronic HBV who were randomly assigned to TDF (300 mg) or adefovir (10 mg) in a ratio of 2:1 [3,4]. Significantly more patients who received TDF achieved an HBV DNA level of <400 copies/mL (approximately 69 international units/mL; 76 versus 13 percent), ALT normalization (68 versus 54 percent), and HBsAg loss (3 versus 0 percent) at week 48. The proportion of patients achieving a ≥2-point reduction in the Knodell necroinflammatory score without worsening fibrosis was similar (74 versus 68 percent), as was the proportion of patients achieving HBeAg seroconversion (21 versus 18 percent).

- A follow-up study of the one described above included data on 248 HBeAg-positive patients who received open-label TDF [5]. Among these 248 patients, including those who dropped out or discontinued therapy, 65 percent had an HBV DNA level <400 copies/mL (approximately 69 international units/mL) after five years of treatment. However, of the patients who remained on treatment and were available for assessment at the end of year 5, 97 percent achieved an HBV DNA of <169 copies/mL (approximately 34 international units/mL) and 49 percent became HBeAg negative. At year 7, 160 patients remained on treatment and were available for assessment; all but one had an HBV DNA <29 international units/mL, and 55 percent became HBeAg negative [6]. HBsAg loss

occurred in 23 patients by year 5 and in 25 patients by year 7. At year 10, 78 of 80 (98 percent) patients with available data achieved HBV DNA <69 international units/mL, and 60 of 77 (78 percent) achieved ALT normalization [7].

- TDF was also effective in suppressing HBV DNA in another randomized trial of 126 treatment-naïve patients who had a positive HBeAg, a high viral load, and a normal ALT (ie, patients in the immune-tolerant phase of infection) [8]. At week 192, TDF suppressed HBV DNA levels to <69 international units/mL in 55 percent of patients (if TDF was used as monotherapy) or 76 percent (if combined with emtricitabine). However, only three patients underwent HBeAg seroconversion (all in the TDF monotherapy group) and none lost HBsAg. Posttreatment follow-up after discontinuing therapy was provided for 52 patients; all but one had a rapid increase in HBV DNA within four weeks, and one patient had a hepatitis flare defined as an increase in ALT to greater than 10 times the upper limit of normal.

Patients with HBeAg-negative chronic hepatitis B — TDF is also effective for the treatment of chronic HBV in patients who are HBeAg negative. The largest study in nucleoside-naïve patients included 375 patients with HBeAg-negative chronic HBV who were randomly assigned to TDF (300 mg) or adefovir (10 mg) in a ratio of 2:1 [3,4]. At week 48, significantly more patients receiving TDF achieved a serum HBV DNA level of <400 copies/mL (approximately 69 international units/mL; 93 versus 63 percent). The proportion of patients achieving ALT normalization was similar (77 versus 78 percent), as was the proportion of patients achieving a ≥2-point reduction in the Knodell necroinflammatory score without worsening of fibrosis (72 versus 69 percent). No patient lost HBsAg. Safety and tolerability were similar.

A follow-up report described the outcomes of 350 HBeAg-negative patients who received open-label TDF [5]. After five years of treatment, 87 percent had an HBV DNA level <400 copies/mL based upon an intention-to-treat analysis where patients lost to follow-up were considered nonresponders. However, among those patients who remained on therapy during the follow-up period, and were available for assessment, 99 percent achieved viral suppression. At year 7, viral suppression was maintained in 99 percent and one patient lost HBsAg [6]. At year 10, all 118 patients with available data achieved HBV DNA <69 international units/mL, and 88 of 106 (83 percent) achieved ALT normalization [7].

Patients with previous exposure to other nucleos(t)ide analogues — Tenofovir (TDF or TAF) should be used to treat patients who have previous exposure to other nucleoside analogues. Most studies have evaluated TDF in patients with lamivudine- or adefovir-resistant virus. Tenofovir is also effective in patients with prior exposure to telbivudine and/or entecavir [9,10]. A discussion of the management of patients with previous exposure to nucleos(t)ide analogues

is presented elsewhere. (See "Hepatitis B virus: Overview of management", section on 'Persistent viremia/breakthrough infection'.)

Lamivudine resistance — Studies have shown viral suppression with TDF in patients with lamivudine-resistant virus [11-17]. TDF monotherapy is effective in providing sustained viral suppression; multiple studies have shown that combining TDF with emtricitabine does not appear to provide any additional benefit. As an example, in a randomized study of 280 patients with lamivudine resistance who were treated with TDF, with or without emtricitabine, the majority of patients (88 percent at 96 weeks and 83 percent at 240 weeks) had an undetectable HBV DNA (<69 international units/mL) [14,17]. There was no additional benefit in those who received combination therapy, and no patient developed tenofovir resistance. (See 'Risk of resistance' below.)

TDF is superior to entecavir for patients with lamivudine-resistant HBV, as resistance to lamivudine constitutes the first step in a two-hit pathway to entecavir resistance. Entecavir resistance is discussed separately. (See "Entecavir in the treatment of chronic hepatitis B virus infection", section on 'Resistance'.)

TDF also has superior efficacy compared with adefovir in patients with lamivudine-resistant HBV [18-20]. As an example, in a study of 53 lamivudine-resistant patients all of those who were switched to TDF achieved viral suppression by 48 weeks, whereas only 44 percent of those who were switched to adefovir achieved viral suppression [19].

Adefovir resistance — TDF and adefovir share similarities in chemical structure, and in-vitro studies have shown that while susceptibility of TDF is largely unchanged with single-resistance mutations A181T/V or N236T to adefovir, susceptibility is lower when both mutations are present.

Clinically, most studies have found that TDF is effective in suppressing HBV replication in patients with adefovir-resistant HBV [9,21-23]. In a prospective study of 105 adefovir-experienced patients who had an incomplete response to adefovir, patients were randomly assigned to receive TDF alone or with emtricitabine [22]. At baseline, 29 had genotypic resistance to adefovir (13 had both lamivudine- and adefovir-associated mutations). Eighty-three percent of patients achieved an undetectable HBV DNA (<69 international units/mL) after 168 weeks of treatment, and the presence of baseline adefovir-associated mutations did not affect response.

