Tenofovir in the treatment of chronic hepatitis B

Chronic hepatitis B (CHB) is prevalent worldwide. It may lead to serious complications including cirrhosis and is the most common risk factor for hepatocellular carcinoma (HCC). Treatment for CHB could potentially be lifelong, and it is mandatory that drug therapies for CHB be efficacious and safe. Tenofovir disoproxil fumurate (TDF) is a nucleotide analog reverse transcriptase inhibitor that was approved in 2008 by the US FDA for the treatment of CHB in adults. Clinical trials of TDF have demonstrated superior efficacy with potent antiviral properties and a high barrier to resistance in addition to a good safety profile. This review will detail results of clinical trials, which have evaluated both efficacy and safety of TDF in the treatment of CHB and include a discussion on the comparative effectiveness of TDF with other licensed treatments for CHB.

KEYWORDS: adverse drug reaction ■ chronic hepatitis B ■ drug interactions ■ hepatitis B virus ■ nephrotoxicity ■ osteomalacia ■ tenofovir disoproxil fumarate

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An estimated 350 million individuals worldwide are chronically infected with hepatitis B virus (HBV) [1]. Prevalence rates of hepatitis B surface antigen (HBsAg) in cross-sectional studies range from 0.3–1.5% in North America and Western Europe [2,3] to as high as 9–12% in some regions of Asia and Africa [2,4]. Although most patients chronically infected with HBV do not develop clinically significant liver disease, serious sequelae such as, cirrhosis, and hepatocellular carcinoma (HCC) will develop in 15–40% during their lifetime [5].

A large population-based study of predominantely males with chronic hepatitis B (CHB), conducted in Taiwan, showed that persistence of HBeAg (+) status over the age of 30 years was associated with a high 9-year risk of HCC [6]. The Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer (REVEAL) study indicated that an elevated serum baseline HBV DNA level in middle-aged men was a strong risk predictor for subsequent HCC [7]. These observations may suggest that effective control of viral replication after antiviral therapy may help reduce the complications of CHB, at the very least in older Asian men. Early randomized control trials (RCT) have indicated that continued viral suppression in those who had active advanced CHB prior to the onset of therapy does lead to improved biochemical, viral, histologic and survival outcomes and suggest a decrease in rate of HCC [8,9].

A total of seven drugs have been evaluated and licensed to treat CHB, including standard and PEGylated IFN-α, lamivudine (LAM), adefovir (ADV), entecavir (ETV), telbivudine and tenofovir disoproxil fumurate (TDF). Before initiating any oral antiviral medication, the advantages and disadvantages of therapy need to be discussed with the patient. It is especially hard for young men and women to comprehend the long-term benefit of intervening with treatment when they feel reasonably well. The disadvantages of treatment include the risk of drug resistance over time, the risk of sudden flare if their medications are stopped at an inappropriate time, and side effects. The ideal drug needs to be potent, possess a high barrier to resistance, lack significant toxicity and have minimal side effects. The most recently licensed drugs for treatment of CHB, tenofovir and entacavir, go a long way to fulfilling most of these characteristics and are the preferable first-line agents in the treatment of CHB [10]. This article will focus on specific aspects of the published clinical trials, which have evaluated both efficacy and safety of TDF in the treatment of CHB and include a discussion on the comparative effectiveness of TDF with other treatments for CHB.

Pharmacology of TDF

■ Mechanism of action

Tenofovir disoproxil fumurate, an oral prodrug, is an acyclic nucleotide phosphonate diester analogue of adenosine 5′-monophosphate. During absorption from the gastrointestinal tract, TDF is hydrolyzed to tenofovir, which is phosphorylated to the active drug tenofovir diphosphate

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once taken up by hepatocytes. TDF inhibits the activity of HBV DNA polymerase by competing with the natural substrate (nucleotide deoxyadenosine 5′triphosphate) for incorporation into the viral DNA, terminating DNA chain elongation, thereby inhibiting DNA replication [11]. It is a weak inhibitor of mammalian DNA polymerase and mitochondrial DNA polymerase. At concentrations of up to 300 µmol/l, it has also shown no effect on the synthesis of mitochondrial DNA or the production of lactic acid in *in vitro* assays.

Pharmacokinetics & drug interactions

The oral bioavailability of TDF ranges between 25% in fasted individuals to 40% following a high-fat meal, with a serum and intracellular half-life of 17 and 10–50 h, respectively. It is eliminated largely unchanged via the kidneys and 70–80% of the dose can be recovered unchanged in the urine up to 72 h after administration. In the proximal renal tubules, the drug is initially secreted from plasma to tubular cell by the human organic anion transporters (hOAT1 and 3) [12]. The drug is then secreted from the tubular cell to the tubular lumen by the multiple drug resistant (MDR4) apical efflux pump. Accordingly, TDF dosing has to be adjusted in patients with moderate-to-severe renal impairment (creatinine clearance [CrCl] <50 ml/min). In patients with impaired hepatic function, dosage adjustment is not required as TDF does not undergo hepatic metabolism for its elimination.

As TDF is not metabolized by cytochrome P450 (CYP450) enzymes, TDF drug interactions mediated via CYP450 enzymes are minimal. Serum concentrations can increase if TDF is coadministered with drugs that are nephrotoxic or compete for active renal tubular secretion (e.g., antiherpetics), subsequently potentiating TDF toxicity. TDF has some drug interactions of clinical importance in HIV-HBV–coinfected patients; with dosage adjustments required for atazanavir and didanosine. A summary of potential drug interactions are reviewed in Table 1.

Clinical trials

Although the definitive goal of treatment of any chronic infection is the eradication of the infectious agent, this cannot be achieved in CHB as circular covalently closed DNA remains in hepatocytes lifelong and may reactivate (even in those who lose HBsAg). Because progression to cirrhosis and/or HCC is slow, these are unrealistic end points when the antiviral therapy is prescribed early in the course of the disease. Treatment of those with already advanced hepatic fibrosis at the time of initiating antiviral therapy, does improve survival and possibly reduction in HCC [8].

Alternative surrogate end points to using these hard clinical end points include:

- Biochemical (aminotransferase levels);
- Virological (HBV DNA levels, clearance of HBeAg +/- HBsAg);
- Histological (based on histological scoring systems) (Table 2) [13].

Natural history studies indicate that loss of HBsAg heralds sustained control of viral replication and is associated with improved survival and reduced risk of HCC [14,15]. Hence HBsAg loss with or without seroconversion to anti-HBs is the most reliable surrogate end point but its uncommon occurrence limits its utility for evaluation of therapies for CHB.

Phase III randomized controlled trials

The efficacy of TDF for treatment of CHB is being investigated in two large randomized, double-blind, multicenter, Phase III clinical trials with exactly the same trial design planned to last for at least 7 years [16]. A summary of the early trial results using TDF in CHB monoinfection are reviewed in Table 3. In this study, 375 HBeAg (-) patients (102 trial) with compensated liver disease were randomized to receive either TDF 300 mg/day versus ADV 10 mg/day, and 266 HBeAg (+) patients (103 trial) were randomized to receive either TDF 300 mg/day versus ADV 10 mg/day [16]. In this large study, a minority of patients had received treatment with either interferon, or nucleoside analogs in the past. The primary efficacy end point was a combined one which used both virologic (HBV DNA <400 c/ml) and histologic (reduction in Knodell necroinflammatory score by ≥2 points, without worsening in Knodell fibrosis response after 1 year of treatment) markers. TDF was demonstrated to be significantly superior in achieving this combined end point (Study 102 – ADV 49%, TDF 71%; Study 103 – ADV 12%, TDF 67%). More patients in Study 103 who received TDF, achieved HBsAg loss (3 vs 0%), while 2 patients (1.2%) also developed antibodies (HBsAb) by week 48. The results of these two trials are summarized in Table 4. After 48 weeks in the trial, all patients were maintained or switched to TDF with the option to continue the trial for 7 years.

