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Emtricitabine/Tenofovir Disoproxil Fumarate

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Contents

Abstract

▲ The nucleoside analogue reverse transcriptase inhibitor (RTI) emtricitabine and the nucleotide analogue RTI tenofovir disoproxil fumarate (tenofovir DF) have each shown antiviral activity against a number of HIV clinical isolates and cell lines.

▲ HIV variants with reduced susceptibility to emtricitabine and tenofovir have been selected for *in vitro* and have also been isolated from patients receiving the agents. Low rates of these variants have been observed in patients experiencing virological failure in large studies of emtricitabine- or tenofovir DF-containing therapy.

▲ Co-formulated oral emtricitabine/tenofovir DF was bioequivalent to the two agents as separate formulations in a pharmacokinetic trial in healthy volunteers.

▲ There are no published data on the clinical antiviral efficacy of co-formulated oral emtricitabine/tenofovir DF. However, each agent is effective in combination regimens with other drugs. Ongoing studies in antiretroviral-naive patients are evaluating the efficacy of the individual formulations given together in combination with efavirenz or lopinavir/ritonavir. In the latter trial, HIV RNA levels were reduced and CD4+ cell counts were increased at 24 and 48 weeks.

▲ Emtricitabine and tenofovir DF are generally well tolerated. Diarrhoea, nausea and vomiting were the most common adverse events reported with coadministered emtricitabine and tenofovir DF as separate formulations as part of combination therapy.

Features and properties of co-formulated emtricitabine/tenofovir disoproxil fumarate (tenofovir DF) [Truvada™]	
Indication	
HIV infection	
Mechanism of action	
Antiviral	Reverse transcriptase inhibitors
Dosage and administration	
Recommended dosage	Emtricitabine/tenofovir DF 200mg/300mg per day
Route of administration	Oral
Frequency of administration	Once daily
Pharmacokinetic profiles of emtricitabine and tenofovir, respectively, after a single oral dose of co-formulated emtricitabine/tenofovir DF 200mg/300mg in healthy volunteers	
Maximum serum concentration	2.13 and 0.254 μg/mL
Area under the serum concentration-time curve from zero to infinity	10.6 and 1.96 μg • h/mL
Elimination half-life	15.5 and 17.6h
Adverse events	
Main events for emtricitabine and tenofovir DF in combination with lopinavir/ritonavir	Diarrhoea, nausea and vomiting

With currently available antiretroviral agents, eradication of HIV is not possible.[1] Consequently, one of the main goals of in the treatment of HIV infection is optimal and prolonged suppression of viral load. Adherence to treatment is a key determinant of long-term virological control. Studies have shown that patients must take 90–95% of the prescribed doses to achieve maximal viral suppression. Suboptimal treatment adherence is associated with virological failure and the selection of drug-resistant mutants. Strategies recommended for improving patients' treatment adherence include reducing the frequency of therapy and the number of pills and simplifying food restrictions.[1] Co-formulating antiretroviral agents is one way of reducing the pill burden.

Recent US guidelines recommend that antiretroviral-naive patients with HIV infection be initially treated with two nucleoside (or nucleotide) analogue reverse transcriptase inhibitors (NRTIs) plus one non-nucleoside reverse transcriptase inhibitor (NNRTI), two NRTIs plus one or two protease inhibitors (PIs) or three NRTIs.[1] However, the latter is recommended only if one of the first two regimens cannot or should not be used as first-line therapy. The most recent US guidelines recommend the double NRTI component of the initial antiretroviral therapy should be tenofovir disoproxil fumarate (tenofovir DF) plus emtricitabine or lamivudine, zidovudine plus lamivudine or emtricitabine or emtricitabine plus didanosine.[2]

A fixed-dose combination tablet containing the two NRTIs emtricitabine and tenofovir DF (Truvada™)[1] has been approved in the US for once-daily treatment of patients with HIV infection, in conjunction with other antiretroviral agents.[3] This review focuses on data relevant to the use of co-formulated emtricitabine/tenofovir DF in patients with HIV infection.

