# Tenofovir disoproxil fumarate for the treatment of hepatitis B virus infection: pharmacokinetics and clinical efficacy

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Tenofovir is an acyclic nucleotide phosphonate diester analogue of adenosine monophosphate with antiviral activity against HIV-1 and hepatitis B virus. After two phosphorylations, tenofovir inhibits HIV-1 reverse transcriptase by competing with the natural substrate, deoxyadenosine 5´-triphosphate. Tenofovir disoproxil fumarate has been approved by the US FDA for the treatment of HIV-1 infection in combination with other antiretroviral agents. Although not approved by the FDA for the treatment of chronic hepatitis B virus infection, tenofovir has anti-hepatitis B virus activity in patients co-infected with HIV and hepatitis B. This paper will review the pharmacology and clinical experience with tenofovir, with a focus on hepatitis B infection.

**Keywords:** hepatitis B virus, HIV, nucleotide analogue, pharmacokinetics, PMPA, tenofovir disoproxil fumarate

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Chronic hepatitis B virus (HBV) infection is thought to affect approximately 400 million individuals worldwide, resulting in 1 million deaths annually from cirrhosis or hepatocellular carcinoma [1]. The majority of hepatocellular carcinoma worldwide is associated with chronic HBV infection. After exposure of neonates at birth (perinatally), chronic infection is the rule. Few patients (<5%) infected as adults develop chronic infection unless the patient is immunocompromised. Persistent infection occurs in 20% of adults with HIV who become infected and is an important cause of morbidity and mortality in these co-infected patients [2]. The prevalence of HBV in HIV-infected individuals varies from 5–10% in the USA and Europe [3] to up to 20–30% in Asia and parts of sub-Saharan Africa [4]. Therapy for HBV has expanded considerably over the last decade. Initially, only lamivudine (LAM) monotherapy or interferon-α were available. Many patients were not candidates for interferon and resistance to lamivudine develops at a rate of approximately 20% per year (60% at 4 years) [5]. The majority of HIV and HBV co-infected patients (90%) treated with LAM as part of antiretroviral therapy develop resistance to HBV after 4 years of therapy [6].

Tenofovir disoproxil fumarate (TDF) is an oral prodrug of tenofovir. Tenofovir is an acyclic nucleotide analogue of adenosine monophosphate with activity against HIV-1 and HBV [7,8]. TDF (Viread®, Gilead Sciences, Inc., CA, USA) is approved by the US FDA for the treatment of HIV-1 infection in combination with other antiretrovirals. In this review, we have used TDF when referring to the drug tenofovir disoproxil fumarate and tenofovir when referring to the active compound.

## Overview of the market

There are currently six drugs licensed in the USA for the treatment of chronic hepatitis B infection. Of these six drugs, four are oral antiviral agents (three nucleoside analogues and one nucleotide analogue) and two are immunomodulatory agents (**Table 1**).

LAM (Epivir®, GlaxoSmithKline) is a synthetic dideoxy analogue of cytidine that was approved by the FDA in 1995 for the treatment of HIV infection at a dosage of 300 mg/day in one or two divided doses. In 1998, LAM was approved at a dosage of 100 mg/day for the treatment of chronic hepatitis B under a different trade name, Epivir-HBV®. Adefovir dipivoxil (ADV; Hepsera®, Gilead Sciences) was the first acyclic nucleotide phosphonate approved for the treatment of chronic hepatitis B in 2001. Entecavir (Baraclude™, Bristol-Myers Squibb, NY, USA) and telbivudine (Tyzeka™, Idenix Pharmaceuticals, MA, USA) are nucleoside analogues with selective activity against HBV that were FDA approved in 2005 and 2006, respectively.

