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REVIEW

Critical appraisal and update on tenofovir in management of human immunodeficiency virus infection

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Abstract: Tenofovir is currently one of the most widely used nucleoside reverse transcriptase inhibitors in the treatment of human immunodeficiency virus (HIV) due to its good efficacy, tolerability, and convenience as a once-daily dosage. It is a drug of choice both for first-line therapy in naïve and pretreated patients, along with two other active drugs as part of a highly active antiretroviral therapy. Moreover, tenofovir can be used to treat hepatitis B virus-infected patients as well as coinfected patients who meet criteria to be treated for HIV or hepatitis B virus infection, and more recently some studies have supported its use as part of pre-exposure prophylaxis. Although large clinical trials and postmarketing studies have shown a gentle renal profile for tenofovir, some prospective cohort studies and case reports have raised concern about renal damage and bone disorders associated with use of tenofovir in a small proportion of patients, and apprehension lingers over its long-term usage. Renal toxicity from tenofovir seems to be linked to tubular damage, so classical markers for monitoring renal function that mainly assess glomerular function would not be advisable to detect early renal impairment. Management of toxicity associated with tenofovir should be based on assessment of optimal biomarkers for the detection and monitoring of renal disease.

Keywords: tenofovir, antiretroviral treatment, kidney, human immunodeficiency virus, hepatitis B

Introduction

Tenofovir disoproxil fumarate (TDF), the first nucleotide analog approved for the treatment of human immunodeficiency virus (HIV) infection, was introduced a decade ago as part of the antiretroviral armamentarium. Since then, this drug has replaced most nucleoside analogs as the backbone of many antiretroviral combination regimens in the Western world, where lipoatrophy and other side effects of nucleoside analogs have become the major drawback of this drug family. The coformulation of tenofovir with emtricitabine (Truvada®) or with emtricitabine and efavirenz (Atripla®) as a single pill to be taken once daily has further increased the popularity of this drug. Other attractive features of TDF are its potent antiviral activity when compared with abacavir in subjects having high viral loads, its relatively high genetic barrier for resistance, and its activity against hepatitis B virus, which makes the drug particularly attractive for treatment of individuals coinfected with HIV and hepatitis B virus. However, widespread use of the drug has allowed the recognition of some mild and long-term side effects in a subset of patients with prolonged TDF exposure, mainly associated with kidney tubular dysfunction and loss of bone density.

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Treatment challenges in management of HIV infection

Since the identification of HIV in 1983[1,2] and until the approval of zidovudine in 1987, neither a cure nor long-term survival was expected for persons infected with the virus. During the years that followed, efforts were focused on developing more and better compounds against the virus. The nucleoside reverse transcriptase inhibitors, to which zidovudine belongs, were soon complemented with other molecules, such as didanosine, zalcitabine, stavudine, and lamivudine. However, it was not until the introduction of the protease inhibitors in 1996 that the expectations of antiretroviral therapy experienced a dramatic shift. Only then was it appreciated that triple combination therapy could provide unprecedented control of HIV replication, CD4 gain, and ultimately prolonged survival. The combination of three drugs, ie, two nucleoside reverse transcriptase inhibitors and one protease inhibitor or non-nucleoside reverse transcriptase inhibitor (NNRTI) is known as highly active antiretroviral therapy, and has become the paradigm for antiretroviral treatment.

TDF, a unique nucleotide analog and the first approved to treat HIV infection, was introduced to the market in 2001. Moreover, further drug families directed to other targets in the life cycle of the virus were developed, including NNRTIs and, more recently, the entry inhibitors and integrase inhibitors.

Nowadays, there are 25 drugs approved for the treatment of HIV infection. Some of these drugs are coformulated in combinations and allow once-daily dosage, thereby simplifying therapy and improving compliance. TDF is currently one of the most widely used nucleos(t)ide reverse transcriptase inhibitors in the treatment of HIV infection due to its excellent combination of good potency, tolerability, and convenience as a once-daily dosage. TDF is marketed either as a single agent (Viread®) or coformulated with emtricitabine, or with emtricitabine + efavirenz, the latter being the "gold standard" in patients initiating antiretroviral therapy. TDF + emtricitabine is also considered to be a combination of choice when antiretroviral therapy is initiated with a boosted protease inhibitor, and in patients with good virological control in whom an alternative nucleoside reverse transcriptase inhibitor has to be substituted to avoid or reverse toxicity. More recently, TDF + raltegravir (the first integrase inhibitor marketed) has been included as an option for initial therapy because it is very effective in terms of virological suppression and CD4 gain, as well as having a good safety profile. In this review we summarize the most relevant aspects of TDF use.

Pharmacology

TDF is the fumarate salt of the prodrug, tenofovir. Following gastrointestinal absorption, tenofovir disoproxil undergoes initial diester hydrolysis and is transformed into tenofovir, a nucleotide analog of adenosine monophosphate, and subsequently undergoes phosphorylation by cellular enzymes to form the active compound, tenofovir diphosphate. Tenofovir diphosphate inhibits HIV reverse transcriptase by competing with the natural substrate, deoxyadenosine 5'-triphosphate, causing DNA chain termination. The in vitro anti-HIV 50% inhibitory concentration (IC_{50}) is in the range of 1–6 μM.[3,4]

TDF has a low bioavailability of 25% in the fasted state. Administration of TDF with a high-fat meal enhances its bioavailability by 40%. Thus, it is recommended that TDF be administered with food. After oral administration, tenofovir is minimally bound to plasma proteins and distributed to most tissues, with the highest concentrations occurring in the kidney, liver, and intestine. In vitro studies have shown that neither TDF nor tenofovir are substrates for the cytochrome P450 (CYP) enzymes. Moreover, tenofovir does not inhibit in vitro drug metabolism mediated by any of the major human CYP450 isoforms, so it is unlikely that clinically significant interactions involving tenofovir and drugs metabolized by CYP450 would occur. The terminal half-life of tenofovir in plasma is approximately 12–18 hours. It is primarily excreted via the kidney by both glomerular filtration and active tubular secretion.[3] Regarding the pathway of active tubular secretion, tenofovir enters the proximal tubule cells via human organic anion transporters 1 and 3[5,6] and is excreted into the urine by multidrug resistant protein 4; the role of MRP2 and MRP7 in this process is under study (Figure 1).[7–12] Coadministration of TDF and drugs that reduce renal function or compete for active tubular secretion via transport proteins, human organic anion transporters, or multidrug resistant proteins (eg, cidofovir and didanosine)[13] may increase serum concentrations of TDF and/or the coadministered drug. TDF should not be coadministered with nephrotoxic agents, ie, the aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir, or interleukin-2.[3]