However, some studies have observed a slower decline in HBV DNA levels in patients with N236T mutation particularly if present along with A181T/V. As an example, early reports suggested that patients with adefovir-resistant HBV experience partial viral suppression after

switching to TDF with persistence of adefovir-resistant mutations [24,25]. In addition, in a retrospective study of 131 patients with chronic HBV infection resistant to lamivudine and/or adefovir, TDF therapy was less effective in suppressing HBV DNA (<400 copies/mL) among patients who had adefovir-resistant virus compared with those who had lamivudine-resistant virus (52 versus 100 percent) after a mean treatment duration of 23 months [13]. An additional discussion of adefovir resistance is found below. (See 'Development of resistance' below.)

In combination with other drugs — Data on the use of TDF combined with emtricitabine in treatment-naïve patients and those refractory to other therapy are presented above. (See 'Patients with HBeAg-positive chronic hepatitis B' above and 'Patients with previous exposure to other nucleos(t)ide analogues' above.)

Studies have also evaluated tenofovir in combination with other agents:

- **Tenofovir disoproxil plus** entecavir — The use of tenofovir disoproxil plus entecavir does not offer any benefit compared with entecavir monotherapy for most treatment-naïve patients. However, the use of this combination may be effective in treatment-naïve patients with high baseline viremia. A trial of 379 previously untreated patients with chronic HBV (HBeAg-positive and HBeAg-negative) evaluated the use of combination therapy with entecavir and tenofovir. Individuals were randomly assigned to receive entecavir (0.5 mg daily) as monotherapy or in combination with tenofovir (300 mg daily) for 100 weeks [26]. At week 96, the proportion of patients achieving the primary endpoint (HBV DNA level <50 IU/mL) was similar in both groups. However, in a subgroup analysis, combination therapy was more effective (79 versus 62 percent) in HBeAg-positive patients who had baseline HBV DNA levels of ≥10^8 IU/mL. There was no evidence of antiviral resistance at the end of the study in either group. The rate of ALT normalization was higher in the patients that received entecavir monotherapy as compared with combination therapy. There was no significant difference in the rates of HBeAg seroconversion and HBeAg loss.

  Combination therapy may also have a role in patients who have experienced treatment failure to sequential courses of nucleos(t)ide analogue therapy and/or have multi-drug resistant HBV. An open-labeled study examined the efficacy of combination therapy with entecavir (0.5 mg daily for lamivudine-naïve or 1.0 mg daily for lamivudine-experienced patients) plus tenofovir (300 mg daily) of 57 treatment-experienced patients [27]. In this study, participants had evidence of antiviral drug-resistant HBV or an incomplete virologic response or failure to previous antiviral therapy regimens and were previously treated with a median of three lines of therapy (most had received an adefovir- or lamivudine-containing regimen). HBV DNA became undetectable in 51 of the 57 patients (89 percent)

after a median of six months on combination therapy. In addition, five patients lost HBeAg and one developed HBsAg seroconversion.

However, several studies have found that TDF monotherapy is as effective as TDF combined with emtricitabine or entecavir in patients with multi-drug resistant HBV [9,10]. More detailed information on the management of patients with treatment failure is presented elsewhere. (See "Hepatitis B virus: Overview of management", section on 'Persistent viremia/breakthrough infection'.)

- **Tenofovir plus pegylated interferon** – The combination of pegylated interferon and TDF may enhance the rate of HBsAg loss, but the benefit is mainly observed in patients infected with HBV genotype A [28]. Data evaluating this combination are discussed in detail elsewhere. (See "Pegylated interferon for treatment of chronic hepatitis B virus infection", section on 'Combination with other nucleos(t)ide analogues'.)

Effect of tenofovir alafenamide on virologic outcomes — Tenofovir alafenamide (TAF) has been evaluated in HBeAg-positive and HBeAg-negative patients with chronic HBV. This agent has been found to have similar efficacy to TDF in both treatment-naïve and treatment-experienced patients [29,30]. However, TAF is associated with less renal and bone toxicity compared with TDF since it achieves lower plasma tenofovir exposures, but higher peripheral blood mononuclear cell intracellular tenofovir-diphosphate concentrations [29]. The data reviewing the toxicity of this agent are found below. (See 'Safety' below.)

Two large, multi-center, randomized controlled studies (one in HBeAg-positive and the other in HBeAg-negative patients) were conducted to compare the efficacy of TAF (25 mg daily) with TDF (300 mg daily) in a 2:1 ratio; in both trials, approximately one-quarter of patients had received previous therapy with one or more nucleos(t)ide analogues. The results are as follows:

- **HBeAg-positive patients** – In this trial, 873 HBeAg-positive patients were enrolled [1]. Of the 581 who received TAF, 371 (64 percent) had an HBV DNA <29 international units/mL at 48 weeks compared with 195 of the 292 (67 percent) patients who received TDF (adjusted difference, –3.6 percent; 95% CI –9.8-2.6). Among those with available data at 48 weeks, approximately 70 percent in each group normalized their ALT. In those who received TAF, HBeAg loss occurred in 78 (14 percent) and HBsAg loss was seen in four patients. This was similar to those who received TDF, where 34 (12 percent) had HBeAg loss and one had loss of HBsAg.

- **HBeAg-negative patients** – This trial was conducted in 425 HBeAg-negative patients with an HBV DNA >20,000 international units/mL and an elevated ALT (>60 units/L in men, >38 units/L in women) [2]. At week 48, 268 of the 285 patients (94 percent) who received TAF

had an HBV DNA <29 international units/mL compared with 130 of the 140 (93 percent) who received TDF (difference, 1.8 percent; 95% CI –3.6-7.2). There was no significant difference in ALT normalization between the groups (83 versus 75 percent for TAF and TDF, respectively), and no patient had loss of HBsAg during the study period.