Interferon-α2b (Intron® A, Schering Corp., NJ, USA) and pegylated (peg)interferon-α2a (Pegasys®, Roche, Basel, Switzerland) are two biological response modifiers that are licensed for the treatment of chronic hepatitis B infection. Interferon-α2b must be administered by

**Table 1. Indications of various antiviral drugs.**

| Drug | Indication |
|---|---|
| Adefovir dipivoxil (Hepsera®) | Chronic hepatitis B infection |
| Entecavir (Baraclude™) | Chronic hepatitis B infection |
| Interferon-α2b (Intron® A) | AIDS-related Kaposi's sarcoma<br>Chronic hepatitis B infection<br>Chronic hepatitis C infection<br>Condylomata acuminata<br>Follicular lymphoma<br>Hairy cell leukemia<br>Malignant melanoma |
| Lamivudine (Epivir®)<br>Lamivudine (Epivir-HBV®) | HIV infection<br>Chronic hepatitis infection |
| Peginterferon-α2a (Pegasys®) | Chronic hepatitis B infection<br>Chronic hepatitis C infection |
| Telbivudine (Tyzeka™) | Chronic hepatitis B infection |
| TDF (Viread®) | HIV infection |
| TDF + emtricitabine (Truvada®) | HIV infection |
| TDF + emtricitabine + efavirenz (Atripla™) | HIV infection |

*TDF: Tenofovir disoproxil fumarate.*

daily injection, while peginterferon-α2a is administered weekly. The interferon preparations are associated with significant adverse effects such as bone marrow suppression, neuropsychiatric and autoimmune disorders during therapy [9].

## Introduction to TDF

TDF (formerly GS-4331-05) is a prodrug of tenofovir. Tenofovir is a nucleotide analogue of adenosine monophosphate that inhibits HIV reverse transcriptase (HIV DNA polymerase) as well as HBV reverse transcriptase (HBV DNA polymerase). Tenofovir belongs to the group of acyclic nucleoside phosphonates, which includes ADV and cidofovir (Vistide®, Gilead Sciences). TDF is used for the treatment of HIV infection in combination with other antiretroviral agents, while adefovir dipivoxil (ADV) is used for the treatment of chronic hepatitis B infection. Cidofovir is administered intravenously for the treatment of cytomegalovirus (CMV) retinitis infection in AIDS patients. **Table 2** lists the spectrum of activity for various antiviral drugs.

## Chemistry

Tenofovir (9-[-(*R*)-2-phosphonomethoxy propyl]adenine [PMPA]) is an acyclic nucleotide analogue of adenosine monophosphate. Tenofovir has a low oral bioavailability owing to the ionic nature of the phosphonate group. To improve oral bioavailability, a prodrug was developed to mask the negative charges of the phosphonate group with lipophilic promoieties. The addition of these two promoieties not only increases absorption from the gastrointestinal tract, but also increases the potency by 50-fold [7]. Tenofovir disoproxil, corresponding to the bis(isopropyloxycarbonyloxymethyl) ester of PMPA, or bis(POC)PMPA is formulated as the salt, TDF or 9-[(*R*)-2-[[bis[[isopropoxycarbonyl)oxy]methoxy]phosphinyl]methoxy]propyl]adenine fumarate (bis[POC]PMPA). Following oral administration, TDF undergoes esterase hydrolysis, which removes the two ester groups to yield tenofovir [10,11]. The molecular formula is $C_{19}H_{30}N_5O_{10}P \bullet C_4H_4O_4$ and the molecular weight is 635.52.

## Pharmacodynamics

The phosphorylation of nucleoside analogues can be a rate-limiting step. Tenofovir, and other nucleotide analogues such as adefovir and cidofovir, do not require this initial phosphorylation. Tenofovir is rapidly taken up by cells and phosphorylated in two steps by adenylate kinase or in one step by 5-phosphoribosyl 1-pyrophosphate (PRPP) synthetase to form the active diphosphate form [12–14]. Following phosphorylation, tenofovir diphosphate is incorporated by reverse transcriptase into the nascent chain of viral DNA [7,8]. Since

**Table 2. Antiviral spectrum of activity.**

| Virus | Adefovir | Tenofovir | Lamivudine | Entecavir | Telbivudine |
|---|---|---|---|---|---|
| ***Herpesvirus*** | | | | | |
| HSV | Active | Inactive | Inactive | Inactive | Inactive |
| CMV | Active | Inactive | Inactive | Inactive | Inactive |
| VZV | Active | Inactive | Inactive | Inactive | Inactive |
| ***Retrovirus*** | | | | | |
| HIV-1 | Active | Active | Active | Inactive | Inactive |
| ***Hepadnavirus*** | | | | | |
| HBV | Active | Active | Active | Active | Active |
| HBV-YMDD mutant | Active | Active | Inactive | Less active | Inactive |

*CMV: Cytomegalovirus; HBV: Hepatitis B virus; HSV: Herpes simplex virus; VZV: Varicella-zoster virus; YMDD: Tyrosine–methionine–aspartate–aspartate.*

tenofovir diphosphate lacks the 3′ hydroxyl group, additional nucleotides cannot be attached, resulting in chain termination and inhibition of viral replication.