Pharmacokinetic studies have demonstrated that coadministration of TDF and protease inhibitors results in increased tenofovir exposure, probably due to increased absorption[14–17] or to a reduction in renal clearance of tenofovir,[18,19] but this seems not to be clinically relevant. However, coadministration of TDF and didanosine is not recommended. Although didanosine has no effect on the pharmacokinetics of TDF, didanosine exposure increases by 40%–60%, increasing the risk of didanosine-related side effects.[20–22] Further, increased

exposure to didanosine could enhance the mitochondrial toxicity of TDF to the kidneys, and may account for the greater risk of renal toxicity in patients treated with a combination of TDF and didanosine.[23]

Clinical experience with tenofovir

The efficacy and safety of TDF has been evaluated in multiple clinical trials conducted in both treatment-naïve and antiretroviral-experienced patients (Table 1). In two prospective, randomized, controlled trials (903 and 934) that evaluated the efficacy and safety of TDF vs either stavudine or zidovudine in combination with efavirenz and lamivudine or emtricitabine in antiretroviral-naïve patients over 144 weeks, the TDF arm demonstrated greater and more prolonged effectiveness in terms of viral suppression and CD4 gain.[24–27] Similar results were observed in two placebo-controlled studies (902 and 907) which included HIV treatment-experienced individuals with detectable viral load on stable combination antiretroviral therapy.[28,29]

Tenofovir + emtricitabine and abacavir + lamivudine are fixed-dose combinations commonly used along with NNRTIs or ritonavir-boosted protease inhibitors as first-line therapy, but there is conflicting evidence concerning their relative efficacy. Several trials have suggested higher efficacy for TDF + emtricitabine,[30–32] especially in the subset of patients with high viral load, whereas other studies have shown no difference in efficacy when comparing these nucleoside reverse transcriptase inhibitor backbones through 96 weeks.[33–35] Lack of human leucocyte antigen (HLA) B*5701 allele determination in patients who initiated abacavir in some of these studies might explain these different results.

Antiretroviral therapy failure can be caused by selection of resistance mutations that decrease susceptibility to a specific antiretroviral drug. The signature mutation for tenofovir is K65R, which is associated with a modest decrease in sensitivity to tenofovir in vitro, although K65R selection occurs infrequently in tenofovir-treated patients.[36] This mutation may also be selected for by prior treatment with nucleoside analogs, such as didanosine, abacavir, stavudine, and lamivudine,[37] thus leading to potential cross-resistance among these drugs. TDF should be avoided in antiretroviral-experienced patients with strains harboring the K65R mutation.[38] Simultaneous presence of the lamivudine-associated M184V reverse transcriptase mutation and K65R further reduces the replicative capacity of the virus. TDF resistance is also associated with thymidine analog resistance mutations. The presence of three or more thymidine analog resistance mutations has been associated with a decreased response to tenofovir, particularly if these mutations include M41L or L210W.[37]

With regard to adverse effects, TDF has not shown the mitochondrial toxicity linked with other nucleoside reverse transcriptase inhibitors. Moreover, TDF has a low risk of lipoatrophy and a favorable effect on the lipid profile compared with the older nucleoside analog agents, such as stavudine or zidovudine.[24–27,39] Nevertheless, when comparing TDF + emtricitabine vs abacavir + lamivudine, greater increases in bone turnover and decreases in bone density were observed in subjects treated with TDF + emtricitabine.[30,33,40] No difference in estimated glomerular filtration rate between the treatment arms was reported, but increases in tubular dysfunction markers were observed in the TDF + emtricitabine arm.[32,35] In the abacavir group, serious (Grade 3/4) adverse events occurred more frequently and earlier than in the TDF group, and were likely related to hypersensitivity reactions to abacavir. Furthermore, abacavir regimens were associated with more serious events unrelated to acquired immunodeficiency syndrome, particularly cardiovascular events.[30,32,33] TDF is frequently administered in combination with protease inhibitors. Most regimens offer comparable levels of virological efficacy,[15,24,41–45] so selection of the regimen will be based on tolerability and convenience of the drugs in order to improve adherence and outcomes of therapy.

Tenofovir-associated renal toxicity

Only 1%–2% of HIV-infected adults receiving TDF show signs of nephrotoxicity.[46–50] In many prospective clinical trials that have compared patients exposed to TDF vs other antiretroviral drugs, renal safety assessed by glomerular filtration rate was found to be similar in both groups of patients.[24,26,27] In addition, some case-control and cohort studies have described no significant renal dysfunction associated with TDF use in clinical practice.[46,47,50,51] However, other studies have found a greater increase in serum creatinine and a modest decline in creatinine clearance in subjects treated with TDF vs patients not exposed to TDF.[52–59] Moreover, in some of these studies, development of renal injury has been attributed to underlying causes unrelated to TDF use.[47,50,51] Nevertheless, it is noteworthy that patients in whom TDF was related to a decline in renal function were on protease inhibitor-based regimens. Coadministration of protease inhibitors and TDF is known to increase TDF exposure and thereby the potential nephrotoxic effect of TDF.[14–19] The influence of protease inhibitors on the renal safety profile of TDF has been evaluated in several studies.[14,18,19,53,54] Although one study found a greater decrease in renal function with protease inhibitors,[54] most agreed that

Table 1 Main trials that have examined the efficacy and safety of tenofovir in HIV-infected patients