Table 1. Potential drug interactions involving tenofovir disoproxil fumarate.

Coadministered drug	Effect on TDF	Effect on coadministered drug	Comment
Abacavir	↔	↑	
Atazanavir	↑	↓	
Didanosine	↔	↑	Avoid coadministration due to increased risk of pancreatitis
Indinavir	↑	↓	
Lopinavir–Ritonavir	↑		
Emtricitabine	↔	↑	Not clinically significant
Entacavir	↔	↑	Not clinically significant
Lamividine	↔	↓	Not clinically significant
Tacrolimus	↑		Close monitoring of renal function if coadministered
Antiherpetics[†]	↑	↑	Clinical significance unknown

[†]Acyclovir, valacyclovir, ganciclovir, valganciclovir.
↑: Increases; ↓: Decreases; ↔: No change; TDF: Tenofovir.

The results of this same large study (Study 102 and 103) at both 144 weeks [17] and 192 weeks (18, 19; abstract only) are available. Based on the discretion of the investigator, emtricitabine (FTC) could be added at week 72 and onward for confirmed HBV DNA ≥400 copies/ml at two consecutive visits. Based on intention to treat (ITT) analysis at 144 weeks, TDF treatment maintained suppression of HBV DNA in 87% of HBeAg (-) (87% TDF-TDF, 88% ADV-TDF) and in 71% of HBeAg (+) (72% TDF-TDF; 71% ADV-TDF) [17]. Among the patients who were viremic at week 72 or later, 34/49 (HBeAg 3/11, HBeAg+ 31/38) had FTC added to their TDF monotherapy with viral suppression in 59% at 144 weeks (HBeAg(-) 3/3; HBeAg(+) 17/31). Of those who remained viremic beyond week 72 maintained on TDF monotherapy (15/49), 67% achieved virologic suppression at week 144. Patient retention was good (87% and 80% for the HBeAg (-) and HBeAg (+) cohorts respectively) up until week 144. Cumulatively, 8% of HBeAg (+) patients lost HBsAg while no patient with HBeAg (-) disease experienced HBsAg loss as of week 144.

Preliminary data at 192 weeks, using ITT analysis, demonstrates TDF treatment maintained suppression of HBV DNA in 86% of the HBeAg (-) patients (85% TDF-TDF, 87% ADV-TDF) and in 77% of HBeAg (+) patients (74% TDF-TDF; 84% ADV-TDF) [18,19]. Of patients originally recruited into this trial, retention at week 192 was 84 and 74% respectively, by which time 10% of patients, who had been HBeAg (+) at the start, cumulatively lost HBsAg and 7.5% seroconverted to anti-HBs, whereas these end points have not to date been observed in those who received TDF for treatment of HBeAg (-) CHB.

Take Home Message: In patients with CHB monoinfection, TDF therapy provides effective long term viral suppression (HBeAg- 86%, HBeAg + 77% at 192 weeks). Prolonged viral suppression with TDF was associated with HBsAg loss in those treated for HBeAg (+) CHB (10% at 192 weeks) but not in those with HBeAg (-) CHB.

TDF in patients with prior failure or resistance to other nucleoside/nucleotide analogs (NA)

A case series of TDF treated HBV-monoinfected patients who experienced viral breakthrough during therapy with LAM (defined as ≥1 log increase of HBV DNA from nadir) and who subsequently sustained an insufficient virologic response to ADV monotherapy (defined as: reduction in HBV DNA of <1 log copy/ml, $>10^6$ copies/ml after 4 months, or $>10^5$ copies/ml after 12 months of treatment), showed that tenofovir was a highly effective rescue therapy [20]. After a median of 12 months of therapy, 20 patients were switched to TDF monotherapy, with a subsequent median decrease in HBV DNA level of 3.8 log copies/ml becoming undetectable in 19 out of 20 patients. The one patient who remained viremic received a reduced dose of TDF dose because of renal insufficiency, present prior to initiating TDF therapy.

In vitro data suggests that HBV strains detected in those with ADV resistance, namely rtN236T and rtA181V mutations, have reduced

Table 2. Surrogate end points on treatment for chronic hepatitis B infection.

Category	Surrogate end point	Clinical significance
Biochemical	Normalization of ALT/AST	Fluctuation (especially HIV–HBV) Not specific to CHB
Virological	HBV DNA suppression	Poor durability of treatment
Histological	Improvement in liver inflammation and/or fibrosis	Clinically relevant Subject to sampling error Fibrosis slow to change Durability of treatment?
Serological	HBeAg loss +/- development of anti-HBe	Predicts favorable outcome if maintained off therapy HBeAg-negative disease may develop
	HBsAg loss +/- development of anti-HBs	Excellent prognosis Relatively rare event with any current therapies

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CHB: Chronic hepatitis B; HBeAg: Hepatitis B e antigen; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus.

susceptibility to TDF (two- to three-fold) [21,22], which would suggest that TDF could be less effective for ADV-resistant HBV than for LAM resistance. This is supported by a retrospective cohort study of 131 HBV-monoinfected patients with prior failure to different NA treatments (failure defined as <1 log decline in HBV DNA in the first 3 months of treatment initiation, measurable HBV DNA after 6 months treatment, or recrudescence of HBV DNA >1 log after initial decrease), who then received TDF monotherapy [23]. Resistance analysis revealed genotypic LAM and ADV resistance in 62 and 19% of patients, respectively. The overall cumulative proportion of patients achieving HBV DNA levels <400 copies/ml was 79% after a mean treatment duration of 23 months. Those with ADV genotypic resistant HBV were significantly less likely to achieve HBV DNA levels <400 copies/ml over the complete observation period than those who did not have genotypic ADV-resistant virus (54 vs 100%), whereas a history of prior treatment with ADV in patients without ADV genotypic resistance or add on combination therapy with LAM appeared to have no influence on subsequent responsiveness to TDF.

By contrast, a prospective open-label study looking at 60 patients with LAM resistance who were subsequently observed to have an inadequate response to ADV therapy (defined as >5 log copies/ml in HBeAg+ or >4 logs copies/ml in HBeAg- after 6 months ADV therapy), did not find an association between subsequent TDF therapy response and baseline ADV genotypic resistance [24]. In this study, 38 patients taking ADV monotherapy were switched to TDF therapy (with the option of also adding LAM if HBV DNA >10^4 copies/ml at ≥6 months of TDF therapy), while 22 taking LAM and ADV, were changed to LAM and TDF. At baseline, substitutions conferring resistance to LAM or ADV were present in 33 and 28% of patients respectively. A total of 64% of patients on TDF therapy had an undetectable HBV DNA (<80 copies/ml) at 96 weeks. The response was independent of combination TDF-LAM therapy or mutations conferring LAM or ADV resistance.