The pharmacodynamics and viral dynamics of TDF in HIV-infected patients has been extensively studied and are reviewed elsewhere [12,15,16]. For a more thorough discussion on the use of TDF for the treatment of HIV-1 infection, see [17–20].

There are limited pharmacodynamic and hepatitis B viral kinetic data in patients with HBV infection. **Table 3** summarizes some of the key publications evaluating TDF in the setting of hepatitis B infection. Tenofovir has antiviral activity against duck hepatitis B (DHV) *in vitro* and woodchuck hepatitis B (WHV) *in vivo* [21,22]. In addition, tenofovir has potent antiviral activity both *in vitro* and *in vivo* against wild-type HBV, as well as LAM-resistant mutants [23–27]. Tenofovir was found to exhibit long-lasting anti-HBV activity in cell culture, with a 50% effective concentration ($EC_{50}$) of 0.03 ± 0.02 µg/ml with continuous exposure, increasing to 6.5 ± 1.0 and 0.8 ± 0.1 µg/ml after just 24 and 48 h of exposure, respectively [23].

HBV dynamics were evaluated in 28 HIV–HBV-co-infected patients treated with TDF. The HBV DNA viral load declined by a mean of 4.6 log copies/ml during a mean of 71 weeks of therapy. HBV DNA levels fell below the detection limit (200 copies/ml) in 21 out of 28 patients after a median of 272 days. Concomitant LAM therapy did not effect the time taken for the HBV DNA levels to become undetectable. Inhibition of viral replication was associated with a decrease in alanine aminotransferase (ALT) levels [28].

The susceptibility of HBV strains resistant to LAM (rtL180M and M204V) and adefovir (rtN236T) to tenofovir was evaluated in Huh7 and HepG2 cells. There was a 3.4-fold resistance (mutant $IC_{50}$/wild type $IC_{50}$) in HBV strains with the rtL180M and M204V mutations, and a 4.5-fold resistance with the N236T mutation. In a constructed strain with the triple mutation (L180M, M204V and N236T), there was a 4.4-fold resistance to tenofovir compared with the wild-type virus. While these mutations confer resistance to LAM and adefovir, tenofovir still exhibits antiviral activity *in vitro* [5]. TDF inhibits viral replication in patients with LAM-resistant HBV mutants. There was a mean decline of 1.37 ± 0.51 log copies/ml after 4 weeks and 4.95 ± 0.9 log copies/ml after 24 weeks when tenofovir 300 mg once daily was added to existing therapy. The median effectiveness of blocking viral replication was 93%. The half-life of free virus and infected hepatocytes was found to be approximately 21 h and 5.7 days, respectively [29].

The suppressive activity of TDF was compared with ADV in 109 patients with LAM resistance. TDF alone or combined with LAM resulted in a 3.65 ± 1.75 $log_{10}$ reduction in HBV DNA at 6 months compared with a 1.94 ± 1.98 $log_{10}$ reduction with ADV. A total of 63% of patients administered TDF had a greater than 3-log reduction in HBV DNA levels compared with 28% of ADV-treated patients [30]. The antiviral effects of TDF were compared with ADV in patients with high HBV DNA levels (>6 $log_{10}$ copies/ml) and genotypic resistance to LAM. TDF resulted in a more rapid and greater decline in HBV DNA levels compared with ADV (-5.5 vs