Trial name	Study design	Patients (n)	Follow-up	Main efficacy results	Adverse events	Main implications
Study 903[26]	Noninferiority, prospective, randomized, multicenter, double-blind, controlled trial TDF vs D4T + 3TC/EFV	602 naïve patients 299 TDF arm, 301 d4T arm	144 weeks	TDF/FTC superior in terms of virologic suppression; the two arms had similar immunological efficacy	Similar renal profile; TDF displayed better lipid profile and less lipodystrophy but greater loss of BMD	TDF + FTC/3TC demonstrates superior durability of viral suppression and safety profile
Study 934[24,27]	Noninferiority, prospective, randomized, multicenter, open-label controlled trial TDF/FTC vs AZT/3TC + EFV	517 naïve patients 258 TDF arm 259 AZT arm	144 weeks	TDF/FTC superior in terms of virologic suppression and CD4 response	Similar renal profile; TDF displayed better lipid profile and less lipodystrophy	
BICOMBO[30]	Randomized, multicenter, open-label clinical trial TDF/FTC vs ABC/3TC + NNRTIs or PIs No HLA-B*5701 screening	335 pretreated patients with RNA-HIV < 200 copies/mL 167 ABA/3TC 168 TDF/FTC	96 weeks	TDF/3TC superior in terms of virologic suppression; no significant difference between groups in CD4 cell count; ABC/3TC did not meet the noninferiority outcome for treatment efficacy compared with TDF/FTC	ABC/3TC had more serious (Grade 3–4) AE. Increases in total and LDL cholesterol; no differences in GFR	Three reasons for TDF use vs ABC: no need for HLA-B*5701 test; greater virological response in patients with VL > 100,000 copies/mL; no CV events
ACTG A5202 study[32]	Prospective, randomized, double-blind equivalence study TDF/FTC vs ABC/3TC + EFV or ATV/r No HLA-B*5701 screening	1858 naïve patients 399 TDF/FTC 398 ABC/3TC	96 weeks	ABC/3TC did not suppress HIV as well as TDF/FTC in patients with high viral load and time to virologic failure was shorter; no significant difference between groups in CD4 cell count	ABC/3TC had more serious (Grade 3–4) AE and higher cholesterol levels; TDF/FTC + ATV/r showed lower CrCl than ABC arm	*Long-term consequences of tubular dysfunction are unclear
STEAL[33]	Noninferiority, randomized, open-label trial of TDF/FTC vs ABC/3TC + NNRTIs or PIs; HLA-B*5701-negative HIV-1-infected adults	360 pretreated patients with RNA-HIV < 50 copies/mL 180 TDF/FTC 180 ABC/3TC	96 weeks	Similar virological efficacy and similar rate of virological failure	ABC/3TC showed more serious non-AIDS events, mainly CV events and lipid endpoints; TDF/FTC caused more BMD loss; no difference in GFR	
HEAT[35]	Noninferiority, randomized, multicenter double-blind, placebo-matched study of TDF/FTC vs ABC/3TC + LPV, no HLA-B*5701screening	688 naïve patients 343 ABC/3TC 345 TDF/FTC	96 weeks	Similar efficacy in patients with baseline HIV-1 RNA > 100,000 copies/mL or CD4 cell counts < 50 cells/μL; comparable safety and tolerability, and similar rate of virological failure	Similar discontinuation due to AE (6%); similar GFR and tubular parameters	
ASSERT[31]	Multicenter, randomized, open-label study of TDF/FTC vs ABC/3TC + EFV, HLA-B*5701-negative HIV-1-infected adults	385 naïve patients 197 TDF/FTC 195 ABC/3TC	96 weeks	TDF greater efficacy for virological suppression; no differences in CD4 gain	AEs similar between arms (but HS for ABC arm); no difference in GFR; TDF/FTC showed increases in markers of tubular dysfunction, bone turnover and decreases in BMD	

Abbreviations: TDF, tenofovir disoproxil fumarate; d4T, stavudine; 3TC, lamivudine; EFV, efavirenz; FTC, emtricitabine; AZT, zidovudine; ABC, abacavir; ATV/r, atazanavir/ritonavir; LPV/r, lopinavir/ritonavir; NNRTIs, non-nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors; CrCl, creatinine clearance; GFR, glomerular filtration rate; AE, adverse effect; CV, cardiovascular; BMD, bone mineral density; HS, hypersensitivity.

the combination of TDF and a protease inhibitor was safe and well tolerated.[14,19,53]

In addition to the data derived from these studies, a large number of case reports have raised concern about cases of renal damage in patients with normal glomerular filtration rate exposed long-term to TDF (Table 2). While some individuals presented with acute renal failure,[48,60–67] most subjects initially showed tubulopathy, occasionally with overt Fanconi syndrome.[68–78] An early sign of tubular dysfunction is hypophosphatemia, although other signs and symptoms of kidney tubulopathy include glucosuria with normal serum glucose levels, mild proteinuria, acidosis, and hypokalemia. A subset of individuals may show evidence of nephrogenic diabetes insipidus.[68–72,76] The chronic consequences of significant loss of phosphate, proteins, and glucose are currently unknown, but are worrisome for an increased risk of premature osteoporosis and osteomalacia.[79,80] In addition, some studies have suggested a link between TDF use, secondary hyperparathyroidism, and low vitamin D levels, which also lead to a greater risk of osteopenia and osteoporosis.[81,82]

In spite of some studies having reported that impaired renal function related to TDF use generally improved after TDF discontinuation,[48,61,70,72,83] in some cases renal function did not fully recover, although renal damage did not progress.[84,85] Those studies in which renal function improved after TDF withdrawal have often been based on short-term follow-up or have looked only at creatinine clearance, a marker of glomerular disease that may not detect abnormalities in renal tubular function.