1. Pharmacodynamic Profile

- Emtricitabine is an NRTI that is converted intracellularly to its active metabolite, emtricitabine 5′-triphosphate.[4] Tenofovir DF is an ester prodrug of the NRTI, tenofovir.[5] The prodrug is hydrolysed intracellularly to tenofovir, which is then converted to the active metabolite, tenofovir diphosphate. The active metabolites of the drugs compete with deoxycytidine 5′-triphosphate (emtricitabine 5′-triphosphate) or deoxyadenosine 5′-triphosphate (tenofovir diphosphate) for incorporation into HIV DNA, thereby terminating viral DNA chain growth and inhibiting the activity of the viral reverse transcriptase.[4,5]

- *In vitro*, emtricitabine and tenofovir have each shown antiviral activity against a number of HIV clinical isolates and laboratory strains in a variety of cell lines.[3] Synergistic antiviral effects were observed in *in vitro* combination studies of emtricitabine plus tenofovir. As separate agents, emtricitabine and tenofovir have shown additive-to-synergistic *in vitro* antiviral activity in combination with the NRTIs abacavir, lamivudine, stavudine, zalcitabine and zidovudine, the NNRTIs delavirdine, efavirenz and nevirapine and the PIs amprenavir, nelfinavir, ritonavir and saquinavir. Additionally, tenofovir has shown additive-to-synergistic *in vitro* antiviral activity with the NRTI didanosine and the PI indinavir.[3]

Resistance

- HIV variants with reduced susceptibility to emtricitabine and tenofovir have been selected for *in vitro* and have also been isolated from patients receiving the agents.[3]

- Resistance to emtricitabine is caused by an amino acid substitution from methionine (M) to either valine (V) or isoleucine (I) at position 184 of the HIV reverse transcriptase gene (M184I/V).[3] Virological failure occurred in 10.1% of antiretroviral-naive patients with HIV infection (n = 710) who were treated with emtricitabine as part of triple therapy in three 48-week trials (median duration of follow-up was 60 weeks).[6] Of the patients who experienced virological failure, 34.7% had HIV with the M184I/V substitution; however, 40.3% of

1 The use of trade names is for product identification purposes only and does not imply endorsement.

patients who experienced virological failure had the same HIV genotype at study end as at baseline.

- HIV isolates resistant to emtricitabine (M184I/V) were cross-resistant to lamivudine and zalcitabine but remained sensitive to abacavir, didanosine, stavudine, tenofovir, delavirdine, efavirenz and nevirapine.[7] An amino acid substitution from lysine to arginine at position 65 of the HIV reverse transcriptase gene (K65R), selected by abacavir, didanosine, tenofovir and zalcitabine, displays reduced susceptibility to emtricitabine (extent and clinical significance of reduction not stated).[7]
- *In vitro*, the K65R substitution in the HIV reverse transcriptase gene is associated with a 2- to 4-fold reduction in susceptibility to tenofovir.[3] After treatment with tenofovir DF, lamivudine and efavirenz for 144 weeks, 47 of 299 patients (15.7%) experienced virological failure: the K65R substitution was observed in eight (17.0%) of these patients.[8] In antiretroviral-experienced patients receiving tenofovir DF-containing therapy, reduced susceptibility to tenofovir was observed in 4.6% of patients experiencing virological failure; the resistant isolates contained the K65R substitution.[3] In addition to tenofovir DF, the K65R substitution confers reduced susceptibility to several other NRTIs (e.g. abacavir, didanosine and zalcitabine).[9]
- Clinical HIV isolates with a mean of three zidovudine-associated reverse transcriptase substitutions demonstrated a 3.1-fold reduction in susceptibility to tenofovir.[3]
- Virological nonresponse occurred in 33–95% of patients (n = 22–102) with HIV infection who received triple combination regimens containing tenofovir DF plus either lamivudine and abacavir,[10,11] lamivudine and didanosine[12] or didanosine plus efavirenz[13] for 8–24 weeks. Similar low efficacy has been seen with triple-NRTI regimens not containing tenofovir DF or emtricitabine.[14,15] In the three triple-NRTI trials,[10-12] K65R and M184I/V mutations were present in 50–92% and 98–100% of nonresponders, respectively. In the other trial,[13] an unusual pattern of resistance was observed; most patients who experienced virological failure had a glycine to glutamic acid or serine substitution at position 190 of the reverse transcriptase gene (five of six patients) and/or a leucine to V or I substitution at position 74 (four of six), along with other substitutions.
- Antiretroviral-naive patients (n = 190) received emtricitabine and tenofovir DF in combination with co-formulated lopinavir/ritonavir for 48 weeks.[16] Of the 15 patients who had HIV RNA levels >500 copies/mL at any time from weeks 12 to 48 (and genotypic results available), three demonstrated resistance to emtricitabine (M184V/I) and none demonstrated resistance to tenofovir DF.