**Table 3. Summary of tenofovir studies in hepatitis B virus infection.**

| Effect Studied | Study design | Key findings | Ref. |
|---|---|---|---|
| Anti-HBV activity in cell culture | *In vitro* study of lamivudine, adefovir, tenofovir, penciclovir and lobucavir sensitivity in HepG2 2.2.15 cells | Adefovir and tenofovir retained significant antiviral activity when the cells were exposed for only a short time | [23] |
| *In vitro* susceptibility of lamivudine-resistant HBV to adefovir and tenofovir | *In vitro* study of drug sensitivity of lamivudine-resistant HBV in HepG2 cells | Lamivudine-resistant HBV with rtL180M and rtM204V mutations had 2.85- and 3.3-fold increase in $IC_{50}$ with adefovir and tenofovir, respectively. Adefovir and tenofovir have activity against lamivudine-resistant strains of HBV | [59] |
| Intracellular metabolism and activity against HBV | *In vitro* study in HepG2 cells | Tenofovir $EC_{50}$ was 1 μM, TDF $EC_{50}$ was 0.02 μM and intracellular half-life was 95 h | [7] |
| Susceptibility of antivirals to HBV strains resistant to lamivudine and adefovir | *In vitro* study of susceptibility of tenofovir to HBV with rtL180M, M204V and/or N236T mutations | Triple mutant showed a sixfold decreased susceptibility to adefovir and fourfold decrease to tenofovir | [5] |
| Pharmacokinetics of tenofovir in patients with hepatic impairment | Single-dose pharmacokinetic study in patients with hepatic insufficiency due to non-HBV/HCV etiologies | Tenofovir pharmacokinetics are not altered in patients with mild or moderate hepatic insufficiency | [33] |
| Efficacy of tenofovir in HIV–HBV-co-infected patients failing interferon-α and lamivudine | A 24-week pilot study of six patients who failed lamivudine and interferon-α | HBV DNA load decreased by 3.1 and 4.3 $\log_{10}$ copies/ml by 12 and 24 weeks, respectively | [60] |
| Comparison of adefovir and tenofovir in lamivudine-resistant HBV infection | Lamivudine-resistant patients (n = 53) with HBV DNA > $10^6$ copies/ml treated with adefovir or tenofovir | HBV DNA levels declined more rapidly and ALT levels normalized more rapidly in tenofovir-treated patients | [31] |
| Efficacy of tenofovir in HBV–HIV-co-infected patients | Retrospective, multicenter cohort study of HBsAg-positive/HIV-coinfected patients who received tenofovir as part of an antiretroviral regimen | Median reduction of serum HBV DNA was 4.56 $\log_{10}$ copies/ml in HBeAg-positive patients and 2.53 $\log_{10}$ copies/ml in HBeAg-negative patients | [35] |
| HBV dynamics in patients with lamivudine-resistant HBV mutants | Chronic hepatitis B patients (n = 11) with breakthrough HBV DNA on lamivudine received TDF 300 mg/day while maintaining existing therapy | TDF treatment resulted in a HBV DNA decrease of 2.54-log after 4 weeks and 4.95-log after 24 weeks. TDF blocked HBV replication in patients with lamivudine-resistant mutants | [29] |
| HBV dynamics in HIV–HBV-co-infected patients | Prospective, open-label study in HIV–HBV-co-infected patients (n = 28) starting TDF-containing regimen to assess long-term HBV dynamics | HBV DNA load declined by mean of 4.6 log copies/ml during a mean of 71 weeks. Baseline factors associated with rapid initial decline of HBV DNA include high HBV load, positive HBeAg and YMDD mutations. Factors associated with increasing time to reach HBV–DNA levels <200 copies/ml include high HBV load and positive HBeAg | [28] |
| Comparison of tenofovir and adefovir in patients with lamivudine-resistant HBV | Case series of patients with chronic hepatitis B (n = 109) with viral breakthrough on lamivudine given TDF or ADV for 6 months or longer | Mean reduction of HBV viral load greater with TDF than ADV at 6 and 12 months | [30] |
| Comparison of noninferiority of TDF compared with ADV in lamivudine-resistant HBV and HIV patients | Randomized controlled trial of 52 HBV–HIV-co-infected individuals, 94% lamivudine resistant given TDF or ADV for 96 weeks | The mean time-weighted average change in $DAVG_{48}$ was -4.44 $\log_{10}$ copies/ml for TDF and -3.21 $\log_{10}$ copies/ml for ADV | [27] |
| Outcome of HIV–HBV-co-infected patients treated with HAART including anti-HBV active drugs | Retrospective analysis of 79 HIV–HBV co-infected patients treated with lamivudine (37%) or lamivudine and tenofovir (58%) | Undetectable plasma HIV-RNA levels (OR: 4.58; 95%CI:1.25–16.78) and greater CD4 gains while on HAART (OR: 1.003; 95% CI: 1.000–1.006) were associated with undetectable serum HBV DNA at end of follow-up | [61] |