It is noteworthy that even though TDF is not yet licensed for use in HIV-infected individuals younger than 18 years of age, it is often used off-label in this age group as part of a salvage regimen. As with adults, some cases of proximal renal tubular dysfunction and bone disorders have been reported.[85–90] Bone density loss tends to occur more often in less skeletally mature children, who are at higher risk of growth disorders. Because children are likely to take antiretroviral therapy for longer than adults, and are more prone to long-term toxicity related to TDF use, alternative TDF dosing regimens and careful monitoring of bone density and renal function is indicated in the pediatric and adolescent population.

The most frequent risk factors for developing TDF-induced nephrotoxicity include baseline renal dysfunction, a low CD4 count, older age, and low body weight.[47,50,91] Classical risk factors associated with renal damage in HIV patients, such as pre-existing systemic conditions, HIV itself, antiretroviral therapy, or use of nephrotoxic agents, may also enhance the potential risk of nephrotoxicity associated with TDF.[91,92]

More recently, TDF-associated renal proximal tubulopathy has been linked to genetic variants in transporter proteins involved in tenofovir excretion (Figure 1).[93] Polymorphisms in these genes would lead to intracellular accumulation of tenofovir. This is the case for polymorphisms in the *ABCC2* gene which encodes for MRP2. The haplotype *CATC* (defined as the combination of the polymorphisms at positions-24, 1249, 3563, and 3972)[94] and the allele -24C[95] have been associated with an increased risk of TDF-associated tubulopathy. Moreover, MRP4, coded by the *ABCC4* gene, is also implicated. The 669-C > T polymorphism at the *ABCC4* gene has been found to be more frequent in patients sustaining renal tubular damage,[94] although this finding has not been confirmed by others.[95] The rs9349256 polymorphism at the *ABCC10* gene that encodes for MRP7 has recently also been associated with urine phosphate wasting and β_2-microglobulinuria, which are indicative of renal tubular dysfunction.[12] Currently, information about the effect of genetic polymorphisms on the risk of renal toxicity using TDF is a matter of controversy and requires further examination.

Few studies have examined the association between tenofovir exposure and renal toxicity. In most cases, patients developing tubulopathy had tenofovir levels above the concentration expected according to pharmacokinetic studies done in HIV-infected patients.[74,76,96] In a recent study, patients with tubulopathy displayed significantly higher tenofovir plasma concentrations than patients with normal tubular function. The threshold established to define tubulopathy in this study was above 160 ng/mL.[97] These results suggest an association between tenofovir plasma exposure and TDF-associated renal toxicity, primarily recognizable as tubular dysfunction. If these data are confirmed, the quantitation of tenofovir plasma levels could be useful in the management of patients.

Tenofovir and bone mineral loss

According to the HIV Outpatient Study, HIV-infected persons seem to experience bone fractures more frequently than people without HIV and, moreover, the decline in bone density seems to be accelerated in HIV-infected persons.[98,99] HIV infection in itself induces inflammation, which may result in accelerated loss of bone mineral density. On the other hand, antiretroviral therapy and some drugs in particular may increase the loss of bone mineral density. In the SMART (Strategies for Management of Anti-Retroviral Therapy) study, 240 HIV patients were randomized either to continue antiretroviral treatment or to interrupt it guided by CD4 cell counts. In patients who continued to be treated, bone mineral density decreased by

Table 2 Cases of renal damage in patients treated with tenofovir (2002–2009). Summary of kidney complications that have been communicated for patients treated with tenofovir between 2002 and 2009

Study	Cases (n)	Median months on treatment with TDF	ARV concomitant/ drugs with potential interaction	Other pathologies	Basal serum Cr (mg/dL)	Serum Cr on TDF (mg/dL)	Diagnosis
Verhelst et al[69]	1	5	ddI, LPV/r/TMP-SMZ	HCV	0.88	2.2	Fanconi syndrome, nephrogenic diabetes insipidus
Coca and Perazella[61]	1	1.5	ddI, ABC	Mild CKD, HCV	1.9	6.2	ATN
Creput et al[70]	1	1	ATV/r, ddI, d4T		0.82	4.0	Fanconi syndrome, nephrogenic diabetes insipidus
Karras et al[72]	3	12	ABC, LPV/r, ddI, 3TC, APV/r, T20		0.91	7.8	Fanconi syndrome
					0.93	1.74	Fanconi syndrome, nephrogenic diabetes insipidus
					1.15	2.71	ATN
Dupont et al[66]	2	13	DDC, LPV/r, 3TC/TMP-SMZ	On hemodialysis	0.84	20	ARF
						2.5	
Rollot et al[76]	1	27	3TC, ddI, LPV/r	Hypertension			Fanconi syndrome, nephrogenic diabetes insipidus; elevated ddI and TDF levels
Schaaf et al[83]	1	2	3TC, d4T, LPV/r/TMP-SMZ	Chronic hepatitis C	0.79	3.5	ARF
Peyriere et al[74]	7	10.3	3TC, EFV, LPV/r, ddI, APV/r, ABC, NVP/IFN, TMP-SMZ	HCV, Crohn's disease	0.77	1.14 CrCl 41 mL/min	ATN (elevated TDF levels)
Rifkin and Perazella[75]	5	12.6	ABC, ATV, 3TC, AZT, SQV, EFV, APV, ddI, ATV, DLV, LPV/r		1.1	1.8	Fanconi syndrome
					1.2	2.1	
					1.1	1.7	
					1.3	2.6	
					1.0	1.6	
Barrios et al[91]	1	1	ddI, EFV	Hypertension, hypercholesterolemia		1.81	Renal dysfunction
Parsonage et al[49]	2	25	ddI, 3TC, LPV/r/ibuprofen, rofecoxib, ABC, diclofenac	HBV, Kaposi's sarcoma, hypertension	0.73	1.9	Osteopenia, osteomalacia
					1.0	3.98	
Zimmermann et al[48]	5	20.2	DDI, d4T, 3TC, NVP, SQV, LPV/r, ATV/r, EFV, TMP-SMZ	HBV, HCV, diabetes mellitus type 2	1.0	3.4	Acute tubular necrosis
					0.8	7.4	ARF
					1.0	1.8	ARF
					0.7	7.1	ARF
					0.8	4.2	Fanconi syndrome
Mathew and Knaus[73]	1	6	3TC, EFV			2.5	Fanconi syndrome
De la Prada et al[78]	1	2	LPV/r, T20	Hypertension	1.24	7.74	Tubular damage