Patients in the two TAF studies described above were followed for eight years [31]. Among those who were available for follow-up at year eight, more than 90 percent of HBeAg-positive and HBeAg-negative patients had an HBV DNA <29 international units/mL, and 80 to 89 percent had normal ALT levels. Among the patients who were HBeAg-positive at the start of treatment, 44 to 46 percent had lost HBeAg and 27 to 33 percent had seroconverted to anti-HBe. HBsAg loss was accomplished in 2 to 5 percent of HBeAg-positive and in 0 to 4 percent HBeAg-negative patients. None of the patients had confirmed genotypic resistance to TAF.

Effect on clinical outcomes — Given the extensive use of TDF, studies have evaluated the impact of this agent on clinical outcomes, such as cirrhosis, fibrosis, and hepatocellular carcinoma.

Regression of fibrosis and cirrhosis — Studies have evaluated the effect of TDF on fibrosis and cirrhosis [3-5,32,33]. The phase 3 studies of TDF found that approximately 70 percent of patients achieved a ≥2-point reduction in the Knodell necroinflammatory score without worsening fibrosis by 48 weeks [3,4]. (See 'Patients with HBeAg-positive chronic hepatitis B' above and 'Patients with HBeAg-negative chronic hepatitis B' above.)

A study evaluating the long-term effects of TDF followed 489 patients over 240 weeks [5]. Of the 348 patients who had a biopsy done at baseline and week 240, 304 (87 percent) had histologic improvement and 176 (51 percent) had regression of fibrosis, defined as a decrease of at least 1 point in Ishak score (range 0 to 6). Of the 96 patients that had cirrhosis at baseline, almost all had an improvement in the Knodell necroinflammatory score of ≥1 unit; in addition, 71 (74 percent) no longer had cirrhosis [5,32]. However, three patients without cirrhosis progressed to cirrhosis at year 5.

Reduced risk of hepatocellular carcinoma — Nucleos(t)ide analogues can reduce the risk of developing hepatocellular carcinoma (HCC) [34,35]. Although there are no randomized studies evaluating the effect of TDF on the incidence of HCC, many studies (retrospective as well as prospective) have demonstrated that long-term nucleos(t)ide analogue therapy including TDF reduces the risk of HCC [36,37]. As an example, a prospective study evaluated the incidence of HCC in 634 patients with chronic HBV (482 without cirrhosis and 152 with cirrhosis) who were treated with TDF in the phase III trial cited above, and were followed for 384 weeks [36]. Over the course of the study, 14 cases of HCC developed (four within the first year). Among those

without cirrhosis, the observed incidence of HCC was significantly lower than the incidence that was predicted using the Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B (REACH-B) model (standardized incidence ratio 0.40, 95% CI 0.199-0.795). In addition, no cases of HCC occurred in patients with cirrhosis after week 192.

One study from Korea suggested that TDF treatment resulted in a greater reduction in incidence of HCC compared with entecavir treatment [38]. Similar findings were observed in some but not all studies [37,39-42]. It has been suggested that delays in approval of TDF in Asia might have resulted in differences in baseline characteristics of patients treated with TDF versus entecavir in Asia, and these differences may not be completely resolved with propensity score matching. Additional information on the incidence of HCC in patients receiving tenofovir versus entecavir is presented elsewhere. (See "Entecavir in the treatment of chronic hepatitis B virus infection", section on 'Effect on long-term outcomes'.)

Preventing HBV reactivation — Tenofovir can also be used to prevent and treat HBV reactivation in patients receiving immunosuppressive therapy. A discussion of HBV reactivation is found elsewhere. (See "Hepatitis B virus reactivation associated with immunosuppressive therapy".)

Risk of resistance — Among patients receiving TDF for the treatment of chronic HBV infection, no signature mutation for tenofovir resistance has been identified, even after eight years of treatment [43-45]. As examples:

- Among 641 treatment-naïve patients treated with TDF over an eight-year period, 88 (14 percent) qualified for sequence analysis (eg, persistent viremia or virologic breakthrough). There was no evidence of tenofovir resistance, and of the 41 episodes of virologic breakthrough, the majority were associated with nonadherence [45].
- In a study of 280 patients with chronic HBV and lamivudine resistance who received TDF alone, or with emtricitabine, no resistance to TDF was detected through 240 weeks of treatment [17].

However, in two cases in which patients had persistent viremia while receiving therapy with tenofovir and entecavir, molecular analyses identified a distinct mutation, rtS78T/sC69, which was associated with decreased susceptibility to both tenofovir and entecavir in vitro [46]. The prevalence and significance of this mutation remains to be determined. Another study reported an alanine-to-threonine substitution (rtA194T) in two patients with HIV/HBV coinfection who had prior lamivudine resistance, and one had virologic breakthrough [47], but this association was not confirmed [48]. A subsequent study identified a quadruple mutation (rtS106C [C], rtH126Y [Y], rtD134E [E], rtM204I/V, and rtL269I [I]) in two patients who experienced breakthrough

during TDF therapy [49]. Both patients had prior exposure to lamivudine, accounting for the M204V/I mutation. In vitro studies demonstrated that the CYEI mutations increase the half maximal inhibitory concentration (IC50) by 15-fold.

The management of patients with persistent viremia while receiving tenofovir is discussed elsewhere. (See "Hepatitis B virus: Overview of management", section on 'While receiving tenofovir or entecavir'.)

Safety — The major adverse events associated with tenofovir include renal insufficiency, renal tubular dysfunction, and decreased bone density.

Renal insufficiency and renal tubular dysfunction

- Tenofovir disoproxil fumarate **(TDF)** – TDF is associated with worsening kidney function in some patients. If possible, TDF should be avoided in patients with reduced kidney function. The approach to treatment of chronic HBV in such patients is presented elsewhere. (See "Hepatitis B virus: Overview of management", section on 'Choice of initial agent'.)

  Patterns of kidney injury due to TDF include proximal tubular dysfunction, acute kidney injury, and chronic kidney disease. This can lead to renal impairment characterized by increases in serum creatinine, proteinuria, glycosuria, hypophosphatemia, and acute tubular necrosis. In HIV-infected patients, TDF has also been reported to cause a Fanconi syndrome with serious complications, including end-stage kidney disease and death [50-52]. (See "Overview of antiretroviral agents used to treat HIV", section on 'Tenofovir'.)