*ADV: Adefovir dipivoxil; ALT: Alanine aminotransferase; CI: Confidence interval; $DAVG_{48}$: Serum HBV DNA from baseline to week 48; HAART: Highly active antiretroviral therapy; HBV: Hepatitis B virus; HCV: Hepatitis C virus; OR: Odds ratio; TDF: Tenofovir disoproxil fumarate; YMDD: Tyrosine–methionine–aspartate–aspartate.*

-2.8 $\log_{10}$ copies/ml at 48 weeks, respectively). No differences in viral response was found between HBV-infected and HIV–HBV-co-infected patients [31]. In a randomized, controlled trial of TDF and ADV in patients co-infected with HIV and HBV, TDF has been shown to be efficacious after 48 weeks of therapy in LAM-resistant and wild-type HBV [27]. The mean time-weighted average change in serum HBV DNA from baseline to week 48 ($DAVG_{48}$) was -4.44 $\log_{10}$ copies/ml for TDF and -3.21 $\log_{10}$ copies/ml for ADV.

## Pharmacokinetics & metabolism

The majority of the available data on the pharmacokinetics of tenofovir are based on clinical trials in patients infected with HIV-1. The oral bioavailability is approximately 21–25% in the fasted state and 34–39% in the fed state [16]. The pharmacokinetics are proportional over the dose range of 75 to 600 mg, and are not affected with multiple dosing. The apparent volume of distribution is approximately 1.3 l/kg and the serum protein binding is approximately 7.2%. **Table 4** summarizes the key tenofovir pharmacokinetic parameters. The pharmacokinetics of an intravenous formulation of PMPA was evaluated in 20 HIV-infected adults. Following a single dose, the maximal serum concentration ($C_{max}$) was dose proportional at 2.7 ± 0.09 and 9.1 ± 2.1 µg/ml in the 1 and 3 mg/kg doses, respectively. The mean AUC was also dose proportional at 4.41 ± 0.93 and 16.6 ± 6.05 µg·h/ml in the 1 and 3 mg/kg groups, respectively. The renal clearance ($CL_R$) in the 1 and 3 mg/kg groups was 161 ± 60.6 and 164 ± 51 ml/h/kg, while the calculated creatinine clearance ($CL_{CR}$) was 81.2 ± 12.3 ml/h/kg. The large $CL_R$ relative to glomerular filtration suggests that PMPA undergoes active tubular secretion by the kidneys [15].

Tenofovir is eliminated primarily by the kidneys via glomerular filtration and active tubular secretion. Following multiple oral dosing, approximately 32% of the dose is recovered in the urine over 24 h [32]. The elimination half-life is approximately 12–18 h. The elimination of tenofovir is altered in patients with renal dysfunction. The clearance of tenofovir decreased, while the $C_{max}$ and $AUC_{0-\infty}$ increased in patients with declining renal function (**Table 5**). Thus, the dosage of TDF should be adjusted in patients with renal dysfunction (**Table 6**).

The pharmacokinetics of TDF were evaluated in healthy subjects with hepatic insufficiency due to non-HBV/HCV etiologies. Following a single 300-mg dose, the pharmacokinetic parameters evaluated were not significantly altered in patients with mild or severe hepatic impairment (**Table 7**) [33]. No dosage adjustment is necessary in patients with hepatic impairment.

## Clinical efficacy

TDF 300 mg, while licensed for the treatment of HIV-1, has been shown in one randomized, controlled trial and a number of case series to be active in mono- and co-infected HBV patients. A prospective, randomized, double-blind, placebo-controlled trial of daily ADV 10 mg versus TDF 300 mg was performed in

**Table 4. Tenofovir pharmacokinetic parameters.**

| Pharmacokinetic parameter | Value |
|---|---|
| Bioavailability (%) | ~25 (fasted)<br>~40 (fed) |
| Volume of distribution (l/kg) | 1.3 ± 0.6 |
| Protein binding (%) | <0.7% (plasma)<br>7.2 (serum) |
| $T_{max}$ (h) | 1.0 ± 0.4 (single dose, fasted) |
| $C_{max}$ (mg/ml) | 296 ± 90 (single dose, fasted)<br>326 ± 119 (multiple dose, fed) |
| Half-life (h) | 17 |
| $CL_{renal}$ (ml/min) | 243.5 ± 33.3 |
| CL/F (ml/min) | 1043 ± 115.4 |
| AUC (ng • h/ml) | 2287 ± 685 (single dose, fasted)<br>3324 ± 1370 (multiple dose, fed) |