TDF in combination therapy for ADV drug resistant CHB

A double-blind, randomized controlled trial, comparing TDF versus TDF plus FTC in ADV-resistant HBV, found there was no benefit in terms of achieving viral suppression (HBV DNA <400 copies/ml) of combination therapy over TDF monotherapy [25]. This study included 105 patients with persistent viral replication while taking ADV (defined as HBV DNA >1000 copies/ml after 6 months therapy). In the TDF monotherapy group, patients with HBV DNA >400 copies/ml at week 24 were changed to open-label TDF-FTC. At week 48, intention to treat (ITT) analysis revealed 81% of patients in each treatment arm had an HBV DNA level <400 copies/ml. When considering intensification to open label TDF-FTC as failure in ITT analysis, there was no significant difference between the groups (TDF-FTC 66%, TDF 77%).

TDF in patients with liver failure

The introduction of effective antiviral therapy for CHB has meant that decompensated liver disease in CHB is rarely encountered, thus experience with TDF in naive patients with chronic liver failure is limited. TDF combined with

Table 3. Summary of studies of tenofovir in hepatitis B virus monoinfection.

Study design	Number of patients (%)		Median duration TDF treatment (weeks)	HBV DNA decrease (log_{10} copies/ml)	Number of patients (%)					Ref.
	Hepatitis B e antigen positive	Previous resistance or failure			HBV undetectable (169–400 c/ml)	Hepatitis B e antigen loss	Hepatitis B e antibody seroconversion	Hepatitis B surface antigen loss	Hepatitis B surface antibody seroconversion	
Tenofovir vs adefovir (NA naive)										
Double-blind randomized controlled trial (n = 266)	266 (100)	N/A	48	N/A	TDF 134/176 (76) ADV 12/90 (13)	N/A	TDF 32/153 (21) ADV 14/80 (18)	TDF 5/158 (3) ADV 0 (0)	TDF 2/158 (2) ADV (0)	[16]
Double-blind randomized controlled trial (n = 375)	0 (0)	N/A	48	N/A	TDF 233/250 (93) ADV 79/125 (63)	N/A	N/A	TDF 0 (0) ADV 0 (0)	TDF 0 (0) ADV 0 (0)	[16]
Prospective open label TDF-TDF, ADV-TDF	238 (44)	N/A	144	N/A	eAg + 181/254 (71) eAg – 313/359 (87)	34% N/A	26% N/A	20 (8) 0 (0)	15 (6) 0 (0)	[17]
Prospective open label TDF-TDF, ADV-TDF	198 (37)	N/A	192	N/A	eAg + 77% eAg – 86%	41% N/A	31% N/A	10% N/A	7.5% N/A	[18,19]
Tenofovir in NA experienced										
Retrospective case series (n = 20)	19 (95)	20 (100) LAM 20 (100) ADV	48	3.8	19 (95)	4/20 (20)	0 (0)	1/20 (5)	1/20 (5)	[20]
Retrospective cohort (n = 131)	85 (65)	121 (93) LAM 110 (85) ADV 3 (2) ETV	92	7.6	79%	20/85 (24)	N/A	4/131 (3)	N/A	[23]
Prospective open label TDF+LAM vs TDF (n = 60)	40 (67)	60 (100) LAM 60 (100) ADV	96	TDF + LAM = 4.35 TDF = 4.86 Overall 4.74	38/59 (64.4)	4/60 (12.1)	0 (0%)	0 (0%)	0 (0%)	[24]
TDF vs TDF and emtricitabine										
Double-blind randomized controlled trial (n = 105)	77 (73)	105 (100) ADV 14 (13) LAM	48	TDF-FTC = 3.54 TDF = 3.58	TDF-FTC = 66% TDF = 77%	TDF/FTC = 4 (8) TDF = 4 (8)	N/A	TDF/FTC = 0 (0) TDF = 1 (2)	N/A	[25]

ADV: Adefovir; ETV: Entecavir; FTC: Emtricitiabine; LAM: Lamivudine; NA: Nucleoside analog; N/A: Not available; TDF: Tenofovir.

Table 3. Summary of studies of tenofovir in hepatitis B virus monoinfection (cont.).

Study design	Number of patients (%)		Median duration TDF treatment (weeks)	HBV DNA decrease (log_{10} copies/ml)	Number of patients (%)				Ref.
	Hepatitis B e antigen positive	Previous resistance or failure			HBV undetectable (169–400 c/ml)	Hepatitis B e antigen loss	Hepatitis B e antibody seroconversion	Hepatitis B surface antigen loss	Hepatitis B surface antibody seroconversion	
TDF in liver failure										
Case series (n = 6)	6 (100)	6 (100) LAM 6 (100) ADV	66	N/A	6/6	N/A	N/A	N/A	N/A	[26]
Double-blind randomized controlled trial; TDF vs TDF/FTC vs ETV (n = 112)	39 (35)	21 (19) LAM	48	TDF = 3.3 TDF-FTC = 3.72 ETV = 3.24	TDF = 31/44 (71) TDF-FTC 36/41 (87.8) ETV 16/22 (72.7)	TDF 3/45 (7) TDF-FTC 4/45 (9) ETV = 0 (0)	TDF 3/45 (7) TDF-FTC 2/45 (4) ETV = 0 (0)	0 (0)	0 (0)	[27]
TDF in acute on chronic liver failure										
Randomized controlled trial; TDF vs placebo (n = 27)	15	15 (56)	N/A	TDF = 3.04 IU/ml	TDF = 3/8 (37) Placebo = 0/7 (0)	TDF = 3/8 (37) Placebo = 0/7 (0)	N/A	N/A	N/A	[30]

ADV: Adefovir; ETV: Entecavir; FTC: Emtricitabine; LAM: Lamivudine; NA: Nucleoside analog; N/A: Not available; TDF: Tenofovir.

LAM was evaluated as rescue therapy for ADV-resistant chronic HBV in six HBeAg-positive patients with advanced CHB [26]. Three patients had compensated cirrhosis, and three had decompensated cirrhosis. These patients initially had virologic breakthrough while taking LAM monotherapy, and were changed to ADV monotherapy, with subsequent development of ADV resistance (defined as >1 log copies/ml increase in HBV DNA from nadir after initial >2 log decline) or nonresponse (defined as inability to decrease HBV DNA by >1 log copies/ml after 6 months of treatment). After 12 months of therapy with TDF 300 mg/day, HBV DNA levels had become undetectable in all six, ALT levels normalized in four out of six patients, and most importantly two out of three patients with decompensated liver disease had improvement in their Child-Pugh (CTP) scores.

