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Emtricitabine/Tenofovir Disoproxil Fumarate

In Combination with a Protease Inhibitor in HIV-1 Infection

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Contents

Abstract

▲ Emtricitabine, a nucleoside reverse transcriptase inhibitor (RTI), and tenofovir disoproxil fumarate (tenofovir DF), a nucleotide RTI, as a fixed-dose combination tablet (emtricitabine/tenofovir DF) for once-daily oral administration, are used as the nucleoside/nucleotide RTI backbone in combination with other antiretroviral agents, including ritonavir-boosted protease inhibitors (PIs), in the treatment of adults with HIV-1 infection.

▲ Emtricitabine and tenofovir DF show good activity against laboratory strains and clinical isolates of HIV-1 *in vitro*, although strains with resistance to emtricitabine or tenofovir have also been reported.

▲ Regimens consisting of once-daily emtricitabine/tenofovir DF 200 mg/300 mg plus lopinavir/ritonavir (in the randomized, double-blind, placebo-matched, multicentre HEAT study) or boosted atazanavir or efavirenz (in the randomized, partially-blind, multicentre ACTG 5202 trial) were effective in the initial treatment of patients with HIV-1 infection (with screening plasma HIV-1 RNA levels of ≥100 000 copies/mL in ACTG 5202).

▲ In other randomized studies, emtricitabine/tenofovir DF 200 mg/300 mg once daily was an effective backbone for boosted PI-based regimens in the initial treatment of HIV-1 infection. Treatment-experienced patients with HIV-1 infection also experienced beneficial virological effects when treated with similar regimens.

▲ Emtricitabine/tenofovir DF in combination with various boosted PIs was generally well tolerated by adults with HIV-1 infection.

Features and properties of emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) fixed-dose combination tablet (Truvada®)	
Indication	
HIV-1 infection in adults	
Mechanism of action	
Antiviral	Reverse transcriptase inhibitors
Dosage and administration	
Dose	FTC/TDF 200 mg/300 mg
Route of administration	Oral
Frequency of administration	Once daily
Pharmacokinetic profiles of FTC and tenofovir after multiple-dose administration of FTC 200 mg plus TDF 300 mg once daily for 7 days [mean values]	
Maximum plasma concentration	1.69 and 0.288 mg/L
Minimum plasma concentration	0.075 and 0.054 mg/L
Area under the plasma concentration-time curve	10.7 and 2.80 mg • h/L
Apparent plasma half-life	10.7 and 15.9 h
Adverse events	
Most common (incidence ≥6%) in the HEAT study: diarrhoea, nausea, increased blood triglycerides; most common in ACTG 5202: general body aches and increases in lipid levels	

One of the key requirements for a successful highly active antiretroviral therapy (HAART) regimen is for patients with HIV-1 infection to understand the need for good adherence.[1,2] Indeed, good adherence correlates strongly with reduced rates of resistance, long-term virological control, prolonged survival and improved quality of life.[1] During the past few years, significant advances have been made in this regard, particularly for antiretroviral therapy-naive patients. Currently, several effective and well tolerated treatments with low pill burdens and convenient administration schedules are available. The importance of good adherence is emphasized in current treatment guidelines, which take into account both the simplicity and efficacy of different treatment regimens.[1]

The most recent US Department of Health and Human Services (DHHS) treatment guidelines for adults with HIV-1 infection recommend various HAART regimens for the first-line treatment of adults with HIV-1 infection.[1] Among the preferred initial treatment options is the combination of dual nucleoside (or nucleotide) reverse transcriptase inhibitor (NRTI) 'backbone' regimens in combination with a ritonavir-boosted (hereafter referred to as 'boosted') protease inhibitor (PI). Emtricitabine, a nucleoside reverse transcriptase inhibitor (RTI), and tenofovir disoproxil fumarate (tenofovir DF), a nucleotide RTI, are available as a fixed-dose combination tablet (emtricitabine/tenofovir DF; Truvada®) for once-daily oral administration. Emtricitabine/tenofovir DF is classified as the only preferred dual NRTI component of PI-based regimens for the initial treatment of adults with HIV-1 infection in the most recent US DHHS treatment guidelines.[1]

This article provides an overview of the pharmacology of emtricitabine and tenofovir DF as individual agents or as the fixed-dose combination and examines the clinical profile of emtricitabine/tenofovir DF in combination with PIs in the treatment of antiretroviral therapy-naive or -experienced adults with HIV-1 infection.

Medical literature on the use of emtricitabine/tenofovir DF in HIV-1 infection was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles.

1. Pharmacodynamic Profile

The pharmacodynamic profiles of emtricitabine and tenofovir DF, alone or administered as the fixed-dose combination formulation, are well established[3-6] and are therefore discussed only briefly in this section together with new data on the resistance profiles of the two drugs.

Mechanism of Action

- Emtricitabine is a synthetic nucleoside analogue of cytidine and undergoes intracellular phosphorylation to form the active metabolite, emtricitabine 5′-triphosphate, which competes with deoxycytidine 5′-triphosphate and becomes incorporated into HIV-1 DNA, resulting in viral DNA chain termination and the inhibition of HIV-1 reverse transcriptase activity.[3,5-7] The intracellular half-life of emtricitabine was 39 hours in healthy volunteers who received 200 mg once daily for 10 days (reviewed by Stevens et al.[8]).
- Tenofovir DF, an acyclic nucleoside phosphonate diester analogue of adenosine monophosphate, undergoes initial diester hydrolysis to tenofovir and subsequent intracellular phosphorylation to produce tenofovir diphosphate. Tenofovir diphosphate competes with deoxyadenosine 5′-triphosphate for incorporation into HIV-1 DNA, thereby, like emtricitabine, terminating viral DNA chain growth.[3,4,6] The intracellular half-life of tenofovir diphosphate was ≥60 hours in eight HIV-infected patients receiving tenofovir DF as a component of a triple antiretroviral drug therapy regimen.[8]
- Emtricitabine 5′-triphosphate and tenofovir diphosphate are both weak inhibitors of mitochondrial DNA polymerase-γ as well as mammalian DNA polymerase-α and -β; weak inhibition of mammalian DNA polymerase-ε also occurs with emtricitabine.[6,9] Emtricitabine and tenofovir, alone or in combination, exhibited minimal or no mitochondrial toxicity in HepG2 human hepatoma cells,

whereas combinations of didanosine, stavudine or zidovudine had more marked adverse effects (vs control) on mitochondrial DNA.[10]

