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Tenofovir Disoproxil Fumarate

Therese M. Chapman, *Jane K. McGavin* and *Stuart Noble*

Adis International Limited, Auckland, New Zealand

Contents

Abstract

▲ Tenofovir disoproxil fumarate (tenofovir DF) is a prodrug of tenofovir, a nucleotide reverse transcriptase inhibitor.

▲ In two large, well designed, placebo-controlled clinical trials, tenofovir DF 300 mg/day resulted in significant reductions in HIV-1 RNA from baseline compared with placebo at 24 weeks in antiretroviral-experienced patients with HIV infection. Patients in both treatment groups continued to receive existing stable antiretroviral therapy.

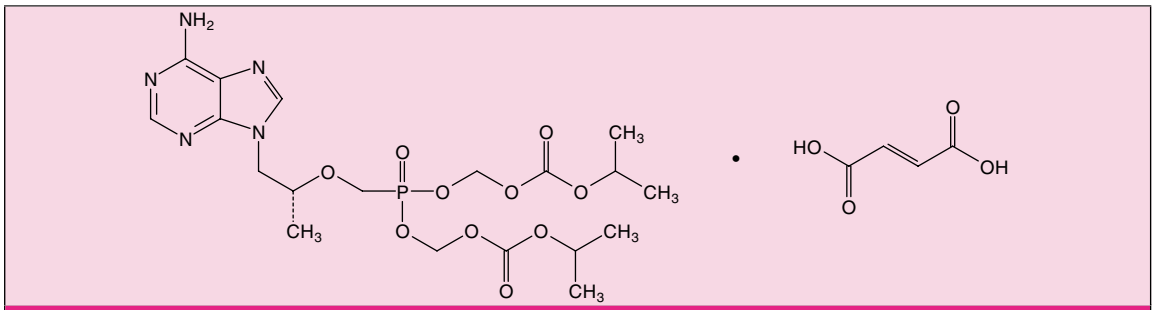
▲ In an extension phase of one trial, these reductions in viral load were maintained after 96 weeks of treatment with tenofovir DF.

▲ Preliminary data from a large, 3-year comparative trial suggest the clinical efficacy of tenofovir DF in combination with baseline antiretroviral therapy is similar to that of stavudine in antiretroviral-naive patients with HIV infection.

▲ Virological substudies showed that viral suppression was maintained in patients who developed new reverse transcriptase mutations during tenofovir DF therapy (in combination with existing stable antiretroviral drugs) for up to 48 weeks. Isolates of HIV infrequently developed the K65R mutation during 96 weeks of tenofovir DF therapy.

▲ Tenofovir DF is generally well tolerated. The most commonly observed adverse events seen with tenofovir DF (in combination with other antiretroviral drugs) were predominantly of a gastrointestinal nature.

Features and properties of tenofovir disoproxil fumarate (Viread®)	
Indication	
HIV infection	
Mechanism of action	
Antiviral	Prodrug of nucleotide reverse transcriptase inhibitor
Dosage and administration	
Recommended dosage	300mg once daily
Route of administration	Oral
Median pharmacokinetic profile of tenofovir (oral tenofovir disoproxil fumarate 300 mg/day for 28 days in fed patients with HIV infection)	
Peak serum concentration	326 ng/mL
Time to peak serum concentration	2.3h
Area under the serum concentration-time curve	3020 ng • h/mL
Serum terminal elimination half-life	14.4h
Adverse events	
Most frequent	Nausea, diarrhoea, asthenia, headache, vomiting, flatulence, abdominal pain and anorexia



Tenofovir disoproxil fumarate (tenofovir DF; Viread®[1]) is an ester prodrug of the nucleotide reverse transcriptase inhibitor tenofovir. Tenofovir, a nucleotide analogue of adenosine 5′-monophosphate with activity against HIV reverse transcriptase, demonstrates poor oral bioavailability.[1] Tenofovir DF was synthesised to enhance oral absorption[2] and to improve cellular uptake of the drug.[3]

This profile focuses on data relevant to the use of tenofovir DF in patients with HIV infection.

1. Pharmacodynamic Properties

This section provides an overview of the effects of both tenofovir DF and tenofovir since the prodrug is rapidly converted to tenofovir after oral administration.