There is one published double-blind, randomized, controlled Phase II study, which included 112 monoinfected patients with HBV and decompensated CHB (Child Turcotte Pugh [CTP] score 7–12) randomized to TDF, TDF + FTC, or ETV (0.5 mg if <6 months of LAM exposure and no LAM genotypic resistance, 1 mg if >6 months of LAM exposure and/or history of LAM genotypic resistance) [27]. At baseline 19% had genotypic resistance to LAM (TDF 18%, TDF-FTC 22%, ETV 14%). The primary end points were safety and included tolerability failures (defined as permanent discontinuation of study drug due to a treatment-emergent adverse event) and/or confirmed increases in serum creatinine greater than 0.5 mg/dl above baseline and/or serum phosphorus values less than 2.0 mg/dl. In this study, both tolerability failure (TDF 6.7%, TDF-FTC 4.4%, ETV 9.1%, p = 0.622) and confirmed changes to creatinine/phosphorus (TDF 8.9%, TDF-FTC 6.7%, ETV 4.5%, p = 1.0) were infrequent. Secondary end points were descriptively summarized and included: fall in HBV DNA, ALT and HBeAg/HBsAg loss and seroconversion, CTP, and model for end-stage liver disease (MELD) scores. At week 48, HBV DNA was <400 copies/ml in 70.5% (TDF), 87.8% (TDF-FTC), and 72.7% (ETV) of patients. CTP and MELD scores improved in all groups. No patient achieved HBsAg loss by week 48.

TDF in patients with acute on chronic liver failure

A significant number of patients with spontaneous acute exacerbation of CHB may present with liver failure (a condition defined

Table 4. Summary of studies 102 and 103, week 48 results 19.

End point	Study 0102 HBeAg (-)			Study 0103 HBeAg (+)		
	Tenofovir (n = 250)	Adefovir (n = 125)	SS	Tenofovir (n = 176)	Adefovir (n = 90)	SS
Complete response (%)	71	49	Yes	66	12	Yes
HBV DNA <400 copies/ml, ITT (%)	93	63	Yes	76	13	Yes
ALT normalization (%)	76	77	No	68	54	Yes
Histological response (%)	72	69	No	74	68	No
HBeAg seroconversion (%)	NA	NA	NA	21	18	No
HBsAg loss (%)	0	0	NA	3.2	0	Yes

ALT: Alanine aminotransferase; HBeAg: Hepatitis B e antigen; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; ITT: Intent-to-treat analysis; NA: Not applicable; SS: Statistically significant.

as acute-on-chronic liver failure [ACLF]). Previously, liver transplantation was the only definitive therapy available to salvage this group of patients as antiviral therapy has not been found to be superior to historical controls [28,29].

A recent randomized study comparing TDF (14 patients) and placebo (13 patients) in patients with CHB who developed ACLF secondary to spontaneous reactivation (defined as: rise in ALT 5X ULN, HBV DNA >10^5 c/ml, bilirubin >5 mg/dl, INR >1.5, development of ascites +/- hepatic encephalopathy <4 weeks; previously diagnosed or undiagnosed chronic liver disease), found that TDF was a highly efficacious therapy in this group [30]. It is not clear if patients had ever received oral antiviral treatment for their CHB in the distant past (excluding patients receiving HBV therapy in preceding 12 months). TDF was found to be significantly superior in achieving the primary end point of survival at 3 months (TDF 57%, placebo 15%). Undetectable HBV DNA (<50 IU/ml) was achieved in 37% of TDF patients at 12 weeks compared to 0% in the placebo group. In addition, there was a significant difference in CTP and MELD scores at day 45 and day 90.

TDF resistance

An important issue to be considered when evaluating the efficacy of any drug in the treatment of CHB is the risk of developing drug resistance. TDF appears to have a favorable resistance profile in patients with CHB, and to date, there have been no reports of virological resistance to TDF among HBV monoinfected patients [31]. *In vitro* studies have suggested ADV associated resistance mutations A181V and N236T have decreased susceptibility to TDF [21,22], but as already discussed, unlikely to be clinically relevant.

Resistance analyses from the pivotal Phase III trial of TDF [18] have not demonstrated any HBV polymerase gene mutations associated with TDF resistance in patients treated with TDF up to 144 weeks [31]. Resistance analyses were performed for all patients at baseline, viremic (>400 copies/ml HBV DNA) patients at week 144 (TDF-TDF 34, ADV-TDF 19), and patients who remained viremic after the addition of FTC (TDF-TDF 7/20, ADV-TDF 5/14). Virological breakthrough (defined as two consecutive HBV DNA values >400 copies/ml if the HBV DNA value was previously <400 copies/ml or a confirmed increase >1 log copies/ml from the HBV DNA nadir) on TDF monotherapy was uncommon at 144 weeks (13/426, 3%) and could be ascribed nonadherence, as determined by undetectable plasma TDF levels, in most (11/13, 85%).

All patients with virological breakthrough remained phenotypically sensitive to inhibition by TDF. Persistent viremia through week 144 was rare (5/641, 0.8%) and was not associated with virological resistance to TDF by population or clonal analyses.

Clinical trials in HIV–HBV coinfected patients

The published literature regarding TDF treatment in coinfected patients with HBV and HIV is fairly heterogeneous, most are small open-label studies and some retrospective analyses of HIV–HBV coinfected individuals. The results of TDF for HBV in HIV–HBV coinfected patients are summarized in Table 5 [32–47].

TDF monotherapy versus combination therapy in ARV naive

A prospective, nonblinded but randomized, controlled trial in antiretroviral naive HIV–HBV coinfected patients did not demonstrate any advantage of combination TDF and LAM over TDF monotherapy [32]. A total of 36 patients were randomized to LAM (13 patients), TDF (12 patients), or TDF plus LAM (11 patients)

as part of their antiretroviral regimens. By intention to treat analysis, overall there was no statistically significant difference in median HBV DNA change or the proportion of patients with undetectable HBV DNA (<170 copies/ml) at 48 weeks between the three, albeit very small sized, groups. But when the HBV DNA limit was raised (<1000 copies/ml), a significant difference was observed (46% LAM, 92% TDF, 91% with combination therapy, p = 0.013).

TDF versus ADV

Several clinical studies, which have evaluated TDF versus ADV in the HIV–HBV coinfected population, have shown what might be expected that the effect of TDF on suppression of HBV replication is significantly greater than that with ADV [33–35].

A prospective, blinded, randomized controlled trial which examined the change in mean time-weighted average in serum HBV DNA from baseline to week 48 for ADV versus TDF patients (ADV = 25, TDF = 27, sample size 52), could only show that TDF was not inferior to ADV [34]. In another similarly small sized prospective nonrandomized study of 85 HIV–HBV coinfected patients comparing ADV (n = 29) versus TDF (n = 56), TDF had a more pronounced effect on rates of HBV DNA viral decay (TDF -66% vs ADV -53% at 12 months, p = 0.0001) and more patients on TDF achieved HBV DNA undetectability (66 vs 28% on ADV, p = 0.04) [35].

Thus all the clinical studies in HIV–HBV coinfected patients suggest that TDF is more effective than ADV in suppressing HBV DNA in the coinfected population [33–35], hence TDF is favored over ADV in patients with HIV coinfected with HBV.

TDF in LAM resistant HBV

There are only small, prospective, open-label studies of TDF therapy in HIV–HBV coinfected patients with LAM-resistant HBV, which demonstrated that the addition of daily TDF (300 mg) leads to a 3.6–5.52 copies/ml log decrease in HBV DNA levels, with undetectable HBV DNA levels ranging from 33–100% at follow-up (24–71 weeks), with a 0–25% HBeAg seroconversion rate [36–38,40–42].