  There are case reports of renal failure developing in patients with HBV monoinfection taking TDF [53]. Large-scale treatment trials and observational studies have reported low rates of renal toxicity (<2 percent) in such patients [54-56]. In a meta-analysis of 11 studies that compared entecavir versus TDF in 1300 patients, no statistically significant differences were found between these agents with regards to renal safety or hypophosphatemia over approximately 18 months [57]. However, in one trial that followed 280 patients on TDF for 240 weeks, renal toxicity (defined as a confirmed increase in serum creatinine ≥0.5 mg/dL from baseline, a decrease in creatinine clearance [CrCL] <50 mL/min, and/or serum phosphorus <2 mg/dL) developed in approximately 8 percent of patients [17].

  The decision to initiate and/or discontinue TDF in patients with kidney disease depends upon whether or not the patient is HBV treatment-naïve prior to starting TDF, the severity of renal disease, and the availability of alternative agents. If TDF is used in patients with renal insufficiency, the dose must be adjusted for creatinine clearance (table 1). If TDF is stopped, patients should be switched to another nucleos(t)ide analogue that is not

nephrotoxic. (See "Hepatitis B virus: Overview of management", section on 'Antiviral therapy' and "Entecavir in the treatment of chronic hepatitis B virus infection".)

- Tenofovir alafenamide **(TAF)** – TAF appears to have less renal toxicity compared with TDF and is approved for use as monotherapy in patients with chronic HBV and an estimated glomerular filtration rate (eGFR) >15 mL/min/1.73m^2. (See "Hepatitis B virus: Overview of management", section on 'Choice of initial agent'.)

  Safety data from the two trials comparing TDF with TAF include:

  - Among HBeAg-positive patients, the mean increase in serum creatinine from baseline to 48 weeks was small in both groups; however, the increase was significantly smaller among the 581 HBeAg-positive patients receiving TAF compared with the 292 receiving TDF (0.01 versus 0.03 mg/dL). Patients receiving TAF also had a significantly smaller decrease in the eGFR (–0.6 versus –5.4 mL/min) [1].

  - Among HBeAg-negative patients (285 receiving TAF and 141 receiving TDF), there was no significant difference in the mean increase in serum creatinine from baseline to week 48 (0.01 versus 0.02 mg/dL) [2]. However, patients receiving TAF had a significantly lower median decrease in the eGFR (–1.8 versus –4.8 mL/min), and a significantly smaller increase in markers of proximal tubular dysfunction (urine retinol-binding-protein-to-creatinine ratio, and urine B_2 microglobulin-to-creatinine ratio).

  Several randomized studies found that switching patients receiving TDF to TAF resulted in improvement in renal function compared to remaining on TDF [58,59].

Bone density

- Tenofovir disoproxil fumarate **(TDF) –** TDF may reduce bone density in patients with chronic HBV monoinfection [14,17,56,60]. As examples:

  - In one study that followed 280 patients receiving TDF, with or without emtricitabine, the mean change in bone mineral density at week 240 was –0.98 and –2.54 percent at the spine and hip, respectively [17].

  - In another study, which analyzed an administrative database of 53,500 patients with chronic HBV who were followed for three years, there was a low rate of hip and spine fractures in those who received nucleos(t)ide analogue therapy (19 of 7046) [56]. However, the 689 patients who were exposed to nucleotide analogues (tenofovir, adefovir) had an increased risk of hip fracture (but not vertebral fracture) compared with the 6357 who received nucleoside analogues such as lamivudine (hazard ratio [HR]

5.69, 95% CI 1.98-16.39), and the 46,454 who received no antiviral therapy (HR 3.84, 95% CI 1.26-11.70).

Decreases in bone density appear to be related to an increased loss of phosphate through the kidneys. Although the effect appears to be mild, the effect is more prominent in children, and therefore tenofovir should generally be avoided in children. (See "Management of hepatitis B virus infection in children and adolescents", section on 'Choice of treatment'.)

- Tenofovir alafenamide **(TAF)** – TAF has less effect on bone density compared with TDF. Safety data from the two clinical trials described above include (see 'Effect of tenofovir alafenamide on virologic outcomes' above):

  - When changes in bone density were compared among 581 HBeAg-positive patients receiving TAF with 292 HBeAg-positive patients receiving TDF, the mean change in bone mineral density at the hip was –0.10 versus –1.72 percent (adjusted difference 1.62 percent, 95% CI 1.27-1.96), and the mean change at the spine was –0.42 percent versus –2.29 percent at week 48 (adjusted difference 1.88 percent, 95% CI 1.44-2.31) [1].

  - When HBeAg-negative patients were compared (285 receiving TAF versus 141 receiving TDF), the mean change in bone mineral density at the hip was –0.29 percent versus –2.16 percent (adjusted difference 1.87 percent; 95% CI 1.42-2.32), and the mean change at the spine was –0.88 percent versus –2.51 percent at week 48 (adjusted difference 1.64 percent; 95% CI 1.01-2.27) [2].

  Several randomized studies found that switching patients receiving TDF to TAF resulted in improvement in renal function compared to remaining on TDF [58,59].

ADEFOVIR

Adefovir dipivoxil is a nucleotide analog of adenosine monophosphate that can inhibit reverse transcriptase and DNA polymerase activity [61,62]. The most important role of adefovir is in the treatment of patients with lamivudine-resistant hepatitis B virus (HBV), preferably in combination with another nucleoside analogue. However, this role has largely been replaced by tenofovir, which is more potent and has a higher barrier to resistance. If used, adefovir is administered orally, and the dose is 10 mg daily. Patients with impaired renal function should have the dosing interval adjusted (table 1).

Effect on virologic outcomes — Monotherapy with adefovir (10 mg daily for 48 weeks) in patients with hepatitis B e antigen (HBeAg)-positive or HBeAg-negative chronic HBV infection has been associated with a 3 to 4 log10 reduction in mean HBV DNA levels [63,64]. The efficacy of adefovir in patients with lamivudine-resistant HBV infection has been demonstrated in several clinical settings, including in those with decompensated liver disease or liver transplantation [65-69]. In patients with lamivudine-resistant chronic HBV infection, the addition of adefovir is associated with a lower risk of adefovir resistance than a switch to adefovir monotherapy. However, the antiviral effect of adefovir is slow, and as many as 25 to 50 percent of patients have primary nonresponse [70].