Kapisinou and Ansari[63]	1	60	EFV, 3TC	HBV, HCV	0.8	9.8	
Vallecillo-Sánchez et al[64]	2	2.5	ATV/r, 3TC, TDF, FTC, Salbutamol inhaler	COPD, hypertension	0.96 1.10	1.8 CrCl 45 mL/min 1.56 CrCl 67 mL/min	Renal insufficiency associated with ATV use
Irizarry-Alvarado et al[71]	3	6.6	ddI, LPV/r, FPV, TMP-SMZ	HCV, HBV		1.0 1.2 2.4	Fanconi syndrome, nephrogenic diabetes insipidus
Di Biagio et al[79]	1	1	3TC, EFV	HCV, osteoporosis, mild chronic renal insufficiency	1.7	1.8	Fanconi syndrome
Heine et al[96]	1		LPV/r, 3TC/diclofenac	HCV		10.43 CrCl 7 mL/min	Elevated TDF and LPV levels
Labarga et al[77]	3	>24	PIs	Diabetes, hypertension		CrCl 79–118 mL/min *Fanconi criteria	Fanconi syndrome with normal GFR
Wood et al[67]	2	20.5	LPV/r		0.9 CrCl 121 mL/min	3.2 CrCl 35.9 mL/min 1.3 GFR 104 mL/min, ↑ALP, ↑β_2-MG, ↓%TRP	CKD Renal tubular injury secondary to TDF nephrotoxicity, rickets

Note: *Proximal tubular renal dysfunction criteria: glucosuria (urine glucose >300 mg/day) with normal glycemia (plasma glucose <100 mg/dL), hyperaminoaciduria (any amino acid in urine, with the exception of histidine, glycine and serine), fractional tubular resorption of phosphorus <0.82; total excretion of phosphorus >1200 mg/day; fractional excretion of uric acid >15%; and β_2-microglobulinuria >1 mg/day. Tubular damage when 2 or more criteria were present, being at least one of the Fanconi syndrome defining alterations (glycosuria in nondiabetic patients, hyperaminoaciduria, or hyperphosphaturia).

Abbreviations: TDF, tenofovir; ddI, didanosine; LPV, lopinavir; ATV, atazanavir; d4T, stavudine; ABC, abacavir; 3TC, lamivudine; APV, amprenavir; FPV, fosamprenavir; T20, enfuvirtide; DDC, zalcitabine; TMP-SMZ, cotrimoxazole; EFV, efavirenz; NVP, nevirapine; RVB, ribavirin; IFN, interferon; SQV, saquinavir; AZT, zidovudine; DLV, delavirdine; r, ritonavir; Cr, creatinine; CrCl, creatinine clearance; ALP, alkaline phosphatase; TRP, tubular reabsorption of phosphate; β_2-MG, betamicroglobulin; HCV, hepatitis C virus; HBV, hepatitis B virus; CKD, chronic kidney disease; ATN, acute tubular necrosis; ARF, acute renal failure; COPD, chronic obstructive pulmonary disease.

0.8% per year at the hip ($P < 0.001$) and 0.4% ($P = 0.04$) or 2.4% ($P < 0.001$) at the spine (depending on the technique used, ie, either dual-energy radiographic absorptiometry or quantitative computed tomography). In contrast, bone mineral density remained stable or increased after 1 year in the group in which antiretroviral therapy was interrupted.[100] Several clinical trials have shown that certain antiretrovirals may have a greater impact than others on loss of bone density. Although initially the protease inhibitors were thought to be associated with the greatest amount of bone loss,[101] more recent studies have failed to confirm this association.[102] Nevertheless, TDF use has been consistently associated with a decrease in bone density. Among other studies supporting this link are the 903 trial,[26] ASSERT,[31,40] and STEAL (Simplification with Tenofovir-Emtricitabine or Abacavir-Lamivudine).[33] In all of these studies, patients receiving TDF had higher rates of bone density loss than those randomized to receive either stavudine or abacavir (Table 3). TDF use is associated with higher rates of renal tubular dysfunction compared with other nucleoside reverse transcriptase inhibitors,[56,77] the phosphate loss associated with this damage being the primary driver of loss of bone density.

Parathyroid hormone is the major systemic determinant of bone turnover. Elevations in parathyroid hormone result in bone mineral loss.[103] In HIV patients on antiretroviral treatment, parathyroid hormone elevations have been reported in up to 20%–40% of cases.[81] In a recent study conducted in 564 HIV patients, some of whom received TDF and others did not, 44% vs 24%, respectively ($P < 0.001$) developed hyperparathyroidism over 71 months. Moreover, a significant decrease in plasma calcium levels was observed in the TDF group,[104] which might explain the elevation in parathyroid hormone.

Vitamin D deficiency causes parathyroid hormone elevations in the general population.[105] This deficit can occur in up to 37% of patients with HIV infection.[106] Vitamin D deficiency causes greater parathyroid hormone elevations in patients treated with TDF than in those treated with other nucleoside reverse transcriptase inhibitors.[82] However, in TDF-treated patients, parathyroid hormone elevations may not only depend on vitamin D deficiency, given that similar vitamin D levels, measured as $25(OH)D_3$ and $1,25(OH)_2D_3$, are seen in patients treated with and without TDF.[104,107] Activation of $25(OH)D_3$ into $1,25(OH)_2D_3$, which is the active form of vitamin D, takes place in the proximal tubule of the nephron and is stimulated by parathyroid hormone. Given that TDF may cause tubular damage, impaired activation of $25(OH)D_3$ may occur, which subsequently may decrease the intestinal absorption of calcium, leading to a greater parathyroid hormone increase in an