In a retrospective cohort analysis of 65 HIV–HBV coinfected patients, TDF, when part of an antiretroviral regimen, was effective against both wild-type and LAM resistant HBV [43]. In this latter study, 80% of patients continued LAM as part of their antiretroviral regimen, although 68.8% had genotypic LAM resistance at baseline. At the 12-month follow-up, HBV DNA was undetectable in 29.6% and 81.6% of the HBeAg-positive and HBeAg-negative patients, respectively. Based on multivariate Cox regression, presence of genotypic LAM resistance was not significantly associated with sustained detectability of HBV DNA.

A larger prospective cohort, which examined the long-term efficacy of TDF in 102 coinfected HIV–HBV patients (80% with detectable HBV DNA at baseline), showed that TDF, when administered as part of their antiretroviral therapy, was a potent anti-HBV agent [44]. Of these patients, 67% were LAM experienced and 40% had proven genotypic LAM resistance. Kaplan Meier analysis, indicated a cumulative probability of achieving undetectable HBV DNA for HBeAg (+) and HBeAg (-) was high (92% and 100% respectively at 5 years) with no significant difference between patients with or without genotypic LAM resistance at baseline.

In another prospective cohort, using 1:2 matched-pair analysis, comparing patients with HIV–HBV coinfection who received an antiretroviral regimen containing TDF and LAM versus patients switched to TDF (stopped LAM) after developing LAM resistance (defined only as HBV DNA >100,000 copies/ml; no genotypic analysis), the data indicated that both regimens were comparable with respect to HBV suppression [45]. After median treatment duration of 129 weeks in the TDF plus LAM group and 116 weeks in the TDF alone group, differences in rates of HBV DNA levels <1000 copies/ml were not statistically significant (76% in combination therapy vs 84% TDF alone, p = 0.53).

TDF resistance

There is limited data available on the emergence of resistance to tenofovir in the patients with HIV–HBV coinfection. One study reported that a HBV polymerase mutation rtA194T developed in 2/43 (4.7%) HIV–HBV coinfected patients treated with TDF and LAM for a mean of 11.2 months [48], but recent clinical data did not indicate that presence of the rtA194T mutation at baseline had any impact on the TDF response in LAM resistant monoinfected patients HBV patients [49].

Safety & tolerability

CHB monoinfection

The long-term safety monitoring of TDF in patients with CHB monoinfection continues

Table 5. Summary of studies of tenofovir in HIV/hepatitis B virus coinfection.

Study design	Number of patients (%)		Median duration tenofovir treatment (weeks)	HBV DNA decrease (log_{10} copies/ml)	Number of patients (%)					Ref.
	HBeAg+ number (%)	Previous resistance or null/incomplete response			HBV undetectable (100–1500 c/ml)	eAg loss	eAb seroconversion	sAg loss	sAg seroconversion	
TDF vs TDF + FTC (naive)										
Prospective nonblinded randomized controlled (n = 16)	11 (69)	Not applicable	48	TDF-FTC 5.32 FTC 3.25	TDF-FTC 9/10 (90) FTC 2/6 (33)	TDF-FTC 3/6 (50) FTC 1/6 (17)	TDF-FTC 2/6 (33) FTC 1/6 (17)	TDF-FTC 0 (0) FTC 1/6 (17)	TDF-FTC 0 (0) FTC 0 (0)	[32]
TDF vs ADV										
Prospective open-label comparative study (n = 53)	47 (89)	53 (100) 3TC	48	TDF 5.5 ADV 2.8	TDF 100% ADV 44%	TDF 11/31(35%) ADV 3/16 (19)	N/A	TDF 5/31 (14) ADV 1/16(5.6)	N/A	[33]
Prospective double-blind placebo-controlled noninferiority trial (n = 52)	41 (79)	47 (90) 3TC	48	TDF 5.74 ADV 4.03	TDF 20% ADV 5.7%	TDF 0/15 (0) ADV 1/18 (6)	N/A	N/A	N/A	[34]
Subanalysis of prospective open-label (n = 52, ADV = 29, TDF = 56)	75 (88)	60 (71) 3TC	48	TDF 4.83 ADV 4.43	TDF 37/56 (66) ADV 8/29 (28)	TDF 8/47 (17) ADV 4/21 (19)	TDF 2/47 (3.9) ADV 1/21 (4.6)	N/A	N/A	[35]
TDF										
Prospective pilot study (n = 6)	6 (100)	6 (100) 3TC	24	3.6	2 (33)	N/A	0 (0)	N/A	N/A	[36]
Prospective open label (n = 20)	20 (100)	15 (75) 3TC	52	4 (24 weeks)	13 (65)	N/A	5/20 (25)	N/A	N/A	[37]
Prospective cohort (n = 12)	12 (100)	10 (83) 3TC	24	3.83	N/A	0 (0)	0 (0)	0 (0)	0 (0)	[38]
Prospective subanalysis (n = 12)	12 (100)	7 (58) 3TC	24	TDF 4.9 Placebo 1.21	N/A N/A	2/10 (20) 0 (0)	1/10 (10) 0 (0)	N/A N/A	N/A N/A	[39]
Prospective observational subgroup analysis (n = 31)	19 (61)	20 (65) 3TC	48	Baseline VL >6 log = 5.52 VL <6 log = 5.23	11/20 (55) 11/11 (100)	1/20 (5) 0 (0)	0 (0) 0 (0)	0 (0) 1 (5)	0 (0) 0 (0)	[40]

3TC: Lamivudine; ADV: Adefovir; dTDF: TDF added at 6 months if 3TC resistance; HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus; N/A: Not available; TDF: Tenofovir; VL: Viral load.

Table 5. Summary of studies of tenofovir in HIV/hepatitis B virus coinfection (cont.).