*$CL_{renal}$: Renal clearance; $C_{max}$: Maximum serum concentration; F: Oral bioavailability; $T_{max}$: Time to $C_{max}$.*

**Table 5. Pharmacokinetic parameters in patients with renal dysfunction.**

| Pharmacokinetic parameter | Baseline creatinine clearance (ml/min) | | | |
|---|---|---|---|---|
| | *>80* | *50–80* | *30–49* | *12–29* |
| $C_{max}$ (ng/ml) | 335.4 ± 31.8 | 330.4 ± 61.0 | 372.1 ± 156.1 | 601.6 ± 185.3 |
| $AUC_{0-\infty}$ (ng • h/ml) | 2184.5 ± 257.4 | 3063.8 ± 927.0 | 6008.5 ± 2504.7 | 15984.7 ± 7223.0 |
| CL/F (ml/min) | 1043.7 ± 115.4 | 807.7 ± 279.2 | 444.4 ± 209.8 | 177.0 ± 97.1 |
| $CL_{renal}$ (ml/min) | 243.5 ± 33.3 | 186.6 ± 27.5 | 100.6 ± 27.5 | 43.0 ± 31.2 |

*AUC: Area under the curve to infinite time; CL: Clearance; $CL_{renal}$: Renal clearance; $C_{max}$: Maximum serum concentration; F: Oral bioavailability.*

patients with HBV and HIV co-infection, on stable antiretroviral therapy, with serum HBV DNA of at least 100,000 copies/ml and plasma HIV-1 RNA of 10,000 copies/ml or less. Of the 52 patients randomized, the majority had compensated liver disease and were hepatitis B e-antigen (HBeAg) positive, with LAM resistance. The mean time-weighted average change in $DAVG_{48}$ was -4.44 $log_{10}$ copies/ml for TDF and -3.21 $log_{10}$ copies/ml for ADV. There was no difference in toxicity between the two treatment arms, with 11 subjects (five ADV and six TDF) experiencing 'flares' or elevations of serum ALT on treatment without adverse events in these well compensated patients. Both drugs were safe and efficacious for patients co-infected with HBV and HIV.

TDF has been shown in case studies to have anti-HBV activity in both HBV mono- and co-infected subjects [31] and to rescue HBV-infected patients who have failed treatment with LAM and ADV [34]. In a recent retrospective study of 65 HIV–HBV-co-infected patients treated with TDF 300 mg/day, 80% were HBeAg positive at entry and serum HBV DNA decreased by 4.56 $log_{10}$ copies/ml on TDF [35]. Another cohort series of HBV–HIV-co-infected patients starting an antiretroviral regimen compared those starting TDF plus LAM with those starting TDF as the only active HBV polymerase inhibitor subsequent to LAM. Undetectable HBV DNA less than 1000 copies/ml was not different between the two strategies and was achieved in 19 out of 25 (76%) patients receiving TDF plus LAM and in 42 out of 50 (84%) receiving TDF alone (p = 0.53). Similar loss of HBeAg was observed in nine out of 25 (36%) patients on TDF plus lamivudine and in 12 out of 50 (24%) patients on TDF (p = 0.29). HBsAg loss was found in one out of 25 (4%) and three out of 50 (6%) patients, respectively. Thus, full HBV DNA suppression was achieved in the majority of patients, independent of whether they started combination anti-HBV therapy or sequential therapy over a median treatment period of 116 weeks [36]. No randomized, controlled studies of combination therapy are available as yet.