Mechanism of Action

- *In vivo*, tenofovir DF is hydrolysed to tenofovir,[4] which is then phosphorylated by cellular kinases to the pharmacologically active metabolite tenofovir diphosphate.[3] Tenofovir diphosphate inhibits the activity of HIV reverse transcriptase by competing with the nucleotide deoxyadenosine 5′-triphosphate for incorporation into viral DNA. Once incorporated into viral DNA, it terminates DNA elongation because of lack of a ribose ring.[5]

In Vitro Activity

Antiviral Activity

- Tenofovir DF had greater inhibitory activity than tenofovir against wild-type virus (HIV-1_{IIIb}) in MT-2 T-lymphocytes (concentration required for 50% inhibition [IC_{50}] 0.003 vs 0.5 μmol/L[6] and 0.007 vs 0.63 μmol/L).[3] A similar result was seen for peripheral blood mononuclear cells (PBMC) [IC_{50} 0.005 vs 0.18 μmol/L].[3] This was attributed to a more rapid intracellular uptake of tenofovir DF than of tenofovir and a resultant >1000-fold higher intracellular accumulation of the active metabolite tenofovir diphosphate.[3]
- Tenofovir (1–100 μmol/L) showed strong synergistic inhibition of HIV replication in HIV-1_{IIIb}–infected MT-2 cells in combination with zidovudine, amprenavir, nevirapine and delavirdine, and mild-to-moderate synergistic inhibition with didanosine, nelfinavir and adefovir; additive inhibition was evident in combination with abacavir, lamivudine, stavudine, zalcitabine, indinavir, ritonavir and saquinavir.[7,8] No significant antagonistic interactions were found for any of the antiretroviral agents with tenofovir.[7,8]
- Mycophenolic acid enhanced the activity of tenofovir against wild-type, tenofovir-resistant (with the K65R mutation) and nucleoside reverse transcriptase inhibitor (NRTI)-resistant strains of HIV in PBMCs.[9]

1 Use of tradename is for product identification purposes only and does not imply endorsement.

Cytotoxicity

• Tenofovir DF showed greater cytotoxicity than tenofovir in HIV-1_{IIIb}–infected MT-2 cells (50 vs 250 μmol/L[6] and 22 vs 1250 μmol/L,[3] respectively, were required to kill 50% of cells [CC_{50}]). Selectivity (CC_{50}/IC_{50}) ratios for tenofovir and the prodrug in MT-2 cells were 500 vs 16 600,[6] and ≈2000 vs ≈3000, respectively.[3]

• High concentrations of tenofovir (up to 2 mmol/L) did not significantly inhibit the *in vitro* growth of human renal proximal tubule epithelial cells (RPTECs), nor did it significantly affect the ability of these cells to maintain the integrity of tight junctions *in vitro* after 10 days of incubation.[10] Conversely, cidofovir inhibited the growth of RPTECs (CC_{50} of 260 μmol/L) and altered the ability of these cells to maintain the integrity of the tight junctions of the renal proximal tubule epithelium (concentration reducing transepithelial electrical resistance by 50% [$CTER_{50}$] 100–120 μmol/L).[10] The effects of adefovir on these cells were mild and dose-dependent.[10] Despite this, tenofovir DF has been associated with changes to renal function in clinical trials and postmarketing surveillance (section 5).

Immunomodulatory Effects

• Tenofovir also displays immunomodulatory effects.[11-13] In *in vitro* studies using murine or human cell lines, tenofovir stimulated secretion of cytokines capable of interfering with HIV replication (interleukin [IL]-1β, IL-10 and tumour necrosis factor-α) and chemokines that inhibit entry of HIV into cells (regulated upon activation normal T cell expressed and secreted [RANTES] and macrophage inflammatory protein 1α); however, no effect was seen on interferon-γ and IL-2 expression.[11-13]

2. Pharmacokinetic Properties

Most of the data reported in this section relate to the pharmacokinetic profile of tenofovir after administration of tenofovir DF monotherapy. The pharmacokinetic properties of tenofovir DF have been described in animals,[14,15] healthy volunteers[16,17] and patients with HIV infection.[18-20] Where possible, this section focuses on data for the recommended dosage of tenofovir DF (300 mg/day) in patients with HIV infection.

• In a pooled analysis of pharmacokinetic data from healthy volunteers and patients with HIV infection, there were no significant differences in the pharmacokinetic parameters of tenofovir on the basis of gender, age (19–57 years) or body weight (50–112kg) after administration of tenofovir DF 300mg (duration of treatment not reported).[20] No published data are available for patients with hepatic impairment, children or the elderly.

Absorption and Distribution

• Transport across Caco-2 intestinal mucosal monolayers,[14] uptake into PBMCs[3] and *in vivo* intestinal absorption in rats[15] were markedly greater for tenofovir DF than for tenofovir (27-fold, >1000-fold and 12-fold, respectively).