Study design	Number of patients (%)		Median duration tenofovir treatment (weeks)	HBV DNA decrease (log_{10} copies/ml)	Number of patients (%)					Ref.
	HBeAg+ number (%)	Previous resistance or null/incomplete response			HBV undetectable (100–1500 c/ml)	eAg loss	eAb seroconversion	sAg loss	sAg seroconversion	
TDF										
Prospective open label (n = 28)	24 (85.7)	24 (85.7) 3TC	71	4.6	21 (75)	N/A	4/24 (17)	N/A	N/A	[41]
Prospective observational (n = 12)	9 (75)	7 (58) 3TC	24	3.78	7/11 (64)	1/11 (9)	N/A	1/11 (9)	N/A	[42]
Retrospective cohort analysis (n = 65)	54 (83)	42 (68.8) 3TC	48	eAg+ 4.56 eAg- 2.53	eAg+ 16 (29.6) eAg- 9 (81.6)	4/54 (7.4)	2/54 (3.7)	0 (0)	0 (0)	[43]
Prospective cohort (n = 102)	67 (66)	33 (40) 3TC	220	N/A	72 (88)	46%	N/A	eAg+ 12% eAg- 2/15 (13%)	N/A	[44]
3TC vs 3TC + TDF										
Prospective subanalysis (n = 11)	10 (91)	4 (36) 3TC	48	3TC 3.0 3TC + TDF 4.7	3TC 1/6 (17) 3TC + TDF 4/5 (80)	3TC 1/6 (17) 3TC + TDF 1/5 (20)	3TC 1/6 (17) 3TC + TDF 1/5 (20)	N/A	N/A	[39]
3TC + TDF vs 3TC + delayed TDF (dTDF)										
Prospective cohort (n = 75)	75 (100)	50 (66) 3TC	3TC + TDF = 129 3TC + dTDF = 116	N/A	3TC + TDF 19/25 (76) 3TC + dTDF 42/50 (84%)	3TC + TDF 9/25 (36) 3TC + dTDF 12/50 (24)	3TC + TDF = 1/25 (4) 3TC + dTDF 3/50 (6)	N/A	N/A	[45]
Retrospective cohort analysis (n = 45)	37 (82)	14 (31) 3TC	48	3TC 2.6 3TC + TDF 4.5 3TC + dTDF 2.7	3TC 9/15 (60) 3TC + TDF 8/10 (80) 3TC + dTDF 11/20 (55)	3TC 2/7 (29) 3TC + TDF 4/10 (40) 3TC + dTDF 3/16 (19)	3TC 0/7 (0) 3TC + TDF 2/10 (20) 3TC + dTDF 3/16 (19)	N/A	N/A	[46]
3TC vs TDF vs 3TC + TDF										
Prospective nonblinded randomized controlled trial (n = 36)	22 (61)	N/A	48	3TC 4.07 TDF 4.57 3TC + TDF 4.73	3TC 46% TDF 78% 3TC + TDF 64%	3TC 3/9 (33) TDF 1/6 (17) 3TC + TDF 3/7 (43)	3TC 1/9(11) TDF 1/6 (17) 3TC + TDF 3/7 (43)	3TC 1/13 (8) TDF 1/12 (8) 3TC + TDF 1/11 (8)	N/A	[47]

3TC: Lamivudine; ADV: Adefovir; dTDF: TDF added at 6 months if 3TC resistance; HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus; N/A: Not available; TDF: Tenofovir; VL: Viral load.

to be evaluated in the two Phase III trials [16]. TDF monotherapy was generally well tolerated in both HBeAg-negative and HBeAg-positive patients with CHB monoinfection for up to 48 weeks. The most common adverse events (incidence >5%) included: headache (13%), nasopharyngitis (10%), nausea (9%), fatigue (8%), abdominal pain (7%), back pain (7%), diarrhea (7%) and dizziness (6%). Nausea was the only adverse event that occurred more frequently in TDF compared to ADV treated patients (9 vs 3%). Only five patients (1%) in the TDF group stopped treatment because of an adverse event.

Serious adverse events occurred in similar proportions in both treatment groups (TDF 6% vs ADV 7%), with 2% considered to be related to the study drug, these included: ALT flare (TDF 1%, ADV 2%), thrombocytopenia (<1% TDF) and toxic myopathy (<1% ADV). There were no reports of sustained increases in serum creatinine greater than 0.5 mg/dl above baseline or confirmed calculated creatinine clearance of less than 50 mm/min through week 48.

In the open-label extension observed to 144 weeks, TDF maintained a favorable safety profile [17]. Treatment related adverse events ≥5% included upper abdominal pain, nasopharyngitis, headache, and influenza. Two patients (<1%) experienced a ≥0.5 mg/dl increase in creatinine, this may have been influenced by prior ADV therapy (both had originally been randomized to receive ADV for 1 year followed by a protocol switch to TDF after 48 weeks). Four patients (<1%) experienced a reduction in serum phosphorus ≤ 2 mg/dl, which resolved on continued TDF therapy without intervention. One patient discontinued TDF secondary to an unconfirmed increase (0.5 mg/dl) in creatinine.

Another recent randomized study comparing TDF versus TDF/FTC found comparable frequencies of treatment related adverse events and no confirmed increases in creatinine [25]. Similarly, in two studies using TDF in nucleoside experienced patients (duration 92–96 weeks), there were no TDF-related clinically significant side effects or increases in creatinine [23,24].

Patients with liver failure due to CHB

The safety profile of TDF in patients with decompensated CHB has been assessed in 112 patients over a 48-week period in a Phase II randomized controlled trial comparing TDF, TDF/FTC and ETV [27]. The percentages of patients with adverse events (TDF 17.8%, TDF/FTC 15.6%, ETV 9.1%) and the number of serious adverse events (TDF 2.2%, TDF/FTC 2.2%, ETV 0%) considered related to the study drug were low and not significantly different between the three treatment groups.

HIV +/- HBV coinfection

One important potential safety issue in the HIV–HBV coinfected population initiating any therapy effective against CHB is the risk of hepatitis flares, which most often relates to an immune reconstitution syndrome. Hepatitis flares (defined as an increase in ALT to 3–5 times upper limit of normal or a 100 u/l increase from baseline) have been documented in 19–25% of previously treatment naive HIV–HBV patients prescribed TDF [32,47]. A total of 33–66% of these flares were associated with HBeAg seroconversion [32,47], while one patient (also taking efavirenz) developed a hepatic flare followed by rapid hepatic decompensation and death [47].

Although there have been no reports of significant deviations in serum creatinine in any of the randomized controlled trials involving patients with HIV–HBV receiving TDF [32,34,47], a recent prospective cohort of 102 patients documented two HIV–HBV coinfected patients with an increase in serum creatinine ≥0.5 mg/dl above baseline after initiation of TDF [44]. In these patients, the creatinine stabilized upon discontinuation of TDF but did not return to baseline. In another study involving a cohort of 54 patients, one case of renal tubular dysfunction, presenting similar to Fanconi syndrome, occurred in a patient with concomitant non-Hodgkin lymphoma, which resolved within a few weeks of TDF withdrawal [43].

Nephrotoxicity

The potential for nephrotoxicity is a principal concern related to the long-term safety and tolerability of TDF. Despite demonstration of a good renal safety profile in the registrational trials (maximum of 4 years follow up data), there have been a number of reports related to nephrotoxicity in patients (both mono- and coinfected) receiving TDF therapy [50–69]. The first report of kidney disease associated with TDF was reported in 2002 [50]. Subsequent case reports included acute renal failure [51–61] and initial tubular dysfunction with occasional overt Fanconi syndrome [50,62–69]. Although unusual, nephrotoxicity associated with TDF

were generally reported during the first months of therapy. Manifestations of mild tubular dysfunction (hypophosphatemia, hypokalemia, mild proteinuria or glucosuria in the setting of normal serum glucose levels) were the more common presentation, although overt Fanconi syndrome is reported.

A review of cases of TDF-associated nephrotoxicity from 2001 to 2006 reported to the US FDA identified 164 cases of Fanconi syndrome [70], although this publication was limited by the inaccuracies of case reporting and lack of validation of the submitted reports. The majority (83%) of these subjects received protease inhibitors along with TDF and in 34% of cases also didanosine. Didanosine is suspected to enhance mitochondrial toxicity in patients receiving TDF and has been reported to cause multiple systemic effects when used in combination with TDF (e.g., pancreatitis, hyperglycemia) [71].

The observed difference in the rates of nephrotoxicity between the post-marketing experience and clinical trials may be because patients were excluded from clinical trials if they had a baseline CrCl <50 ml/min or if they were on nephrotoxic agents [72]. Risk factors identified for developing nephrotoxicity in patients treated with TDF, include older age, low body weight (<60 kg), male gender, pre-existing renal impairment, concomitant use of nephrotoxic medications, HCV coinfection, gene polymorphisms of transporter proteins, and higher levels of plasma TDF (160 ng/ml) [71].