## Safety & tolerability

Most of the clinical safety and tolerability experience with TDF is derived from its use for the treatment of HIV infection in conjunction with other antiretrovirals. TDF is generally well tolerated in this patient population. Commonly reported adverse events include asthenia, pain, nausea, diarrhea, flatulence and dizziness. Nephrotoxicity is a dose-limiting toxicity that is associated with the use of cidofovir and high-dose ADV [37–39]. Milder forms of injury without cellular necrosis or apoptosis, such as Fanconi-like syndrome and distal

**Table 6. Dosage adjustment for patients with renal dysfunction.**

| | Creatinine clearance (ml/min) | | | Hemodialysis |
|---|---|---|---|---|
| | *≥50* | *30–49* | *10–29* | |
| TDF 300 mg | Every 24 h | Every 48 h | Twice weekly | Every 7 days or after a total of ~12 h of dialysis |
| TDF 300 mg/ emtricitabine 200 mg | Every 24 h | Every 48 h | Not recommended | Not recommended |

*TDF: Tenofovir disoproxil fumarate.*

**Table 7. Pharmacokinetic parameters in patients with hepatic impairment.**

| Pharmacokinetic parameter | Control (Child's class A) | Moderate impairment (Child's class B) | Severe impairment (Child's class C) |
|---|---|---|---|
| $C_{max}$ (ng/ml) | 223 (120–353) | 289 (163–552) | 305 (210–440) |
| $T_{max}$ (h) | 1.00 (0.5–1.00) | 1.00 (0.5–1.00) | 0.75 (0.5–2.0) |
| Half-life (h) | 17.3 (10.1–23.2) | 17.0 (13.1–19.3) | 18.0 (9.74–26.5) |
| AUC $_{0-\infty}$ (ng • h/ml) | 2050 (1090–4060) | 2310 (1220–4340) | 2740 (1460–5230) |

*AUC $_{0-\infty}$: Area under the curve to infinite time; $C_{max}$: Maximum serum concentration; $T_{max}$: Time to $C_{max}$.*

tubular acidosis, have been associated with acyclic nucleotide phosphonates (e.g., ADV and cidofovir) and foscarnet. Increased cellular uptake mediated by human renal organic transporter (hOAT)1 is believed to cause proximal tubular dysfunction. This has been shown to occur *in vitro* with cidofovir and ADV, but not tenofovir [40]. Unlike other nucleotide phosphonates, TDF appears to have a low nephrotoxic potential and rarely causes serious renal impairment [41]. In a 3-year clinical trial comparing TDF with stavudine in treatment-naive patients, the renal safety profile (serum creatinine and serum phosphorus levels) was similar. No patients experienced grade 4 hypophosphatemia (phosphorus <1 mg/dl) or elevated serum creatinine levels over 6 mg/dl. The incidence of glycosuria and proteinuria were also similar [42,43]. A small but statistically significant rise in the mean time-weighted change from baseline in anion-gap (0.78 mmol/l) and a decrease in the creatinine clearance (-6.8 ml/min) was noted in patients receiving TDF-based highly active antiretroviral therapy (HAART) compared with non-TDF-based HAART [44]. In the randomized, controlled study of ADV and TDF, transient mild hypophosphatemia was noted but no elevations in serum creatinine of at least 0.5 mg/dl above baseline were noted, nor changes in serum creatinine in either arm over the course of the study [27]. However, tenofovir-induced proximal tubulopathies manifesting as normoglycemic glycosuria, mild proteinuria and hypophosphatemia have been reported [45,46]. Tenofovir-related nephrotoxicity typically manifests after approximately 20 weeks of therapy, but resolves after a median of 4.7 weeks following discontinuation of the drug [47].

Human DNA polymerase-γ is the enzyme that is responsible for replication of mitochondrial DNA. Inhibition of DNA polymerase-γ by nucleoside and nucleotide analogues has been implicated in the development of dose-limiting toxicities, such as peripheral neuropathy, pancreatitis, myopathy, lactic acidosis and steatosis. Tenofovir is a weak inhibitor of human DNA polymerase-γ and is incorporated into nascent mitochondrial DNA less efficiently than other nucleoside reverse transcriptase inhibitors [48]. Tenofovir is less cytotoxic compared with other nucleoside analogues, with weak antiproliferative effects on human liver and skeletal muscle cells [40]. The co-administration of TDF and didanosine has been associated with the development of pancreatitis [49,50]. The combination of TDF and didanosine may lead to increased toxicity due to the drug–drug interaction between these two agents. There is increased didanosine exposure when co-administered with tenofovir [51]. Three subjects in one study developed pancreatitis, two of whom received concomitant didanosine (ddI) [27].