Safety — Renal toxicity (a concern with the higher doses of adefovir) was uncommon in patients receiving the 10 mg dose except in those with decompensated cirrhosis or who had undergone liver transplantation. Renal toxicity appears to be more likely in patients who are older, have baseline renal insufficiency, have hypertension, and/or have diabetes mellitus [71]. Renal tubular dysfunction was observed in up to 15 percent of patients in one study of 42 patients treated for a mean of seven years [53].

Development of resistance — Resistance occurs at a slower rate during adefovir treatment compared with lamivudine. However, mutations conferring resistance to adefovir (rtN236T, A181V, and A181T) have been described [72-75]. A study analyzing pooled data from all studies sponsored by the manufacturer concluded that A181T mutation was not associated with adefovir resistance [75]. The rtA181T mutation leads to a stop codon mutation in the overlapping surface gene with resultant impairment in virion secretion [76]. This may account for the low serum HBV DNA level associated with initial emergence of rtA181T mutation.

The cumulative rate of resistance was estimated to be 15 percent by 192 weeks in one report that included data from five studies [77]. In one of the studies cited above in which 67 HBeAg-negative nucleoside-naïve patients received adefovir monotherapy, the cumulative rate of resistance was 0, 3, 11, 18, and 29 percent at weeks 48, 96, 144, 192, and 240, respectively [78]. In the study of HBeAg-positive nucleoside-naïve patients, the cumulative rate of resistance was approximately 30 percent after five years of treatment.

In vitro and human studies found that adefovir-resistant HBV mutants are susceptible to tenofovir and entecavir [70], although the double variant, A181V and N236T, is less responsive to tenofovir.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Management of hepatitis B".)

SUMMARY AND RECOMMENDATIONS

- **Tenofovir** – Tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) are nucleotide reverse transcriptase inhibitors that have activity against hepatitis B virus (HBV) and HIV. Compared with adefovir (another nucleotide reverse transcriptase inhibitor), tenofovir has more potent antiviral activity and a better safety profile. (See 'Introduction' above and 'Formulations' above.)

  - **Efficacy of TDF compared with** adefovir – In patients with hepatitis B e antigen (HBeAg)-positive chronic HBV who had not previously received treatment, TDF (300 mg daily) was significantly more effective than adefovir (10 mg daily) at reducing serum HBV DNA levels and achieving normalization of serum alanine aminotransferase (ALT). However, the degree of histologic benefit and the proportion of patients achieving HBeAg seroconversion were similar. (See 'Patients with HBeAg-positive chronic hepatitis B' above.)

    In patients with HBeAg-negative chronic HBV who have not previously received treatment, TDF (300 mg daily) was significantly more effective than adefovir (10 mg daily) at reducing HBV DNA. The proportions of patients achieving normalization of serum ALT and improvement in histology were similar. (See 'Patients with HBeAg-negative chronic hepatitis B' above.)

  - **Efficacy of TDF in treatment experienced patients** – Studies of patients who had previously received treatment with other nucleos(t)ide analogues found that TDF is effective in suppressing lamivudine-, adefovir-, and entecavir-resistant HBV as well as multi-drug resistant HBV, and TDF monotherapy is as effective as TDF combined with emtricitabine or entecavir. However, there may be a slower decline in HBV DNA levels when tenofovir is used to treat patients with virus that has dual resistance mutations to adefovir. (See 'Patients with previous exposure to other nucleos(t)ide analogues' above.)

  - **Efficacy of TAF** – TAF (25 mg daily) has been evaluated in HBeAg-positive and HBeAg-negative patients with chronic HBV. This agent has been found to have similar efficacy to TDF in both treatment-naïve and treatment-experienced patients with less adverse

effects on kidney function and bone density. (See 'Effect of tenofovir alafenamide on virologic outcomes' above.)

- **Risk of developing tenofovir resistance** – Among patients receiving tenofovir for the treatment of chronic HBV infection (both those who are treatment-naïve and those with lamivudine resistance prior to treatment), no signature tenofovir-resistance mutations have been identified. (See 'Risk of resistance' above.)

- **Safety of tenofovir** – Tenofovir is associated with renal and bone toxicity; however, TAF has significantly less effect on kidney function and bone mineral density compared with TDF. (See 'Safety' above.)

- Adefovir – Adefovir dipivoxil is a nucleotide analog of adenosine monophosphate, which can inhibit reverse transcriptase and DNA polymerase activity. However, this agent has been replaced by tenofovir, which is more potent and has a higher barrier to resistance. (See 'Adefovir' above.)

REFERENCES

1. Chan HL, Fung S, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol 2016; 1:185.
2. Buti M, Gane E, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol 2016; 1:196.
3. Marcellin P, Heathcote EJ, Buti M, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. N Engl J Med 2008; 359:2442.
4. Heathcote EJ, Marcellin P, Buti M, et al. Three-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B. Gastroenterology 2011; 140:132.
5. Marcellin P, Gane E, Buti M, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. Lancet 2013; 381:468.
6. Buti M, Tsai N, Petersen J, et al. Seven-year efficacy and safety of treatment with tenofovir disoproxil fumarate for chronic hepatitis B virus infection. Dig Dis Sci 2015; 60:1457.