Multiple studies have specifically evaluated the safety of TDF in comparison with other antiretroviral agents. Several prospective clinical trials have demonstrated no or minimal reduction in renal function when comparing patients exposed to TDF versus other antiretroviral drugs as part of an antiretroviral regimen [73–75]. Whereas, other studies have reported renal injury associated with TDF used as part of an antiretroviral regimen [76,77]. A 1-year prospective observational cohort study of patients with HIV, which included one group of 344 taking TDF and one group of 314 taking alternative nucleoside reverse transcriptase inhibitors, found that the TDF group had a significantly greater median increase in serum creatinine level (+0.15 vs +0.10 mg/dl) and decline in calculated CrCl by the Cockcroft–Gault equation (-13.3 vs -7.5 ml/min) [76]. In a German cross-sectional study comparing patients with HIV treated with TDF containing ARV regimen compared with patients treated with non-TDF containing ARV regimen, patients on TDF showed a lower mean glomerular filtration rate (GFR) (97 vs 107 ml/min) and higher levels of proteinuria (124 vs 94 mg/day) compared with non-TDF patients [77].

Prolonged treatment with TDF may cause progressive renal tubular dysfunction before any decline in GFR occurs. In a cross-sectional study of 284 HIV-infected patients (154 patients on TDF), in whom both glomerular and tubular function was measured, three cases of Fanconi syndrome were identified all of whom were receiving TDF (CrCl levels within normal limits) and whose GFR was within normal limits and comparable among study groups at baseline [78].

Two possible mechanisms have been proposed to explain the cause of renal damage associated with TDF. The first mechanism incriminates mitochondrial DNA toxicity (mtDNA) in the renal proximal tubules, similar to the known effect of ADV. Antivirals may induce mtDNA toxicity when nucleos(t)ide analogs are incorporated into the human mtDNA polymerase causing oxidative stress and ultimately mtDNA mutations [79]. Two recent experimental animal models have shown clear evidence for tubular damage caused by TDF induced mtDNA toxicity [80,81]. Several kidney biopsies in humans treated with TDF who developed Fanconi syndrome indicate mtDNA toxicity within the proximal tubules [51,54,64,74].

The second mechanism involves the interference of TDF with the normal function tubular cells. Competitive interactions involving transporter proteins could lead to increased renal toxicity secondary to reduced efflux and increased intracellular concentrations of TDF. In animal models TDF may induce a down-regulation of genes coding for transporter proteins [82], producing a concentration-dependent inhibition of multidrug resistance-associated proteins, which in turn could lead to an accumulation of toxic compounds that may cause cell damage [83].

Although severe renal damage associated with TDF use is uncommon and in most instances appears to have been multifactorial, physicians must consider the potential for nephrotoxicity in patients treated with TDF. In patients on TDF with the aforementioned risk factors for TDF nephrotoxicity, TDF should be used cautiously. In clinical practice when the renal function is compromised on TDF, physicians should adjust the frequency of TDF dosing to avoid a

worsening of renal function as early recognition of renal dysfunction is key to avoiding the development of serious renal damage.

Effects on bone

Multiple case reports have been published describing osteomalacia in patients with HIV who have received TDF and were noted to have a proximal renal tubulopathy [84–88]. A proposed mechanism to explain proximal tubular dysfunction and osteomalacia relates to increased urinary wasting of phosphate causing direct effects on bone metabolism, perhaps promoting premature osteopenia and osteomalacia [72,89]. In a case series of 22 patients with documented renal toxicity (determined by graded increases in serum creatinine, progressive decline in GFR and/or development of clinical proteinuria) attributed to a TDF-containing antiretroviral regimen, 19 were found to have hypophosphatemia at the time of initial diagnosis of renal toxicity and seven with confirmed osteomalacia on bone scan [89]. In a prospective study of 90 patients with HIV receiving TDF therapy, 29 patients (32%) were found to have impaired phosphate transport (ratio of the maximal tubular reabsorption rate of phosphate and the glomerular filtration rate) [90]. Of the 29, six were found to have osteopenia based on bone mineral density scans. The prevalence of osteomalacia and other bone complications is unknown, as studies represent a highly biased population, where bony investigations were only performed in a selected subgroup.

We now need long term serial evaluations to specifically assess the effect of TDF on renal tubular function and bone mineral content in individuals with normal pretreatment renal function to better determine the relationship between bone toxicity and TDF. In patients who develop TDF nephrotoxicity or sustained hypophosphatemia, an evaluation for renal loss of phosphate, and bone toxicity should be considered.

Use of TDF during pregnancy

TDF has been assigned a FDA Pregnancy Category B status. Reproduction studies performed in rats and rabbits at doses up to 14 and 19 times the human dose, based on body surface area comparisons, revealed no evidence of impaired fertility or harm to the fetus due to TDF [101]. There were no effects on mating or fertility parameters. Experiments in infant Rhesus monkeys have demonstrated that exposure to high-dose TDF, estimated to be 30–40-fold higher than a 300-mg TDF dose in an adult human, led to bone-related toxicity and severe growth restriction in approximately 25% of the monkey infants [91]. A subsequent study using a similar maternal TDF dose, showed a significant reduction in circulating insulin-like growth factor and a small reduction in overall body weight and crown-rump lengths and bone porosity in newborn infant rhesus monkeys compared with age-matched controls [92].

The experience with TDF in pregnant women consists of 606 women in their first trimester and 336 in their second trimester [102]. The rate of birth defects associated with TDF ranges from 1.5% (second-trimester use) to 2.3% (first-trimester use), similar to the background rate. There are, however, no adequate and well-controlled studies in pregnant women. Based on animal studies, it is presumed that TDF can be secreted in breast milk and thus breastfeeding of infants by mothers on TDF is not currently recommended, as the potential effects of TDF exposure in neonates is unknown [101].

Comparative treatment efficacy of TDF

Over the past two decades, several new antiviral treatments for CHB have become available. The first drug approved was interferon, an immune modulator and antiviral. The focus has now shifted toward the development of potent oral antiviral medications in the form of nucleos(t)ide analogs that may be taken over the long term. Because the randomized controlled studies comparing these treatments have been restricted to comparing two or three drugs at a time, the relative efficacies of the various different drugs compared to one another are not available.

As traditional methods of meta-analyses are limited to evaluating two treatments at a time, they cannot provide information on the relative benefits of the multiple treatment regimens. A Bayesian MTC method can be used to perform direct (head-to-head) comparisons, as well as indirect comparisons of treatments not compared directly within any of the individual trials (Figure 1). A recent systematic review of 20 randomized controlled trials (15 HBeAg+, 8 HBeAg-) involving medications used to treat CHB, as mono- or combination therapies, used Bayesian Mixed Treatment Comparisons (MTC) to evaluate and rank the relative efficacies of these treatments across six surrogate clinical outcomes at the end of 1 year of treatment [10].

Surrogate outcomes included: rates of virologic (undetectable HBV DNA) and biochemical response, HBeAg loss, HBeAg seroconversion, HBsAg loss, and histologic improvement.