• Tenofovir DF showed dose-proportional pharmacokinetics after administration of 75–600 mg/day for 28 days in a randomised, double-blind, placebo-controlled, dose-escalation study in patients with HIV infection (n = 49).[19]

• The oral bioavailability of tenofovir after administration of tenofovir DF 300 mg/day was 25% and increased to 39% when tenofovir DF was administered with a standardised high fat meal.[19]

• Median steady-state maximum serum tenofovir concentrations (C_{max}) and the area under the serum tenofovir concentration-time curve (AUC) were 326 ng/mL and 3020 ng • h/mL in patients infected with HIV who received tenofovir DF 300 mg/day with food for 28 days.[19] The median time to C_{max} was 2.3 hours.[19]

• Binding of tenofovir to human plasma or serum proteins *in vitro* is <0.7% and <7.2%, over the tenofovir concentration range 0.01–25 μg/mL.[4,21] The US prescribing information states that the mean steady-state volume of distribution for intravenous tenofovir 1 and 3 mg/kg was 1.3 L/kg and 1.2 L/kg.[4]

Metabolism and Elimination

- Tenofovir concentrations in serum decline in a biphasic manner.[19] Administration of tenofovir DF 300 mg/day with food for 28 days to patients with HIV infection resulted in a median serum terminal elimination half-life for tenofovir of 14.4 hours and clearance rate of 0.51 L/h/kg.[19] In an *in vitro* study, the half-life of tenofovir diphosphate in activated PBMCs preincubated with tenofovir DF or tenofovir was 11 hours; however, the half-life of tenofovir diphosphate in resting PBMC preincubated with tenofovir was 49 hours.[3]
- After administration of intravenous tenofovir 1 mg/kg for 7 days to patients with HIV infection, 72.4% of the dose was recovered in the urine within 24 hours, suggesting renal elimination is the main elimination pathway.[18] The US prescribing information reports that within 72 hours of an intravenous administration of tenofovir (dosage not reported) approximately 70–80% of the dose is recovered in the urine as unchanged drug.[4] The renal clearance of tenofovir exceeded the calculated creatinine clearance of recipients, indicating elimination occurs via a combination of active tubular secretion and glomerular filtration.[18,19]

Patients with Renal Impairment

- The absorption and clearance of a single oral dose of tenofovir DF 300mg were not significantly different in otherwise healthy patients with mild renal impairment (creatinine clearance [CL_{CR}] 50–80 mL/min) from those in healthy volunteers (>80 mL/min) [presented in a poster].[22] However, otherwise healthy patients with moderate to severe renal impairment (CL_{CR} <50 mL/min) had greater reductions in renal elimination and higher exposure to tenofovir (C_{max} and AUC) than healthy volunteers (p values not reported).[22]
- Tenofovir was efficiently removed from the circulation during standard high-flux haemodialysis sessions in end-stage renal disease patients (n = 9) [median extraction coefficient 54%].[22]
- In the US it is currently recommended that tenofovir DF should not be administered to patients with renal impairment (CL_{CR} <60 mL/min)[4] whereas in Europe tenofovir DF is contraindicated in patients with severe renal impairment (CL_{CR} not reported).[21] However, adjustments to the tenofovir DF dosage interval have been suggested for this patient population (section 6).[22]

Drug Interactions

- The potential for a pharmacokinetic interaction between tenofovir DF and drugs metabolised by cytochrome P450 (CYP450) enzymes is low.[4,21] *In vitro* studies have shown that tenofovir is not metabolised by the CYP450 enzymes, nor does it inhibit drug metabolism by CYP3A4, CYP2D6, CYP2C9 or CYP2E1; however, a 6% reduction in CYP1A2 metabolism was observed.[4,21]
- As tenofovir is eliminated by the kidney, the coadministration of other drugs that reduce renal activity or compete for renal elimination may result in increased serum concentrations of either tenofovir or the coadministered drug.[4]
- Although various quantitative differences in the pharmacokinetic profiles of tenofovir and coadministered antiretroviral drugs have been documented, no clinically significant interactions were apparent when tenofovir DF and lamivudine, efavirenz, indinavir or lopinavir/ritonavir were coadministered in two crossover studies in healthy volunteers.[16,17] Tenofovir DF 300 mg/day was administered with lamivudine 150mg twice daily or indinavir 800mg three times daily for 7 days and with efavirenz 600 mg/day for 2 weeks (all in the fasted state) and with lopinavir/ritonavir 400/100mg twice daily with food for 14 days.[16,17]
- Coadministration of tenofovir DF 300 mg/day and buffered or enteric-coated didanosine in healthy volunteers did not alter the pharmacokinetic profile of tenofovir. However, the C_{max} and AUC of didanosine were increased relative to didanosine 400mg alone in the fasted state (increases of 28–64% and 44–60%);[16,23,24] buffered didanosine 400 mg/day (250 mg/day if bodyweight <60kg) was administered 1 hour prior to tenofovir DF (both in the fasted state)[16,23] and enteric-coated didanosine 400mg

was administered either 2 hours before or with tenofovir DF and a light meal (373 kcal, 20% fat).[24]

- The administration of a reduced dosage of enteric-coated didanosine (250mg) 2 hours before, or with tenofovir DF 300mg (with or without a light meal) resulted in a C_{max} and AUC similar to that of enteric-coated didanosine 400mg alone.[25] Although no formal recommendations for modifications to the didanosine dosage are available, it is recommended that caution be exercised when tenofovir DF and didanosine are to be coadministered and patients receiving this combination be monitored closely for didanosine-associated adverse events[4,21] and in the US it is recommended that treatment with didanosine should be discontinued in patients who develop didanosine-associated adverse events (section 6).[4]

3. Clinical Efficacy

In the treatment of HIV infection, the antiviral efficacy of tenofovir DF has been compared with that of placebo in two clinical trials in antiretroviral-experienced patients[26,27] and with that of stavudine in one trial in antiretroviral-naive patients.[28] However, there are no data on the clinical progression of HIV (e.g. AIDS-defining events and mortality).