2. Pharmacokinetic Profile

Where possible, this section focuses on data for the co-formulated emtricitabine/tenofovir DF 200mg/300mg tablet. Where pharmacokinetic data for the individual drugs are included, these are mostly derived from US[7,9] and EU[17,18] prescribing information; whether values are means or medians was not always reported.

Absorption and Distribution

- The arithmetic mean values for the maximum serum concentration (C_{max}) and area under the serum concentration-time curve from time zero to infinity (AUC_∞) for emtricitabine were 2.13 μg/mL and 10.6 μg • h/mL when a single dose of co-formulated emtricitabine/tenofovir DF 200mg/300mg was administered to 44 fasting, healthy volunteers in a crossover trial.[19] Respective values for tenofovir DF were 0.254 μg/mL and 1.96 μg • h/mL.
- In the same trial, co-formulated emtricitabine/tenofovir DF was bioequivalent to the two agents administered as separate formulations (figure 1).[19] For both emtricitabine and tenofovir DF, the 90% confidence intervals for the geometric mean ratio (combination dose **:** individual formulations) for the C_{max} and AUC_∞ values were contained within 80–120%, thus meeting the predefined criteria for bioequivalence.
- After oral administration, emtricitabine is rapidly and extensively absorbed.[3] The mean absolute bioavailability of emtricitabine was 92% following sin-

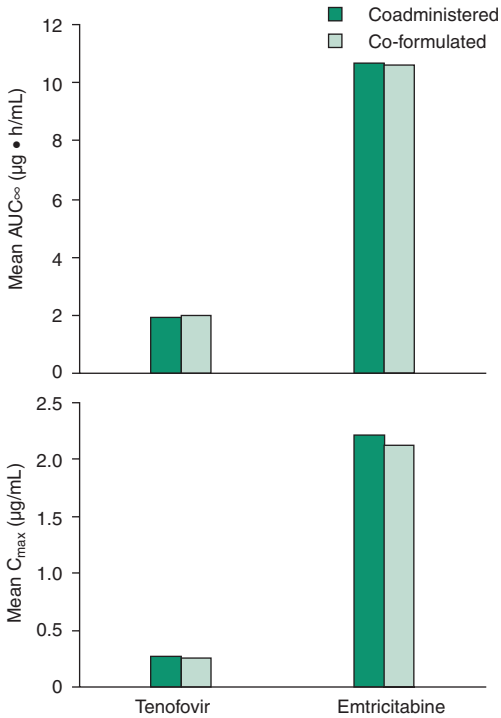

Fig. 1. Bioequivalence of co-formulated emtricitabine/tenofovir disoproxil fumarate (tenofovir DF) and the coadministered individual drug formulations. In a crossover trial,[19] 44 fasting, healthy volunteers received a single dose of co-formulated emtricitabine/tenofovir DF 200mg/300mg and single doses of coadministered emtricitabine 200mg and tenofovir DF 300mg (1wk washout period). **AUC_∞** = area under the serum concentration-time curve from time zero to infinity; **C_{max}** = maximum serum concentration.

gle-dose administration to healthy volunteers.[3,20] The oral bioavailability of tenofovir from tenofovir DF is approximately 25% in fasting patients.[9] For both emtricitabine and tenofovir, C_{max} is reached within 1–3 hours after administration to fed or fasting patients or volunteers.[9,21-23]

- Over a concentration range of 0.02–200 µg/mL, <4% of emtricitabine was bound to human plasma protein in *in vitro* studies.[7] At C_{max}, the drug partitions approximately equally into the plasma and blood cells and the mean concentration in the semen is approximately four times that in the plasma. Over the concentration range of 0.01–25 µg/mL, binding of tenofovir to human plasma and serum proteins *in vitro* was <0.7% and <7.2%.[9] Following intravenous administration of tenofovir 1.0 and 3.0 mg/kg, the steady-state volume of distribution was 1.3 and 1.2 L/kg.