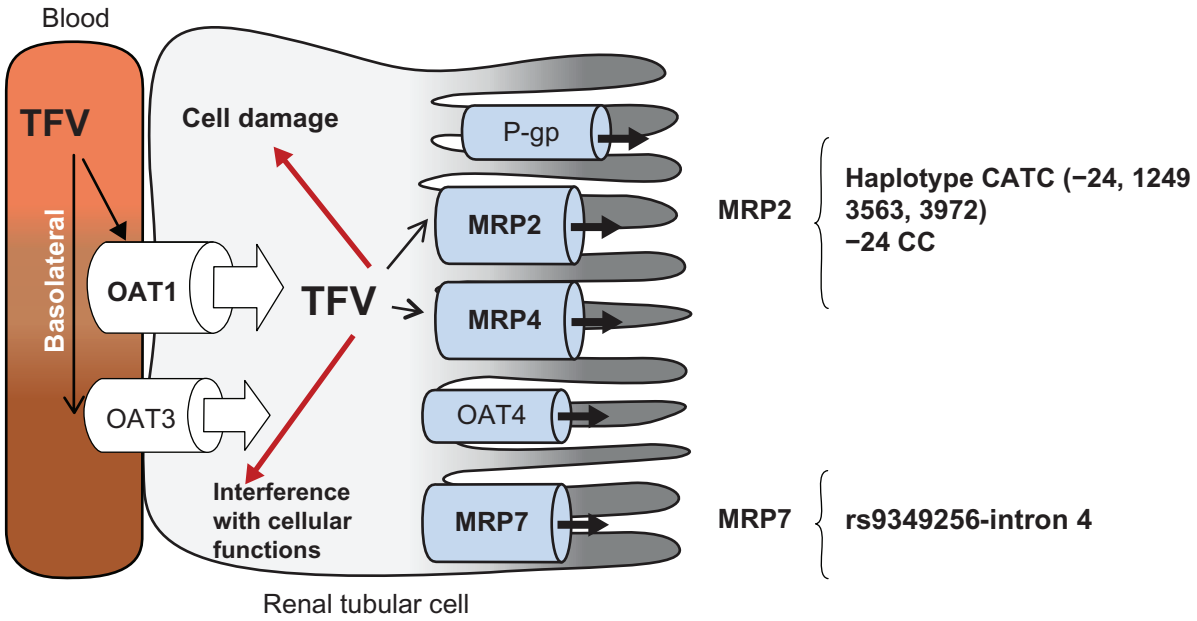

Figure 1 Main transporter proteins involved in elimination of tenofovir from tubular renal cells. TFV enters kidney cells using OAT1 and in a lesser extent, OAT3 and it is eliminated by MPR4. Genetic polymorphisms in transporter proteins may influence the elimination of TFV. The more relevant polymorphisms associated with tubulopathy are listed on the right side of the figure.
Abbreviations: TFV, tenofovir; OAT1, organic anion transporter protein-1; OAT3, organic anion transporter protein-3; MRP4, multidrug resistant protein-4; MRP2, multidrug resistant protein-2; MRP7, multidrug resistant protein-7.

attempt to correct this imbalance. Whatever the mechanism, it seems clear that patients treated with TDF have an imbalance between parathyroid hormone, vitamin D, and calcium in plasma. Recognition of this abnormality has provided a rationale for empiric administration of vitamin D to patients treated with TDF. Although a decrease in parathyroid hormone levels may occur, it happens regardless of baseline $25(OH)D_3$ levels, something that is not seen in patients who do not receive TDF.[108]

Tenofovir for prevention of HIV infection

The recent publication of two trials, ie, CAPRISA (Centre for the AIDS Program of Research in South Africa)[109] and

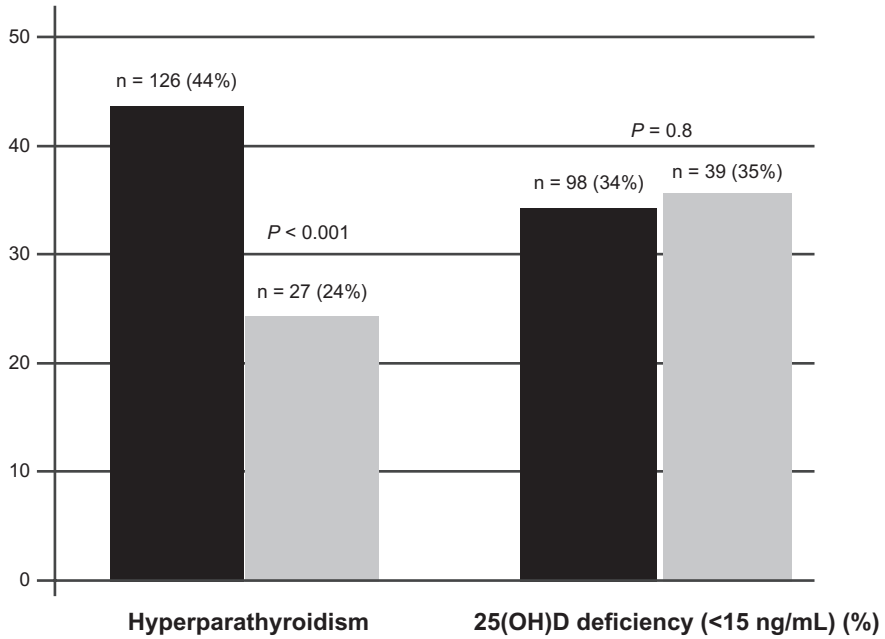

Figure 2 Prevalence of hyperparathyroidism and 25-hydroxyvitamin D deficiency according to TDF use. Light grey bars represent TDF users while the black ones represent those patients not taking TDF. Frequency of hyperparathyroidism differs significantly among TDF and non-TDF users, whereas no difference was found for 25(OH)D levels between groups.