With the exception of one fully published placebo-controlled trial,[26] the results of these randomised, double-blind trials have been presented as abstracts and/or posters. Data are from the intent-to-treat analysis.[26-28]

Comparisons with Placebo

In both placebo-controlled trials, patients received existing stable antiretroviral therapy (≤4 agents for ≥8 weeks prior to study entry) in addition to tenofovir DF or placebo.[26,27] At 24 weeks, placebo recipients in both trials were switched to tenofovir DF 300 mg/day for a further 24 weeks.[26,27] At baseline, 94% of patients in the trials had HIV isolates with NRTI-associated resistance mutations (NAMs).[26,27]

- Tenofovir DF 300 mg/day was significantly more effective than placebo for the primary viral load endpoint at 24 weeks in both placebo-controlled trials.[26,27]

Dose-Ranging Trial

In a dose-ranging trial, 186 antiretroviral-experienced patients (overall mean duration of treatment 4.6 years) were included in the intent-to-treat analysis and received tenofovir DF 75 (n = 53), 150 (n = 51) or 300mg (n = 54) or placebo (n = 28).[26] The overall mean baseline CD4+ cell count was 374 cells/μL and the overall mean baseline HIV-1 RNA level was 3.7 $\log_{10}$ copies/mL.[26]

- Tenofovir DF 75, 150 and 300 mg/day produced significantly greater reductions from baseline in plasma HIV-1 RNA (assessed using a time-weighted mean change [D_{AVG}]) than placebo (figure 1).[26] Significant differences were seen as early as 4 weeks ($p < 0.01$) and remained significant after 24 weeks ($p < 0.02$) [figure 1].[26]

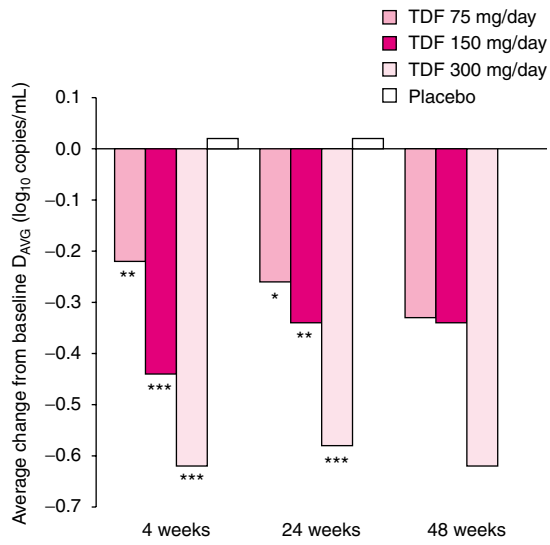


Fig. 1. Comparative antiviral efficacy of oral tenofovir disoproxil fumarate (TDF) 75–300 mg/day and placebo.[26] Change from baseline HIV-1 RNA levels in antiretroviral-experienced patients with HIV infection included in the intent-to-treat analysis (n = 186). Patients were randomised to receive double-blind TDF 75, 150 or 300mg or placebo administered once daily in addition to existing antiretroviral therapy for 24 weeks. Patients receiving placebo were treated with TDF 300 mg/day from week 24. Baseline status: mean CD4+ cell count = 374 cells/μL; mean HIV-1 RNA level = 3.7 $\log_{10}$ copies/mL. * $p < 0.02$, ** $p < 0.01$, *** $p < 0.001$ vs placebo.

• The greatest reduction in viral load at 48 weeks was achieved by patients receiving tenofovir DF 300 mg/day (figure 1).[26] However, there was no significant difference between the treatment groups for the mean change in CD4+ cell count at any timepoint up to 48 weeks.[26]

• After 48 weeks of treatment in the above study, 135 patients originally randomised to tenofovir DF 75–300 mg or placebo once daily elected to receive tenofovir DF 300 mg/day in a nonblind extension to 96 weeks.[29] Viral suppression was maintained in 94 patients who were originally randomised to receive tenofovir DF 75–300 mg/day, with a mean reduction from baseline in HIV-1 RNA of 0.65–0.87 $\log_{10}$ copies/mL at 96 weeks.[29]