Metabolism and Elimination

- Emtricitabine undergoes limited metabolism and is primarily excreted by the kidneys.[17] Emtricitabine was completely recovered (≈86% in the urine and ≈14% in the faeces) following ^{14}C-labelled administration; approximately 13% of the administered dose was recovered as metabolites in the urine.[7]
- Elimination of tenofovir occurs by both glomerular filtration and active tubular secretion.[3] Over 24 hours, following multiple doses of oral tenofovir DF, 32% of the administered dose was recovered in urine. Within 72 hours of intravenous administration of tenofovir, ≈70–80% of the dose was recovered as unchanged drug.
- The median terminal elimination half-lives of emtricitabine and tenofovir were 15.5 and 17.6 hours when healthy volunteers received a single dose of co-formulated emtricitabine/tenofovir DF 200mg/300mg on two separate occasions.[19] Respective values when volunteers received the two drugs concomitantly as individual formulations were 14.5 and 17.7 hours.[19] Additionally, the active metabolites of both drugs have long intracellular half-lives in peripheral blood mononuclear cells (39 hours for emtricitabine 5′-triphosphate[17] and ≥60 hours for tenofovir diphosphate[24]).

Special Patient Populations

The pharmacokinetics of emtricitabine and tenofovir when administered together have not been studied in children or the elderly.[3] There have been no pharmacokinetic studies with emtricitabine in patients with hepatic impairment and, similarly, the effects of race on the pharmacokinetics of tenofovir have not been evaluated.[3]

- The pharmacokinetics of emtricitabine or tenofovir are similar in male and female patients.[3] Race does not appear to alter the pharmacokinetics of emtricitabine. The pharmacokinetics of tenofovir in patients with moderate-to-severe hepatic impair-

ment did not differ substantially from those in unimpaired patients, following a single dose of tenofovir DF. [3]

- In patients with renal impairment, the pharmacokinetics of both emtricitabine and tenofovir (following administration of tenofovir DF) are altered.[7,9] C_{max} and AUC values are increased in patients with creatinine clearance <50 mL/min or those with end-stage renal disease requiring dialysis. Co-formulated emtricitabine/tenofovir DF should not be administered to patients with a creatinine clearance of <30 mL/min, and the dosing interval should be increased to 48 hours in patients with a creatinine clearance of 30–49 mL/min.[3]

Drug Interactions

- The steady-state pharmacokinetics of oral emtricitabine 200mg and tenofovir DF 300mg were not altered to a clinically significant degree when the two drugs were coadministered.[22] Nineteen healthy volunteers received the two drugs together for 7 days as well as individually for 7 days each in a crossover study.
- Neither emtricitabine nor tenofovir is metabolised by cytochrome P450 (CYP) enzymes, and thus they have limited potential for interaction with other agents metabolised by these enzymes.[7,9] *In vitro* studies indicate that tenofovir does not inhibit metabolism mediated by CYP3A4, CYP2D6, CYP2C9 or CYP2E1; however, a statistically significant reduction (6%) in CYP1A metabolism occurred (p-value not stated).[9]
- Given that both emtricitabine and tenofovir are primarily eliminated by the kidneys, coadministration of these agents with drugs that are eliminated by active tubular secretion (e.g. cidofovir, ganciclovir) may cause increased serum concentrations of emtricitabine or tenofovir or the other agents.[9,17]
- Coadministration of emtricitabine with indinavir, famciclovir, stavudine or zidovudine did not affect the pharmacokinetics of emtricitabine or the other agents.[17] No clinically relevant pharmacokinetic interactions were observed when tenofovir DF was coadministered with abacavir, adefovir dipivoxil, efavirenz, indinavir, lamivudine, lopinavir/ritonavir, methadone, oral contraceptives, ribavirin, rifampicin (rifampin) or saquinavir/ritonavir (reviewed by Kearney et al.[25]). Additionally, there was no evidence of intracellular interactions between the active metabolites of tenofovir DF and abacavir in patients with HIV infection (n = 15).[24]
- When tenofovir DF was coadministered with buffered didanosine over 7 days, the C_{max} and AUC values of didanosine increased significantly by 28% and 44% (p-values not stated).[9] Symptomatic pancreatitis developed in 5 of 185 tenofovir DF 300mg plus didanosine 200–400mg recipients, 1 of 183 patients receiving didanosine without tenofovir DF and none of 208 patients receiving tenofovir DF without didanosine in a community-based study.[26] Patients with symptomatic pancreatitis were all women who weighed 47–56kg and received didanosine 250 or 400mg. When tenofovir DF and didanosine are coadministered, the didanosine dose should be reduced to 250mg in patients weighing >60kg; no recommendations are available for patients weighing <60kg.[9]
- When tenofovir DF and atazanavir were coadministered for 14 days, the AUC and C_{max} values and the minimum serum concentration of tenofovir DF increased by 24%, 14% and 22%, respectively; the same parameters for atazanavir decreased by 23–28% (statistical analysis not reported).[9]