The use of tenofovir in patients with chronic hepatitis B infection with or without HIV-co-infection is generally well tolerated. There were no changes in renal function, phosphate levels or serum creatinine reported [29,31]. However, headache and decreased urine volume was reported in one study [33]. The number of patients in these studies were small, making interpretation of the actual incidence of adverse events difficult. There has been one report of a Q215S mutation in the DNA polymerase with resistance to TDF [52].

Decreased bone mineral density has emerged as a long-term consequence among HIV-infected patients [53]. Bone loss has been possibly linked to the use of highly active antiretroviral therapy, particularly those utilizing protease inhibitors [53–55]. Metabolic bone disorders have been observed in animals given high-dose tenofovir [56,57] and in humans [42]. TDF has been associated with a decrease in bone mineral density in children, which may stabilize after 24 weeks. Markers of bone turnover,

such as calcium excretion, are elevated, indicating that TDF may increase bone resorption. Decreases in viral load and young age are correlated with reduced bone mineral density, suggesting that younger treatment responders are at greater risk of tenofovir-related bone toxicity [58].

## Expert commentary

Addition of TDF to the armamentarium for the treatment of HBV infection will be of great value. Resistance to LAM leads to cross resistance to emtricitabine and telbivudine and requires an increased dosage of entecavir. Adefovir resistance begins to emerge after 2 years of therapy, and while there is only one reported case of TDF resistance as yet, more may emerge with time. TDF has been shown to be successful as *de novo* therapy as well as in rescuing nucleoside-resistant and decompensated HBV disease. We await randomized, controlled studies in HBV mono-infected patients and expect that approval for HBV will follow after completion of these studies.

When treating HIV–HBV-co-infected patients, recent Department of Health and Human Services (DHHS) [101] and other expert panel guidelines recommend treating all such HIV–HBV-co-infected patients with two active HBV drugs when HIV or both viruses require treatment. In fact, the panel recommended TDF and emtricitabine (or LAM) as the preferred agents, although TDF does not have FDA approval for HBV management as yet. Co-infected patients who require therapy for HBV but not HIV should not receive any HBV medications with anti-HIV activity; instead, they should be treated with agents with HBV activity alone, such as entecavir, interferon, telbivudine or ADV. There is a theoretical risk of HIV resistance to ADV 10 mg/day, but this has not been shown as yet in *in vivo* or *in vitro* studies. It is important, when changing antiretroviral regimens, to continue agents with anti-HBV activity as there is a risk of 'flares' or marked elevation in transaminases in an immunocompetent patient.

## Regulatory affairs

TDF was approved by the FDA in October 2001 for the treatment of HIV infection. The European Commission granted marketing authorization for TDF in 2002 for all 15 member states of the EU. In addition, TDF was granted marketing approval in Australia, Iceland and Norway in 2002. TDF is currently undergoing Phase III trials for the management of chronic hepatitis B.

Truvada® is a fixed-dose combination of TDF and emtricitabine (Emtriva®) that was approved for use in the USA in August 2004 and in Europe in 2005 for the treatment of HIV-1 infection in adults. Atripla™ (Bristol-Myers Squibb and Gilead Sciences) is a combination product of efavirenz, emtricitabine, and TDF that was approved in July 2006. It is the first single-tablet, once-daily regimen approved for the treatment of HIV infection alone or in combination with other antiretrovirals. Although not approved by the FDA for the treatment of chronic hepatitis B, TDF or the combination product of TDF and emtricitabine (Truvada) can be used for the treatment of chronic HBV infection, and are logical choices as part of an antiretroviral regimen in patients with HIV–HBV co-infection.

### Disclosure

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**Executive summary**

- Tenofovir disoproxil fumarate (TDF) was the first nucleotide analogue approved by the US FDA for the treatment of HIV-1 infection.
- TDF is active against HIV, hepatitis B virus (HBV) and lamivudine-resistant strains of HBV.
- Tenofovir is eliminated by glomerular filtration and active tubular secretion. The dosage of TDF must be adjusted in the setting of renal dysfunction.
- The pharmacokinetics of TDF are not significantly altered in mild-to-moderate liver disease. No dosage adjustment is necessary in patients with hepatic dysfunction.

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