Table 3 Most relevant studies that have examined bone parameters in subjects with HIV treated by TDF vs patients not exposed to TDF

Study (reference)	Comparative groups	Patients (n)	Bone-related parameters	Main findings
Study 903[26]	TDF vs d4T + 3TC/EFV	299 TDF 301 d4T	Change in BMD Lumbar spine: −2.2% TDF vs −1.0% d4T; $P = 0.01$. Hip: −2.8% TDF vs −2.4% d4T; $P = 0.06$	Greater loss of BMD in the TDF arm
ASSERT study[31,40]	TDF/FTC vs ABC/3TC + EFV	197 TDF/FTC 195 ABC/3TC	Change in BMD: Lumbar spine: −2.4% TDF vs −1.6% ABC; $P = 0.036$ Hip: −3.6% TDF vs −1.6% ABC; $P < 0.001$. BMD loss >6: 13% TDF vs 3% ABC in the hip. 10% TDF vs 5% ABC in the spine	TDF/FTC: Increases in markers of tubular dysfunction, bone turnover and decreases in BMD
STEAL study[33]	TDF/FTC vs ABC/3TC + NNRTIs or PIs	180 TDF/FTC 180 ABC/3TC	Mean difference in hip t score, 0.16; 95% CI: 0.08–0.23; $P < 0.001$ Rates of bone disorders: 8.5 TDF vs 4.4 ABC; $P = 0.0032$	Greater loss of BMD in the TDF arm
Kinai and Hanabusa[56]	TDF vs other NRTI	40 TDF 23 NRTI	Change in % TRP from baseline to 96 weeks: 94 to 90% $P = 0.04$ TDF 96 to 94% $P = 0.33$ NRTI	Consider close monitoring or TDF discontinuation if persistent decline of % TRP
Labarga et al[77]	TDF vs non-TDF	154 TDF 49 non-TDF 181 naïve	TRP rate in TDF vs non-TDF and naïve: 0.82, 0.85 and 0.87	Close monitoring of accelerated bone mineral loss and renal insufficiency
Rosenvinge et al[82]	TDF vs non-TDF	108 TDF 86 non-TDF	PTH levels: 7.2 TDF vs 4.3 non-TDF (pg/mL) PTH in VVD (<50 nmol/L): 8.2 TDF vs 4.6 non-TDF (pg/mL)	VDD is associated with TDF linked Hyper-PTH
Pocaterra et al[107]	TDF vs non-TDF	214 TDF 232 PIs	Overall: 17.5% patients Hyper-PTH (ULN = 65 pg/mL) 77.4% patients VDD (<30 mg/dL) TDF group: 75.4% PTH > 65 vs 55.9% PTH < 65 in TDF group, $P = 0.002$	Association between hyper-PTH, TDF use and 25(OH)D levels beside classical factors
Labarga et al[104]	TDF vs non-TDF	433 TDF 131 non-TDF	Hyper-PTH: 37% TDF vs 14% non-TDF; $P < 0.001$ Hyper-PTH + VDD (<15 ng/mL): 44% TDF vs 10% non-TDF; $P < 0.001$	Hyper-PTH and bone resorption might develop in the subset of patients taking TDF with suboptimal 25(OH)D levels
Childs et al[81]	TDF vs non-TDF	45 HAART	PTH levels: 80 pg/mL TDF vs 55 pg/mL non-TDF; $P = 0.02$ In VDD (< 30 ng/mL): PTH elevated in 41% TDF vs 0% non-TDF; $P = 0.018$	Use of TDF and the level of 25(OH)D were independently associated with PTH levels

Abbreviations: TDF, tenofovir disoproxil fumarate; d4T, stavudine; 3TC, lamivudine; EFV, efavirenz; FTC, emtricitabine; ABC, abacavir; NNRTIs, non-nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors; NRTI, nucleoside reverse transcriptase inhibitors; PL, placebo; BMD, bone mineral density; TRP, tubular reabsorption of phosphate; PTH, parathyroid hormone; hyper-PTH, hyperparathyroidism; ULN, upper limit of normal; VDD, vitamin D deficiency.

iPrEX (Pre Exposure Prophylaxis Initiative),[110] has raised unprecedented interest in pre-exposure prophylaxis as a way to combat the HIV pandemic. CAPRISA examined nearly 900 heterosexually active women in South Africa and demonstrated that use of topical vaginal TDF reduced the risk of HIV acquisition by 39% overall, rising to 54% in the subset of women with high gel adherence.

The iPrEX trial examined nearly 2500 homosexual men in South America, South Africa, Thailand, and the US, and was the first to show that daily oral TDF + emtricitabine

could reduce the risk of HIV infection by 44% overall, increasing to 73% in the subset of men with sustained good drug adherence.

These trial results have been greeted with huge enthusiasm, especially in the wake of disappointing results from several prior studies, but have also raised numerous questions about who could potentially benefit, the long-term risks of these interventions, and cost and access issues. Moreover, antiretroviral use for preventing infection in HIV-seronegative individuals at risk must be considered in the context of other interventions that may help equally to reduce HIV acquisition.

While Truvada has not been approved so far for HIV prevention, doctors may prescribe drugs for off-label use, and some individuals engaged in high-risk behaviors might consider immediate use of the drug as pre-exposure prophylaxis. For these reasons, on January 28, 2011, the Centers for Disease Control and Prevention (CDC) released new guidance intended to offer instructions and cautions for people interested in using pre-exposure prophylaxis immediately, while awaiting more extensive clinical trial data for longer-term use and other at-risk populations. The CDC guidance is available at: http://www.cdc.gov/nchhstp/newsroom/PrEPMSMGuidanceGraphic.html.

Briefly, the CDC recommendations for pre-exposure prophylaxis are:

- Confirm that the person seeking pre-exposure prophylaxis is at substantial ongoing high risk for acquiring HIV infection
- Test for HIV, including, if symptomatic, acute HIV infection that may not be detectable with a standard antibody test, given that using just two antiretroviral drugs could lead to resistance if HIV is present; repeat HIV testing every 3 months while on pre-exposure prophylaxis
- Screen for and treat other sexually transmitted diseases, including syphilis, gonorrhea, hepatitis B and C, and repeat testing every 6 months while on pre-exposure prophylaxis
- Test for kidney function (creatinine clearance), because tenofovir may produce renal injury in some individuals, and monitor kidney function after 3 months and then annually while on pre-exposure prophylaxis
- Screen for, and if uninfected, vaccinate against hepatitis B; if infected, consider the dual use of Truvada for treatment, because TDF and emtricitabine are both active against HBV and HIV
- Provide pre-exposure prophylaxis as part of a comprehensive prevention approach, along with risk-reduction counseling and condoms; assess risk behavior every 3 months while on pre-exposure prophylaxis
- Stress importance of and offer support for drug adherence.