Efficacy Trial

The 300 mg/day regimen of tenofovir DF has also been compared with placebo in a large, multicentre study in 550 antiretroviral-experienced (mean duration of antiretroviral therapy 5.4 years) patients. Patients received tenofovir DF 300mg (n = 368) or placebo (n = 182) once daily for 24 weeks.[27] The mean baseline plasma HIV-1 RNA viral load and CD4+ cell count were 3.36 $\log_{10}$ copies/mL and 427 cells/μL.[27]

• Tenofovir DF 300 mg/day was significantly more effective than placebo in reducing viral load at 24 weeks.[27] The D_{AVG} at 24 weeks, the primary efficacy endpoint, was reduced to a significantly greater extent in patients who received tenofovir DF 300 mg/day than in those receiving placebo (–0.61 vs –0.03 $\log_{10}$ copies/mL; $p < 0.0001$).[27] In addition, significantly more tenofovir DF recipients than placebo recipients achieved decreases in HIV-1 RNA levels to ≤400 copies/mL (45% vs 13%) and ≤50 copies/mL (22% vs 1%) at 24 weeks ($p < 0.0001$ for both).[27]

• At 24 weeks, tenofovir DF resulted in a significant increase from baseline in the mean CD4+ cell count compared with placebo (12.5 vs –10.8 cells/μL; $p = 0.0008$).[27] Additionally, in patients receiving tenofovir DF who achieved HIV-1 RNA levels <50 copies/mL the mean CD4+ cell count increased by 57 cells/μL.[30]

• The efficacy of tenofovir DF 300 mg/day was sustained over 48 weeks (D_{AVG} –0.57; viral load ≤400 and ≤50 copies/mL 41% and 18%; mean increase in CD4+ cell count 13 cells/μL).[27]

• A subgroup analysis found that tenofovir DF 300 mg/day resulted in a significant antiretroviral response (measured by D_{AVG} at 24 weeks) compared with placebo regardless of age (≤40 years or >40 years), gender and race (Caucasian or non-Caucasian) or baseline HIV-1 RNA level (<5000 or ≥5000 copies/mL) or CD4+ cell count (<200 or ≥200 cells/μL).[31]

Comparison with Stavudine

Interim (96-week) results of a large, 3-year, randomised, double-blind comparative trial of tenofovir DF 300 mg/day versus stavudine 40mg twice daily in antiretroviral-naive patients with plasma HIV-1 RNA levels >5000 copies/mL have been reported (available as a poster).[28] In both treatment groups, patients received the study drug in combination with lamivudine 150mg twice daily and efavirenz 600 mg/day.[28]

• At 96 weeks, tenofovir DF 300 mg/day (n = 299) had similar antiviral efficacy to stavudine 40mg (30mg if bodyweight <60kg) twice daily (n = 301).[28] Similar proportions of tenofovir DF and stavudine recipients achieved reductions in HIV-1 RNA to <400 copies/mL and <50 copies/mL (figure 2).[28] The mean increase in the CD4+ cell count was also similar for the two treatment groups at 96 weeks (261 vs 266 cells/μL).[28]

4. Potential for Viral Resistance

As with other antiretroviral agents, treatment with tenofovir DF may result in the development of viral resistance.

In Vitro

• Eight *in vitro* passages of HIV-1_{IIIb} in the MT-2 cell line in increasing concentrations of unmodified tenofovir produced viral strains able to grow in the presence of 2 μmol/L of tenofovir (5-fold above the IC_{50} for wild-type virus).[32] Sequence analysis of 15

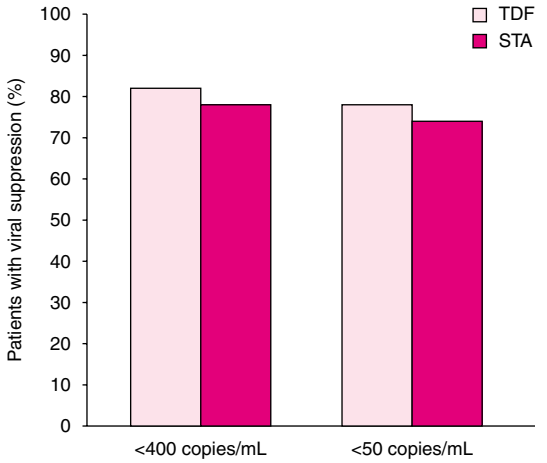


Fig. 2. Antiviral efficacy of tenofovir disoproxil fumarate (TDF) compared with that of stavudine (STA).[28] Proportion of antiretroviral-naive patients with HIV infection (intent-to-treat analysis, n = 600) receiving TDF or STA with HIV-1 RNA levels <400 copies/mL and <50 copies/mL at 96 weeks. In a randomised, double-blind clinical trial, patients received TDF 300 mg/day or STA 40mg (30mg if bodyweight <60kg) twice daily in combination with lamivudine 150mg twice daily and efavirenz 600 mg/day. Baseline status: mean CD4+ cell count for patients receiving TDF = 276 cells/μL and mean CD4+ cell count for patients receiving STA = 283 cells/μL; mean HIV-1 RNA level = 81 300 copies/mL for each treatment group.