7. Marcellin P, Wong DK, Sievert W, et al. Ten-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B virus infection. Liver Int 2019; 39:1868.
8. Chan HL, Chan CK, Hui AJ, et al. Effects of tenofovir disoproxil fumarate in hepatitis B e antigen-positive patients with normal levels of alanine aminotransferase and high levels of hepatitis B virus DNA. Gastroenterology 2014; 146:1240.
9. Lim YS, Gwak GY, Choi J, et al. Monotherapy with tenofovir disoproxil fumarate for adefovir-resistant vs. entecavir-resistant chronic hepatitis B: A 5-year clinical trial. J Hepatol 2019; 71:35.
10. Yim HJ, Suh SJ, Jung YK, et al. Tenofovir-based combination therapy or monotherapy for multidrug-resistant chronic hepatitis B: Long-term data from a multicenter cohort study. J Viral Hepat 2020; 27:1306.
11. Kuo A, Dienstag JL, Chung RT. Tenofovir disoproxil fumarate for the treatment of lamivudine-resistant hepatitis B. Clin Gastroenterol Hepatol 2004; 2:266.
12. Manns M, Jeffers L, Dalekos T, et al. The antiviral response to tenofovir disoproxil fumarate (TDF) is comparable in lamivudine (LAM)-naive and LAM-experienced subjects treatment for chronic hepatitis B (CHB) (abstract). J Hepatol 2008; (Suppl):S32.
13. van Bömmel F, de Man RA, Wedemeyer H, et al. Long-term efficacy of tenofovir monotherapy for hepatitis B virus-monoinfected patients after failure of nucleoside/nucleotide analogues. Hepatology 2010; 51:73.
14. Fung S, Kwan P, Fabri M, et al. Randomized comparison of tenofovir disoproxil fumarate vs emtricitabine and tenofovir disoproxil fumarate in patients with lamivudine-resistant chronic hepatitis B. Gastroenterology 2014; 146:980.
15. van Bommel F, Mauss S, Schurmann D, et al. No evidence for tenofovir resistance in patients with lamivudine-resistant HBV infection during long-term treatment for up to 5 years (abstract). Hepatology 2006; 44(Suppl 1):549A.
16. Wang HL, Lu X, Yang X, Ning Q. Efficacy of tenofovir-based rescue therapy in patients with lamivudine-resistant hepatitis B virus: A systematic review and meta-analysis. Clin Res Hepatol Gastroenterol 2016; 40:447.
17. Fung S, Kwan P, Fabri M, et al. Tenofovir disoproxil fumarate (TDF) vs. emtricitabine (FTC)/TDF in lamivudine resistant hepatitis B: A 5-year randomised study. J Hepatol 2017; 66:11.
18. van Bömmel F, Zöllner B, Sarrazin C, et al. Tenofovir for patients with lamivudine-resistant hepatitis B virus (HBV) infection and high HBV DNA level during adefovir therapy. Hepatology 2006; 44:318.

19. van Bömmel F, Wünsche T, Mauss S, et al. Comparison of adefovir and tenofovir in the treatment of lamivudine-resistant hepatitis B virus infection. Hepatology 2004; 40:1421.
20. van Bömmel F, Berg T. Reactivation of viral replication after replacement of tenofovir by adefovir. Hepatology 2005; 42:239.
21. Berg T, Marcellin P, Zoulim F, et al. Tenofovir is effective alone or with emtricitabine in adefovir-treated patients with chronic-hepatitis B virus infection. Gastroenterology 2010; 139:1207.
22. Berg T, Zoulim F, Moeller B, et al. Long-term efficacy and safety of emtricitabine plus tenofovir DF vs. tenofovir DF monotherapy in adefovir-experienced chronic hepatitis B patients. J Hepatol 2014; 60:715.
23. Lee HW, Park JY, Lee JW, et al. Long-term Efficacy of Tenofovir Disoproxil Fumarate Monotherapy for Multidrug-Resistant Chronic HBV infection. Clin Gastroenterol Hepatol 2019; 17:1348.
24. Tan J, Degertekin B, Wong SN, et al. Tenofovir monotherapy is effective in hepatitis B patients with antiviral treatment failure to adefovir in the absence of adefovir-resistant mutations. J Hepatol 2008; 48:391.
25. van Bömmel F, Trojan J, Deterding K, et al. Evolution of adefovir-resistant HBV polymerase gene variants after switching to tenofovir disoproxil fumarate monotherapy. Antivir Ther 2012; 17:1049.
26. Lok AS, Trinh H, Carosi G, et al. Efficacy of entecavir with or without tenofovir disoproxil fumarate for nucleos(t)ide-naïve patients with chronic hepatitis B. Gastroenterology 2012; 143:619.
27. Petersen J, Ratziu V, Buti M, et al. Entecavir plus tenofovir combination as rescue therapy in pre-treated chronic hepatitis B patients: an international multicenter cohort study. J Hepatol 2012; 56:520.
28. Marcellin P, Ahn SH, Ma X, et al. Combination of Tenofovir Disoproxil Fumarate and Peginterferon α-2a Increases Loss of Hepatitis B Surface Antigen in Patients With Chronic Hepatitis B. Gastroenterology 2016; 150:134.
29. Agarwal K, Brunetto M, Seto WK, et al. 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. J Hepatol 2018; 68:672.
30. Cathcart AL, Chan HL, Bhardwaj N, et al. No Resistance to Tenofovir Alafenamide Detected through 96 Weeks of Treatment in Patients with Chronic Hepatitis B Infection. Antimicrob Agents Chemother 2018; 62.