It should be kept in mind that the iPrEX trial did not provide evidence that using Truvada only before or after sex encounters is effective. Pre-exposure prophylaxis has the potential to contribute to effective and safe HIV prevention for homosexual men engaged in high-risk behaviors, but its maximal cost-effectiveness will be obtained taking into consideration a number of factors, including the following:

- Homosexual men at high-risk for HIV acquisition need to be targeted
- Pre-exposure prophylaxis must be delivered as part of a comprehensive set of prevention services, including risk-reduction and medication adherence counseling, ready access to condoms, and diagnosis and treatment of sexually transmitted diseases
- Monitoring of HIV status, side effects, adherence, and risk behaviors at regular intervals is mandatory.

Finally, all these efforts for helping to reduce HIV acquisition must be accompanied by appropriate information and education about safer lifestyles, particularly high-risk sexual practices.

Tenofovir for hepatitis B treatment

TDF was licensed in 2008 for the treatment of hepatitis B infection. It is a potent inhibitor of hepatitis B virus reverse transcriptase, with an IC_{50} of 0.14–1.5 μM.[3] TDF along with entecavir are currently the preferred first-line choices for treatment in hepatitis B-monoinfected patients. TDF has been demonstrated to be effective either in nucleos(t)ide analogs-naïve patients or in patients with prior resistance to lamivudine and/or adefovir, although in the latter situation the response tends to be lower.[111–113]

Of 350 million people worldwide infected with the hepatitis B virus, approximately four million are coinfected with HIV. HIV modifies the natural history of the hepatitis B virus, favoring chronification and accelerating progression to cirrhosis and end-stage liver disease.[114] In patients who need to be treated for either HIV or hepatitis B virus infection, early initiation of antiretroviral treatment, including drugs active against hepatitis B virus (lamivudine, emtricitabine, TDF) is recommended. At this time, TDF is preferred to lamivudine as the only active anti-hepatitis B virus agent in this context, given its higher genetic barrier to resistance. Thus, the coformulation of TDF + emtricitabine is the most popular nucleoside reverse transcriptase inhibitor backbone

in coinfected patients.[115] Because prolonged TDF exposure may cause kidney dysfunction in a small proportion of treated individuals, renal function should be carefully and periodically monitored in individuals coinfected with HIV and hepatitis B virus.

Patient-focused perspectives

The availability of highly active antiretroviral therapy has markedly improved survival rates and quality of life in patients infected with HIV. The natural history of HIV infection has been changed into a manageable chronic disease requiring long-term antiretroviral treatment. Because patients need to continue their treatment lifelong, the preferred antiretroviral regimen will be one that, along with efficacy, optimizes the likelihood of patient compliance. One strategy to improve adherence is to facilitate the intake of medication, for example, by reducing the pill burden, including drugs that allow once-daily dosage or those with no food restrictions.

Antiretroviral drugs are characterized by differing rates of response and adverse events. It is known that drug metabolism and drug toxicity may vary greatly between individuals, affecting both efficacy and toxicity. Strategies aimed at individualizing therapy would help to diminish this variability. Genetic variations might explain a proportion of this variability. In recent years, a number of associations between human genetic variants and predisposition to drug toxicity and risk of virologic failure have been described. These include the HLA class II allele *HLA-DRB*0101* associated with nevirapine hypersensitivity,[116,117] *HLA-B*5701* with abacavir hypersensitivity reaction,[118–121] CYP2B6 alleles, with the central nervous system side effects of efavirenz,[122–125] *UGT1A1* alleles or polymorphisms in genes encoding for P glycoprotein both related to atazanavir-associated hyperbilirubinemia,[126–128] and polymorphisms in genes encoding for transporter proteins with renal proximal tubulopathy in patients taking TDF.[7,12,93,95] Moreover, therapeutic drug monitoring may be helpful, allowing dose adjustments, especially when using a drug with a narrow therapeutic range, because small changes in drug levels lead to loss of efficacy and/or increased risk of toxicity. It may also be of aid in those cases in which information about drug interactions is still scarce, ie, for agents which have recently entered the marketplace.[129–131]

Conclusion

TDF is one of the most widely used antiretroviral drugs in clinical practice due to its potent antiviral activity, acceptable safety profile, and convenient administration. The antiretroviral regimen currently recommended for initial therapy is the combination of TDF + emtricitabine, with addition of a convenient third agent, ie, efavirenz, raltegravir, or one of the newer ritonavir-boosted protease inhibitors (darunavir or atazanavir). TDF is also indicated in other situations, tt for replacing other nucleoside reverse transcriptase inhibitors in patients already with undetectable viremia, in an attempt to avoid or reverse the development of mitochondrial-related side effects, mainly lipoatrophy. TDF maintains its activity in most patients harboring drug-resistant variants, with only a few thymidine-associated mutations selected in prior episodes of treatment failure. Other situations in which TDF is being used include the treatment of patients coinfected with HIV and hepatitis B virus, and more recently, with great anticipation as part of pre-exposure prophylaxis. TDF is generally well tolerated in the short-term. However, a subset of individuals on prolonged TDF therapy may develop kidney tubular dysfunction and/or bone mineral loss. Periodic monitoring of renal function, in particular for tubular abnormalities, examining both plasma and urine biochemistry, may enable early recognition of individuals in whom the drug should be stopped to prevent more serious tubular damage and compromise of glomerular function. In this regard, information derived from pharmacogenetics and pharmacokinetics may help to identify the subset of individuals at greater risk for developing more severe renal injury.

Disclosure

The authors report no conflicts of interest in this work.

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