clones expressing HIV reverse transcriptase genes from the eighth passage showed that the reverse transcriptase mutation K65R was present in 4 of the 15 clones.[32] The recombinant viruses expressing the K65R mutation were 3- to 4-fold less susceptible to tenofovir than the wild-type strain.[32]

- Recombinant isolates with mutations associated with resistance to other antiretroviral drugs (e.g. K70E and T69D) had either wild-type or <3-fold reduced susceptibility susceptibility to tenofovir *in vitro*.[32]

- A 1.3-fold increase in susceptibility to tenofovir was seen for HIV strains expressing the lamivudine-resistance–associated M184V mutation compared with wild-type strains in MT-2 cells (no significant difference); however, the increase in susceptibility for M184V strains was significant compared with wild-type strains in cord-blood mononuclear cells (4.6-fold increase; $p < 0.05$).[32] Moreover, HIV strains that contained both the K65R and M184V mutations displayed susceptibility to tenofovir similar to that of the wild-type strain (1.1-fold decrease in susceptibility compared with wild-type strain).[32]

- The relatively small reduction in susceptibility to tenofovir (≤2.5-fold compared with wild-type virus) for isolates showing up to 24-fold resistance to zidovudine has been attributed to differential rates of excision of these chain-terminating molecules.[33] Removal of tenofovir from the reverse transcriptase binding site by wild-type virus and HIV isolates with thymidine analogue-associated mutations (TAMs) by pyrophosphorolysis was 2- to 3-fold less efficient than the removal of zidovudine.[33] ATP-dependent removal of tenofovir was less efficient than removal of stavudine and zidovudine by wild-type virus (15-fold for both comparisons) and HIV isolates with TAMs (22- and 35-fold).[34]

In Vivo

Effect of Baseline Resistance Mutations

The effect of the number and type of TAMs in HIV isolates at baseline on the viral response to therapy with tenofovir DF was assessed in a pooled analysis[35] of the genotypic resistance data in patients (n = 333) in the two placebo-controlled clinical trials.[26,27]

- After 24 weeks of therapy with tenofovir DF, significant reductions ($p < 0.0001$) in viral load were observed in patients with HIV isolates without TAMs, with 1–2 TAMs and with ≥3 TAMs not including M41L or L210W receiving tenofovir DF compared with those receiving placebo (figure 3).[35] Although significant compared with placebo ($p < 0.013$), responses to tenofovir DF therapy were smaller in patients with HIV isolates with ≥3 TAMs including M41L or L210W than in the other subgroups (figure 3).[35] The greatest response at 24 weeks was seen in a subgroup of tenofovir DF recipients with isolates with the M184V mutation and no TAMs (–0.96 $\log_{10}$ copies/mL; $p < 0.001$).[35] Patients with a >4-fold reduction in baseline tenofovir DF susceptibility had a reduced response to tenofovir DF therapy.[35]

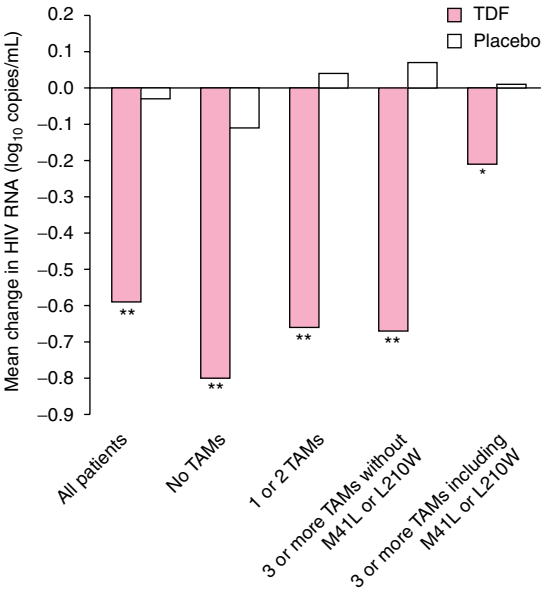


Fig. 3. Antiviral efficacy of tenofovir disoproxil fumarate (TDF) against HIV isolates with varying type and number of baseline thymidine-associated resistance mutations (TAMs).[35] In a pooled analysis (n = 333) of prospective virological substudies, baseline genotypes of HIV isolates from antiretroviral-experienced patients with HIV infection randomised to double-blind TDF 300 mg/day or placebo were analysed for the effect of different patterns of TAMs on the antiviral efficacy of treatments at 24 weeks (see text for further details). * $p = 0.02$, ** $p \leq 0.001$ vs placebo.

Emergence of Resistance

The emergence of reverse transcriptase mutations after tenofovir therapy was evaluated in virological substudies[36-39] of the clinical trials reviewed in section 3.