31. Buti M, Agarwal K, Ly Chan H, et al. Long-term efficacy of tenofovir alafenamide in HBeAg-positive. J Hepatol 2023; OS-067.
32. Buti M, Fung S, Gane E, et al. Long-term clinical outcomes in cirrhotic chronic hepatitis B patients treated with tenofovir disoproxil fumarate for up to 5 years. Hepatol Int 2015; 9:243.
33. Wang T, Smith DA, Campbell C, et al. Hepatitis B virus (HBV) viral load, liver and renal function in adults treated with tenofovir disoproxil fumarate (TDF) vs. untreated: a retrospective longitudinal UK cohort study. BMC Infect Dis 2021; 21:610.
34. Varbobitis I, Papatheodoridis GV. The assessment of hepatocellular carcinoma risk in patients with chronic hepatitis B under antiviral therapy. Clin Mol Hepatol 2016; 22:319.
35. Huang ZH, Lu GY, Qiu LX, et al. Risk of hepatocellular carcinoma in antiviral treatment-naïve chronic hepatitis B patients treated with entecavir or tenofovir disoproxil fumarate: a network meta-analysis. BMC Cancer 2022; 22:287.
36. Kim WR, Loomba R, Berg T, et al. Impact of long-term tenofovir disoproxil fumarate on incidence of hepatocellular carcinoma in patients with chronic hepatitis B. Cancer 2015; 121:3631.
37. Papatheodoridis GV, Idilman R, Dalekos GN, et al. The risk of hepatocellular carcinoma decreases after the first 5 years of entecavir or tenofovir in Caucasians with chronic hepatitis B. Hepatology 2017; 66:1444.
38. Choi J, Kim HJ, Lee J, et al. Risk of Hepatocellular Carcinoma in Patients Treated With Entecavir vs Tenofovir for Chronic Hepatitis B: A Korean Nationwide Cohort Study. JAMA Oncol 2019; 5:30.
39. Hsu YC, Wong GL, Chen CH, et al. Tenofovir Versus Entecavir for Hepatocellular Carcinoma Prevention in an International Consortium of Chronic Hepatitis B. Am J Gastroenterol 2020; 115:271.
40. Tan DJH, Ng CH, Tay PWL, et al. Risk of Hepatocellular Carcinoma With Tenofovir vs Entecavir Treatment for Chronic Hepatitis B Virus: A Reconstructed Individual Patient Data Meta-analysis. JAMA Netw Open 2022; 5:e2219407.
41. Kim WR, Telep LE, Jump B, et al. Risk of hepatocellular carcinoma in treatment-naïve chronic hepatitis B patients receiving tenofovir disoproxil fumarate versus entecavir in the United States. Aliment Pharmacol Ther 2022; 55:828.
42. Choi WM, Yip TC, Wong GL, et al. Hepatocellular carcinoma risk in patients with chronic hepatitis B receiving tenofovir- vs. entecavir-based regimens: Individual patient data meta-analysis. J Hepatol 2023; 78:534.

43. Kitrinos KM, Corsa A, Liu Y, et al. No detectable resistance to tenofovir disoproxil fumarate after 6 years of therapy in patients with chronic hepatitis B. Hepatology 2014; 59:434.
44. Corsa AC, Liu Y, Flaherty JF, et al. No resistance to tenofovir disoproxil fumarate through 96 weeks of treatment in patients with lamivudine-resistant chronic hepatitis B. Clin Gastroenterol Hepatol 2014; 12:2106.
45. Liu Y, Corsa AC, Buti M, et al. No detectable resistance to tenofovir disoproxil fumarate in HBeAg+ and HBeAg- patients with chronic hepatitis B after 8 years of treatment. J Viral Hepat 2017; 24:68.
46. Shirvani-Dastgerdi E, Winer BY, Celià-Terrassa T, et al. Selection of the highly replicative and partially multidrug resistant rtS78T HBV polymerase mutation during TDF-ETV combination therapy. J Hepatol 2017; 67:246.
47. Sheldon J, Camino N, Rodés B, et al. Selection of hepatitis B virus polymerase mutations in HIV-coinfected patients treated with tenofovir. Antivir Ther 2005; 10:727.
48. Delaney WE 4th, Ray AS, Yang H, et al. Intracellular metabolism and in vitro activity of tenofovir against hepatitis B virus. Antimicrob Agents Chemother 2006; 50:2471.
49. Park ES, Lee AR, Kim DH, et al. Identification of a quadruple mutation that confers tenofovir resistance in chronic hepatitis B patients. J Hepatol 2019; 70:1093.
50. Tourret J, Deray G, Isnard-Bagnis C. Tenofovir effect on the kidneys of HIV-infected patients: a double-edged sword? J Am Soc Nephrol 2013; 24:1519.
51. Gupta SK. Tenofovir-associated Fanconi syndrome: review of the FDA adverse event reporting system. AIDS Patient Care STDS 2008; 22:99.
52. Verhelst D, Monge M, Meynard JL, et al. Fanconi syndrome and renal failure induced by tenofovir: a first case report. Am J Kidney Dis 2002; 40:1331.
53. Gara N, Zhao X, Collins MT, et al. Renal tubular dysfunction during long-term adefovir or tenofovir therapy in chronic hepatitis B. Aliment Pharmacol Ther 2012; 35:1317.
54. 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.
55. Lampertico P, Chan HL, Janssen HL, et al. Review article: long-term safety of nucleoside and nucleotide analogues in HBV-monoinfected patients. Aliment Pharmacol Ther 2016; 44:16.
56. Wong GL, Tse YK, Wong VW, et al. 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.

57. Lok AS, McMahon BJ, Brown RS Jr, et al. Antiviral therapy for chronic hepatitis B viral infection in adults: A systematic review and meta-analysis. Hepatology 2016; 63:284.

58. Lampertico P, Buti M, Fung S, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in virologically suppressed patients with chronic hepatitis B: a randomised, double-blind, phase 3, multicentre non-inferiority study. Lancet Gastroenterol Hepatol 2020; 5:441.

59. Byun KS, Choi J, Kim JH, et al. Tenofovir Alafenamide for Drug-Resistant Hepatitis B: A Randomized Trial for Switching From Tenofovir Disoproxil Fumarate. Clin Gastroenterol Hepatol 2022; 20:427.

60. Fontana RJ. Side effects of long-term oral antiviral therapy for hepatitis B. Hepatology 2009; 49:S185.

61. Gilson RJ, Chopra KB, Newell AM, et al. A placebo-controlled phase I/II study of adefovir dipivoxil in patients with chronic hepatitis B virus infection. J Viral Hepat 1999; 6:387.

62. Tsiang M, Rooney JF, Toole JJ, Gibbs CS. Biphasic clearance kinetics of hepatitis B virus from patients during adefovir dipivoxil therapy. Hepatology 1999; 29:1863.

63. Marcellin P, Chang TT, Lim SG, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. N Engl J Med 2003; 348:808.

64. Zeng M, Mao Y, Yao G, et al. A double-blind randomized trial of adefovir dipivoxil in Chinese subjects with HBeAg-positive chronic hepatitis B. Hepatology 2006; 44:108.

65. Xiong X, Flores C, Yang H, et al. Mutations in hepatitis B DNA polymerase associated with resistance to lamivudine do not confer resistance to adefovir in vitro. Hepatology 1998; 28:1669.