In HBeAg positive patients, TDF was consistently ranked within the top three treatments for all surrogate outcomes except HBeAg loss, for which no data was available. It was ranked first for the proportion of patients with undetectable HBV DNA, normalization of ALT levels, HBeAg seroconversion and HBsAg loss. Among HBeAg negative patients, TDF ranked first for HBV-DNA suppression and histologic improvement, and second for ALT normalization. Based on the results, the authors concluded TDF and ETV, which also ranked consistently in the top three treatments, were the most potent oral antiviral agents for HBeAg-positive patients while TDF was most effective for HBeAg-negative patients.

However, at present the question of optimal long treatment choices cannot be stated. This future data on both long-term efficacy and safety is very important as the treatment for CHB will in some instances need to be taken for an extended period of time, perhaps lifelong.

Conclusion

Tenofovir is an orally bioavailable nucleotide analog reverse transcriptase inhibitor with potent activity against HBV DNA polymerase. The data analyzed in this review suggests that TDF has a potent and sustained antiviral effect and is safe for the treatment of both noncirrhotic and cirrhotic CHB. It has demonstrated efficacy in patients with documented resistance or virologic failure while taking other nucleos(t)ide analogs (e.g., LAM and ADV). Recent data suggest that tenofovir may be a safe therapeutic option for the treatment of liver failure due to CHB. In addition, TDF has shown good efficacy in HIV–HBV coinfection and in CHB presenting with ACLF.

Until now, no genotypic resistance to TDF has been demonstrated in patients treated for HBV monoinfection for up to 4 years of TDF therapy. Although previously described rtA194T amino acid substitution has been suggested to play a role in genotypic resistance in the HIV–HBV coinfected population, there is to date no data which shows this to be the case.

TDF is well tolerated with minimal adverse effects; although there are reports of nephrotoxicity. Some preliminary reports have suggested TDF may promote renal +/- bone toxicity, mostly in the HIV–HBV coinfected population taking ARV therapies. Future studies will be needed to better determine this relationship and examine closely those treated with long-term TDF monotherapy for CHB monoinfection.

Owing of its potent antiviral activity, high barrier to the development of resistance, and favorable safety profile, it is appropriate that TDF should be considered as a first-line option in the treatment of CHB monoinfection. In the HIV–HBV-coinfected population, TDF is a good treatment option but both glomerular and tubular renal function require close monitoring in this population.

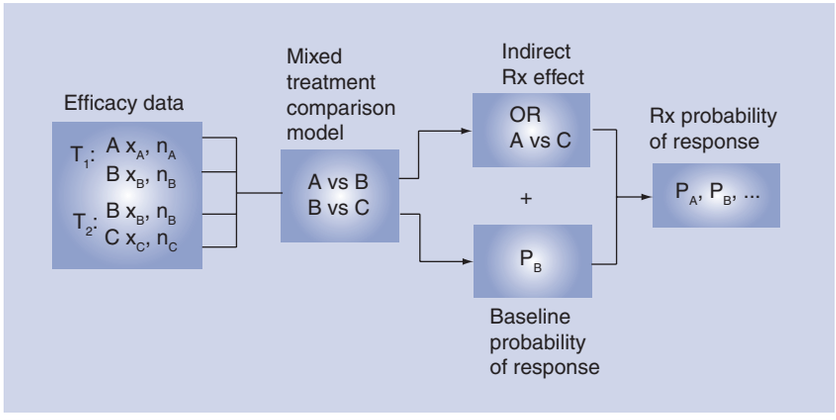

Figure 1. Bayesian MTC method. Binary efficacy data of pair-wise comparisons are entered into a Bayesian MTC model that calculates indirect treatment effects and the probability of a response from the common comparator treatment (P_B). The indirect treatment effects (OR of A vs C) and probability of response of the common comparator (P_B) are used to calculate the probability of response for each of the treatments (P_A and P_C).
n_A: Number of patients on treatment A; n_B: Number of patients on treatment B; n_C: Number of patients on treatment C; P_A: Probability of a response from treatment A; P_B: Probability of response from treatment B; Rx: Treatment effect; T_1: Trial 1; T_2: Trial 2; x_A: Number of responders on treatment A; x_B: Number of responders on treatment B; x_C: Number of responders on treatment C.

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Executive summary

Clinical trials in HBV-monoinfected patients

- Phase III randomized controlled trials:
  - In patients with CHB monoinfection, TDF therapy provides effective long-term viral suppression (HBeAg- 86%, HBeAg + 77% at 192 weeks). Prolonged viral suppression with TDF was associated with HBsAg loss in those treated for HBeAg (+) CHB (10% at 192 weeks) but not in those with HBeAg (-) CHB.
- TDF in patients with prior failure or resistance to other nucleoside/nucleotide analogs:
  - TDF is highly effective in patients with LAM drug resistance mutations but may not be as effective against ADV drug-resistant mutations.
- TDF in combination therapy for ADV drug-resistant CHB:
  - In patients with ADV resistant CHB, there is no benefit of adding FTC to TDF over TDF monotherapy.
- TDF in patients with liver failure:
  - TDF monotherapy given to patients with advanced CHB +/- liver failure may be as effective and as well tolerated as TDF + FTC or with monotherapy ETV.
- TDF in patients with acute on chronic liver failure:
  - In patients with spontaneous reactivation of CHB presenting as ACLF, TDF is highly effective with a significant mortality benefit.
- TDF resistance in HBV mono-infected patients:
  - To date, no drug resistant HBV mutations to TDF have been identified in up to 4 years of therapy.

Clinical trials in HIV–HBV coinfected patients

- TDF monotherapy versus combination therapy in ARV naive:
  - Small studies suggest there is no benefit to LAM + TDF over TDF monotherapy in HIV–HBV coinfected individuals. Despite this observation, dual therapy continues to be recommended.
- TDF versus ADV:
  - TDF rather than ADV should be first-line therapy for CHB in HIV–HBV coinfection.
- TDF in LAM resistant HBV:
  - TDF is equally effective for both wild-type HBV and LAM-resistant patients with HIV–HBV coinfection.
- TDF resistance in HIV–HBV coinfected patients:
  - The evidence suggests there is no difference in the efficacy of TDF according to whether or not the rtA194T HBV mutant is present, in both monoinfected HBV and coinfected HIV–HBV patients.

Safety & tolerability

- Patients with liver failure due to CHB:
  - TDF monotherapy given to patients with liver failure due to CHB is well tolerated and has a similar rate of adverse events compared to ETV or TDF + FTC.
- HIV +/- HBV coinfection:
  - Treatment-naive patients with HIV–HBV coinfection may be at increased risk for a hepatitis flare or renal impairment with initiation of TDF and should be monitored closely.
- Nephrotoxicity:
  - Notably in the absence of pretreatment renal impairment, long-term TDF is rarely associated with significant alteration in renal function with up to 4 years of therapy. Nevertheless, both glomerular and/or tubular dysfunction have been reported particularly in the HIV–HBV coinfected population on TDF containing ARV therapy.
- Effects on bone:
  - Renal tubular loss of phosphate in HIV–HBV coinfected individuals receiving TDF as part of their ARV therapy appear to be at risk of osteomalacia.
- Use of TDF during pregnancy:
  - US FDA Pregnancy Category B

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