- After 48 weeks of treatment with tenofovir DF 300 mg/day in the dose-ranging study, the K65R mutation was detected as a new mutation in isolates from 2% of patients, while new NAMs were detected in isolates from 42% of patients.[36] Isolates that developed the K65R mutation had 3- to 4-fold reductions in tenofovir susceptibility compared with wild-type; however, none of the patients showed evidence of viral load rebound.[36] Similarly, after 96 weeks of treatment, two additional patients (1.5%) had virus which developed the K65R mutation; however these patients maintained viral suppression (–0.39 log 10 copies/mL).[37]

- Furthermore, an analysis of 21 patients with viral rebound (>0.5 $\log_{10}$ increase in HIV RNA) between weeks 48 and 96 found that most patients developed NAMs or mutations associated with resistance to non-nucleoside reverse transcriptase inhibitors or protease inhibitors; no phenotypic changes to tenofovir susceptibility were observed in these patients.[37]

- In a prospective virological genotyping substudy (n = 274)[38] of the larger placebo-controlled clinical trial (section 3),[27] the percentage of tenofovir DF-treated patients that developed TAMs (19%) and NAMs (23%) during the nonblind phase was similar to that of patients receiving placebo (14% and 24%) or tenofovir DF (11% and 16%) in the placebo-controlled phase, suggesting baseline antiretroviral therapy was associated with the development of these mutations.[38] However, patients that developed new mutations maintained HIV-1 RNA suppression at 48 weeks (mean D_{AVG} –0.09 to –0.99 $\log_{10}$ copies/mL).[38]

- The K65R mutation occurred in isolates from 3% of patients treated with tenofovir DF.[38] The average mean D_{AVG} at 48 weeks in these patients was –0.28 $\log_{10}$ copies/mL (range: 0.86 to –1.15).[38] Low-level (<2-fold) phenotypic resistance to tenofovir DF was associated with the K65R mutation in four evaluable patients; only one evaluable patient with the K65R mutation had reduced susceptibility (6.4-fold) to tenofovir DF.[38]

- Eight patients receiving tenofovir DF in the above substudy were classified as having viral rebound (at week 24 they had HIV-1 RNA levels of <50 copies/mL and at 48 weeks had >500 copies/mL).[38] Although most of these patients developed genotypic resistance to other agents present in their baseline antiretroviral therapy, viral rebound was not associated with the development of resistance to tenofovir DF.[38]

- In a genotypic and phenotypic analysis of HIV strains isolated from antiretroviral-naive patients with virologic failure during the first 48 weeks of treatment with tenofovir DF or stavudine in combination with lamivudine and efavirenz (n = 54), the most common genotypes were efavirenz-resistant

(4.7%), wild-type (3.6%) or M184V (3.3%).[39] The K65R mutation occurred infrequently in both the tenofovir DF and stavudine treatment groups (2.3% and 0.7%); however, it was observed only in combination with the efavirenz-resistance genotype.[39] Genotypic or phenotypic tenofovir-associated resistance was detected in 24% of patients with virological failure who received tenofovir DF plus lamivudine and efavirenz.[39]

5. Tolerability

Data in this section are from the clinical trials of tenofovir DF as part of combination therapy (section 3), including two pooled analyses of both placebo-controlled trials in a total of 443 patients receiving tenofovir DF and 210 patients receiving placebo.[4,40]