3. Therapeutic Efficacy

No efficacy trials of the co-formulated emtricitabine/tenofovir DF 200mg/300mg tablet have been conducted. However, relevant supporting data are outlined below.

- Emtricitabine[4] and tenofovir DF,[5] as individual agents in combination with other antiretroviral agents, have shown efficacy in reducing HIV RNA levels from baseline in well designed trials.
- Emtricitabine, in combination with other antiretroviral agents including didanosine and efavirenz, stavudine and nevirapine, or stavudine and efavirenz, has shown antiviral efficacy in several trials of up to 4 years' duration.[27-31] For example, the efficacy of triple therapy containing once-daily emtricitabine was equivalent to that of triple therapy con-

taining lamivudine in two 48-week trials in patients with HIV infection (both n > 400).[31] Additionally, emtricitabine-containing therapy was significantly more effective than stavudine-based therapy (HIV RNA ≤50 copies/mL was achieved and maintained in 76% vs 54% of patients after 60 weeks; p < 0.001)[29] or PI-based therapy (95% vs 87% at week 48; intention-to-treat, missing = failure population [ITT, M=F]; p = 0.01).[30]

- Tenofovir DF was as effective as stavudine (both in combination with lamivudine and efavirenz) after treatment for 144 weeks in a randomised, double-blind, multicentre study in antiretroviral-naive patients (n = 600) with HIV infection (analyses based on ITT, M=F population).[8] At this timepoint, 67.9% of tenofovir DF-containing therapy recipients and 62.5% of stavudine-containing therapy recipients had HIV RNA levels <50 copies/mL (95% CI −1.8, 13.3 for the between-group difference [a lower limit higher than −10.0 indicated non-inferiority]). The respective proportions of patients with HIV RNA levels <400 copies/mL were 70.6% and 64.1% (95% CI −0.8, 14.0).
- Oral, once-daily therapy with concomitant separate formulations of emtricitabine 200 mg/day and tenofovir DF 300 mg/day in combination with once- or twice-daily co-formulated lopinavir/ritonavir (PI) reduced HIV RNA levels in an ongoing, randomised, open-label study in 190 antiretroviral-naive patients with HIV infection (ITT analysis).[32,33] At 48 weeks in the once- and twice-daily PI-containing treatment groups, 70% and 64% of patients had HIV RNA levels <50 copies/mL and CD4+ cell counts had increased from baseline by 185 and 188 cells/μL.[33] These results confirmed the efficacy outcomes seen at the interim 24-week analysis.[32]
- No data are available at present for an open-label, multicentre trial that will compare emtricitabine, tenofovir DF and efavirenz with co-formulated lamivudine/zidovudine plus efavirenz in antiretroviral-naive patients (n = 517).[34]

4. Tolerability

As individual agents in combination with other antiretroviral agents, emtricitabine[4] and tenofovir DF[5] are generally well tolerated in patients with HIV infection.