66. Perrillo R, Schiff E, Yoshida E, et al. Adefovir dipivoxil for the treatment of lamivudine-resistant hepatitis B mutants. Hepatology 2000; 32:129.

67. Benhamou Y, Bochet M, Thibault V, et al. Safety and efficacy of adefovir dipivoxil in patients co-infected with HIV-1 and lamivudine-resistant hepatitis B virus: an open-label pilot study. Lancet 2001; 358:718.

68. Peters MG, Hann Hw Hw, Martin P, et al. Adefovir dipivoxil alone or in combination with lamivudine in patients with lamivudine-resistant chronic hepatitis B. Gastroenterology 2004; 126:91.

69. Perrillo R, Hann HW, Mutimer D, et al. Adefovir dipivoxil added to ongoing lamivudine in chronic hepatitis B with YMDD mutant hepatitis B virus. Gastroenterology 2004; 126:81.

70. Fung SK, Chae HB, Fontana RJ, et al. Virologic response and resistance to adefovir in patients with chronic hepatitis B. J Hepatol 2006; 44:283.

71. Ha NB, Ha NB, Garcia RT, et al. Renal dysfunction in chronic hepatitis B patients treated with adefovir dipivoxil. Hepatology 2009; 50:727.
72. Angus P, Vaughan R, Xiong S, et al. Resistance to adefovir dipivoxil therapy associated with the selection of a novel mutation in the HBV polymerase. Gastroenterology 2003; 125:292.
73. Villeneuve JP, Durantel D, Durantel S, et al. Selection of a hepatitis B virus strain resistant to adefovir in a liver transplantation patient. J Hepatol 2003; 39:1085.
74. Lacombe K, Ollivet A, Gozlan J, et al. A novel hepatitis B virus mutation with resistance to adefovir but not to tenofovir in an HIV-hepatitis B virus-co-infected patient. AIDS 2006; 20:2229.
75. Borroto-Esoda K, Miller MD, Arterburn S. Pooled analysis of amino acid changes in the HBV polymerase in patients from four major adefovir dipivoxil clinical trials. J Hepatol 2007; 47:492.
76. Warner N, Locarnini S. The antiviral drug selected hepatitis B virus rtA181T/sW172* mutant has a dominant negative secretion defect and alters the typical profile of viral rebound. Hepatology 2008; 48:88.
77. Locarnini S, Qi X, Arterburn S, et al. Incidence and predictors of emergence of adefovir resistant HBV during four years of adefovir dipivoxil therapy for patients with chronic hepatitis B (abstract). J Hepatol 2005; 42 (Suppl 2):17A.
78. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. Gastroenterology 2006; 131:1743.

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GRAPHICS

Adjustment of adult dose of nucleos(t)ide analogues for treatment of chronic hepatitis B in accordance with creatinine clearance

Creatinine clearance (mL/min)*	Recommended oral dose
Entecavir[¶] (nucleoside)	
NA treatment naïve	
≥50	0.5 mg daily
30 to 49	0.25 mg daily or 0.5 mg every 48 hours
10 to 29	0.15 mg daily or 0.5 mg every 72 hours
<10 or hemodialysis[Δ] or continuous ambulatory peritoneal dialysis	0.05 mg daily or 0.5 mg every 7 days
Lamivudine refractory/resistant	
≥50	1 mg daily
30 to 49	0.5 mg daily or 1 mg every 48 hours
10 to 29	0.3 mg daily or 1 mg every 72 hours
<10 or hemodialysis[Δ] or continuous ambulatory peritoneal dialysis	0.1 mg daily or 1 mg every 7 days
Tenofovir disoproxil fumarate (TDF, nucleotide)	
≥50	300 mg daily
30 to 49	300 mg every 48 hours
10 to 29	300 mg every 72 to 96 hours
<10 with hemodialysis[Δ]	300 mg once a week or after a total of approximately 12 hours of dialysis
<10 without hemodialysis	Insufficient data; no recommendation[◇]
Continuous ambulatory peritoneal dialysis	Insufficient data; no recommendation[◇]
Tenofovir alafenamide (TAF, nucleotide)	
≥15	25 mg daily
<15 with hemodialysis	25 mg on hemodialysis days; dose after dialysis
<15 without hemodialysis	Insufficient data; no recommendation[◇]
Lamivudine (3TC, nucleoside)	
≥50	100 mg daily

30 to 49	100 mg first dose, then 50 mg daily
15 to 29	100 mg first dose, then 25 mg daily
5 to 14	35 mg first dose, then 15 mg daily
<5 or hemodialysis[Δ] or continuous ambulatory peritoneal dialysis	35 mg first dose, then 10 mg daily
Adefovir dipivoxil (nucleotide)	
≥50	10 mg daily
30 to 49	10 mg every 48 hours
10 to 29	10 mg every 72 hours
<10 (not receiving hemodialysis)	Insufficient data; no recommendation[◇]
Hemodialysis	10 mg every seven days following dialysis
Continuous ambulatory peritoneal dialysis	Insufficient data; no recommendation[◇]
Telbivudine (LdT, nucleoside)[§]	
≥50	600 mg daily
30 to 49	600 hours mg every 48 hours
10 to 29 (not receiving hemodialysis)	600 mg every 72 hours
Hemodialysis	600 mg every 96 hours following dialysis[Δ]
Continuous ambulatory peritoneal dialysis	Insufficient data; no recommendation[◇]

Doses are for patients without HIV coinfection.

NA: nucleoside or nucleotide analogue.

* Can be estimated by using the Cockroft-Gault equation. Separate calculators for creatinine clearance using conventional and SI units are available in UpToDate.

¶ For doses <0.5 mg, entecavir oral solution is recommended.

Δ Administer after intermittent hemodialysis.

◇ Data establishing the safety, efficacy, and optimal dosing in end-stage kidney disease (with or without dialysis) are not available.

§ Discontinued in the United States; may be available in other countries.

Data from:

1. *Terrault NA, Bzowej NH, Chang KM, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016 Jan; 63:261.*
2. *Lexicomp Online. Copyright 1978-2023 Lexicomp, Inc. All Rights Reserved.*

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Contributor Disclosures

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Conflict of interest policy

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