- Tenofovir DF is generally well tolerated.[4,40] In a pooled analysis the severity and incidence of adverse events were similar for those receiving tenofovir DF or placebo over the initial 24 weeks.[40]
- In one pooled analysis,[4] the most common treatment-related adverse events during the 24-week placebo-controlled period of treatment were of a predominantly gastrointestinal nature and included: nausea (11% in tenofovir DF recipients vs 10% in placebo recipients), diarrhoea (9% vs 8%), asthenia (8% for both treatment groups), headache (6% vs 7%), vomiting (5% vs 2%), flatulence (4% vs 0%), abdominal pain (3% for both treatment groups) and anorexia (3% vs 1%).
- Three percent of patients discontinued the study drug due to adverse events in both the tenofovir DF and placebo treatment groups during the initial 24 weeks of the trials.[40] With a mean treatment period of 95 weeks, the incidence of therapy discontinuation due to adverse events in patients receiving tenofovir DF was 9%.[40]
- There was also no significant difference between the tenofovir DF and placebo treatment groups in the incidence of grade 3 or 4 laboratory abnormalities such as creatinine kinase >782 U/L (12% vs 18%), triglycerides >750 mg/dL (8% vs 13%), serum amylase >175 U/L (5% vs 7%), serum glucose >250 mg/dL (2% vs 4%) and neutrophils <650 cells/μL (1% for both treatment groups) in the initial 24 weeks.[4]
- In antiretroviral-naive patients, there was no significant difference between tenofovir DF and stavudine in the incidence of grade 3 or 4 adverse events (23% vs 22%) or laboratory abnormalities (34% vs 39%) after 96 weeks of treatment.[28]
- However, at 96 weeks, significantly ($p < 0.001$) fewer tenofovir DF than stavudine recipients had adverse events potentially associated with mitochondrial dysfunction (e.g. peripheral neuropathy, lactic acidosis and lipodystrophy) [4% vs 20%], peripheral neuritis or neuropathy (3% vs 10%) and lipodystrophy (1% vs 12%).[28] Furthermore, three patients receiving stavudine experienced lactic acidosis (not reported with tenofovir DF).[28] Additionally, the tenofovir DF treatment group had significantly smaller increases in fasting triglycerides, total cholesterol and direct low density lipoprotein levels ($p < 0.001$) and a significantly higher increase in direct high density lipoprotein ($p = 0.032$) than the stavudine treatment group.[28]
- A retrospective analysis using pooled data from patients receiving didanosine as part of baseline antiretroviral therapy in the two placebo-controlled clinical trials (n = 197) at 24 weeks suggests that the tolerability of didanosine in combination with tenofovir DF is similar to that of didanosine with placebo (pancreatitis 1% vs 2%, neuropathy <1% vs 3%, amylase elevations 41% vs 44%).[41]
- Although tenofovir did not show any significant cytotoxicity in isolated human RPTECs in an *in vitro* study (section 1), tenofovir has been associated with changes in renal function *in vivo*. Pooled tolerability data from the placebo-controlled trials in antiretroviral-experienced patients showed that elevations in serum creatinine and serum phosphorus occurred occasionally but were transient in nature and resolved without the need for discontinuation of treatment.[40] Changes in renal function (incidence of hypophosphataemia and elevations in serum creatinine) in antiretroviral-naive patients were similar for those receiving tenofovir DF- or stavudine-based therapy after 96 weeks.[28] However, rare episodes of acute renal failure have been observed in patients

receiving tenofovir DF in combination with other antiretroviral drugs.[42,43]

- Preclinical studies have shown that tenofovir DF caused bone toxicity in animals at exposures 6–12 times those observed in humans.[4] Changes in bone mineral density were monitored in 62 patients in the dose-ranging clinical trial.[26] At week 24, there was no significant between-group differences in the change from baseline in bone mineral density; for tenofovir DF 75, 150 or 300 mg/day and placebo, median changes were –0.16%, –0.15%, –1.19% and –2.00%, respectively. Although there was no evidence of any dose-related effect at 24 or 48 weeks,[26] the long-term effect of tenofovir DF on bone is not known.
- Tenofovir DF has also been associated with pancreatitis, hypophosphataemia, lactic acidosis, dizziness, dyspnoea, rash, renal insufficiency, kidney failure and Fanconi syndrome during postmarketing surveillance.[4]

6. Dosage and Administration

In the US, oral tenofovir DF is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents.[4] The original approval for tenofovir DF in Europe was for use in combination with other antiretroviral agents for the treatment of HIV infection in adult patients experiencing early virological failure with their existing treatment.[21] However, this recommendation has recently been expanded to include antiretroviral-naive patients as well as antiretroviral-experienced patients.[44] The recommended dosage of tenofovir DF is 300mg once daily administered with a meal.[4,21]

Although it is currently recommended that tenofovir DF should not be administered to patients with renal impairment (CL_{CR} <60 mL/min) in the US[4] or in patients with severe renal impairment in Europe[21] (section 2), adjustments to the tenofovir DF dosage interval have been suggested in patients with renal impairment (presented in a poster).[22] In patients with moderate (CL_{CR} 30–49) or severe (CL_{CR} 10–29) renal impairment, the proposed dosage interval for tenofovir DF 300mg is increased to 48 hours or 72–96 hours, respectively.[22] For those with end-stage renal disease (CL_{CR} <10 mL/min), it is suggested that tenofovir DF 300mg be administered every 7 days.[22] It is also suggested that patients requiring haemodialysis should receive tenofovir DF 300mg following the completion of a total of 12 hours of haemodialysis.[22]

Caution and close monitoring of patients is advised for the coadministration of tenofovir DF and didanosine,[4,21] and in the US it is recommended that didanosine should be discontinued in patients who develop didanosine-associated adverse events.[4]

7. Tenofovir Disoproxil Fumarate: Current Status

Tenofovir DF is approved for the treatment of HIV infection in the US and Europe (see section 6 for specific indication). When combined with stable antiretroviral therapy, tenofovir DF has shown antiviral efficacy in antiretroviral-experienced and -naive patients with HIV infection in well controlled trials and was generally well tolerated. The clinical trial in antiretroviral-naive patients is ongoing and studies in children with HIV infection are currently underway.

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Correspondence: *Therese M. Chapman*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 10, New Zealand.
E-mail: demail@adis.co.nz