- The most frequent (13–30% of patients) adverse events occurring with emtricitabine-containing combination therapy in clinical trials of ≤48 weeks' duration were headache, diarrhoea, nausea and rash.[7] In clinical trials, skin discoloration occurred at a higher frequency in patients receiving emtricitabine-containing therapy than in those in control treatment groups (statistical analysis not reported).[7]
- Overall, the incidence of adverse events occurring with emtricitabine-containing therapy was similar to that with lamivudine-containing therapy, whereas the incidences of nausea, diarrhoea, paraesthesia and symptomatic hyperlactacidaemia/lactic acidosis were significantly lower in patients receiving emtricitabine-containing therapy than in those receiving stavudine-containing therapy (all p ≤ 0.05).[4] In general, the incidence of laboratory abnormalities with emtricitabine-containing therapy was similar to that with lamivudine- or stavudine-containing therapy.[7]
- The incidence of adverse events with tenofovir DF was generally similar to that with placebo in clinical trials; gastrointestinal events (nausea, diarrhoea, vomiting, flatulence) occurred commonly (3–16% of patients).[5,9] After treatment for 144 weeks in one trial, significantly fewer tenofovir DF-containing therapy recipients than stavudine-containing therapy recipients experienced neuropathy, lipodystrophy and adverse events potentially associated with mitochondrial dysfunction (e.g. peripheral neuropathy, lactic acidosis and lipodystrophy) [all p < 0.001].[8]
- Additionally, tenofovir DF-containing therapy recipients had a significantly smaller mean increase from baseline in fasting triglyceride, total cholesterol and low-density lipoprotein cholesterol levels and a significantly lower incidence of grade 3–4 hypertriglyceridaemia (3% vs 14% of patients) than stavudine-containing therapy recipients (all p < 0.001).[8] The incidence of other grade 3–4 laboratory abnormalities with tenofovir DF did not differ significantly from that with placebo or stavudine in clinical studies in patients with HIV infection.[5]

• Renal impairment has been observed in some patients receiving tenofovir DF-containing antiretroviral regimens.[9] Grade 3 or higher abnormalities in serum creatinine and phosphorus levels were observed in 0.3% and 0.6% of >1500 antiretroviral-experienced patients who received tenofovir DF-containing antiretroviral therapy for a median of 178 days in an expanded access programme.[35]

• There were no significant between-group differences in renal parameters when 592 antiretroviral-naive patients received either tenofovir DF or stavudine plus lamivudine and efavirenz for 144 weeks.[36] In both arms of the trial, <1% of patients had serum creatinine levels >2.0 mg/dL and 3% of patients had serum phosphorus levels <2.0 mg/dL.

• When emtricitabine and tenofovir DF were administered simultaneously as separate formulations in patients also receiving lopinavir/ritonavir, the most common moderate-to-severe, drug-related adverse events were diarrhoea, nausea and vomiting.[33]

• Emtricitabine 200mg plus tenofovir DF 300mg, either as a co-formulated tablet[19] or as separate formulations,[19,22] was generally well tolerated in two pharmacokinetic trials. One volunteer discontinued treatment because of moderate vomiting when 19 healthy volunteers received the two separate tablets once daily for 7 days.[22] When 44 healthy volunteers received one dose of the two agents as separate tablets and as a co-formulated tablet in a crossover study,[19] eight individuals (18%) experienced an adverse event (combined data); the most common adverse event was grade 1 headache (n = 3). There were no grade 3 or 4 or serious adverse events. One volunteer discontinued treatment because of a mild rash that was considered to be treatment related.

5. Dosage and Administration

The fixed-dose combination emtricitabine/tenofovir DF 200mg/300mg oral tablet should be taken once daily and may be administered without regard to food.[3] Emtricitabine/tenofovir DF should be administered in combination with other antiretroviral agents such as NNRTIs and PIs; it is not recommended for use as part of a triple NRTI regimen.

6. Emtricitabine/Tenofovir Disoproxil Fumarate: Current Status

Co-formulated emtricitabine/tenofovir DF is approved in the US for once-daily oral use in conjunction with other antiretroviral agents in adults with HIV infection. Although no clinical trials of the efficacy of this formulation have been published to date, the fixed-dose co-formulation was bioequivalent to the two separate components given concomitantly in a pharmacokinetic study. Advantages of the emtricitabine/tenofovir DF co-formulation include a reduced pill burden and the fact that it can be administered without regard to food.

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