Antiretroviral Activity

- Emtricitabine and tenofovir each show good activity against clinical isolates and laboratory strains of HIV-1 *in vitro*.[3,6]
- The 50% effective concentration (EC_{50}) values for emtricitabine ranged from 0.0013 to 0.64 μmol/L against clinical isolates and laboratory strains of HIV-1 in lymphoblastoid cell lines, the MAGI-CCR5 cell line and peripheral blood mononuclear cells (PBMCs).[6] In cell culture experiments, emtricitabine was active (EC_{50} values 0.007–0.075 μmol/L) against HIV-1 clades A, B, C, D, E, F and G.[6] Emtricitabine is a 5′-fluorinated derivative of lamivudine and shows 4 to 10-fold greater activity against HIV than lamivudine.[10]
- EC_{50} values for tenofovir against clinical isolates and laboratory strains of HIV-1 ranged from 0.04 to 8.5 μmol/L.[6] In cell culture, tenofovir displayed activity (EC_{50} values ranged from 0.5 to 2.2 μmol/L) against HIV-1 clades A, B, C, D, E, F, G and O.[6]
- *In vitro* data support the clinical use of emtricitabine in combination with tenofovir DF as a dual NRTI backbone in patients with HIV-1 infection.[6,9] The combination of emtricitabine plus tenofovir displayed additive to synergistic *in vitro* activity against wild-type HIV-1 in human PBMCs and robust synergistic activity against wild-type and mutant HIV-1 strains (with mutations at K65R and M184V) in the human T leukaemic MT-2 cell line.[9]
- Active triphosphate metabolites of both emtricitabine and tenofovir were efficiently produced in PBMCs and human T leukaemic cell line CEM cells with significant increases in concentrations of emtricitabine triphosphate ($p = 0.0069$) and tenofovir diphosphate ($p = 0.047$) achieved at 24 hours when the drugs were incubated in combination, compared with concentrations after incubation with the individual drugs. The additive to synergistic *in vitro* activity of the two drugs against HIV-1 correlated with the levels of intracellular phosphorylation measured.[9]

Resistance

- Clinical isolates of HIV-1 with decreased susceptibility to emtricitabine and tenofovir have been obtained from patients with HIV-1 infection receiving the two drugs in combination.[6,9] The presence of the K65R mutation is associated with resistance to tenofovir,[6] particularly in the presence of the M184V mutation (reviewed by Gianotti and Lazzarin[11]). Resistance to emtricitabine is associated with a substitution at codon 184 manifest as the substitution of methionine with valine or isoleucine (M184V/I).[6] However, the risk of selection for NRTI resistance is reduced when emtricitabine and tenofovir are administered in combination with boosted PIs or efavirenz.[11]
- Cross resistance has been observed *in vitro* among several NRTIs, including emtricitabine, tenofovir, lamivudine, abacavir or didanosine and cross resistance to these drugs may occur in patients infected with HIV-1 harbouring the M184V/I and/or K65R mutations.[6]
- Clinical isolates of HIV-1 with the single M184V mutation have been identified in patients with virological failure while receiving treatment with emtricitabine and tenofovir DF[12] and it has been suggested that longer-term treatment failure may arise in patients with HIV-1 isolates harbouring the K65R and M184V/I double mutation.[13]
- In clinical trials evaluating the efficacy of emtricitabine/tenofovir DF as a dual NRTI backbone in combination with PIs (boosted atazanavir,[14,15] darunavir[16] or lopinavir[17]) in treatment-naive patients with HIV-1 infection (section 3), mutations associated with resistance to emtricitabine were only occasionally observed. For example, the M184V mutation was identified in a single patient in the BATON (Boosted Atazanavir and Truvada Given Once Daily) trial[14] and in two patients who did not respond to treatment in the ARTEMIS (AntiRetroviral Therapy with TMC114 ExaMined In naive Subjects) trial[16] as well as in three patients in the trial reported by Johnson et al.[17] The M184V mutation was the most common resistance mutation that emerged in 66 treatment-naive patients receiving emtricitabine/tenofovir DF in combination with

once-daily boosted PI regimens (reported as an abstract).[18]

- Minority quasispecies of HIV-1 with low-frequency mutations may impair the efficacy of antiretroviral therapy.[13] However, the presence of these variants was not associated with therapy failure after 24 weeks' treatment with emtricitabine/tenofovir DF in combination with a boosted PI or a non-nucleoside reverse transcriptase inhibitor (NNRTI) [data reported in an abstract].[13] In a retrospective analysis of baseline samples collected (between April 2005 and August 2006) from 220 antiretroviral therapy-naive patients with chronic HIV-1 infection in Germany, mutations identified in the minority quasispecies were: K65R (in 4 [1.8%] of 219 patients), K103N (10 [4.6%] of 216) and M184V (17 [7.9%] of 215), representing 0.8–21.4%, 0.06–12.1% and 0.3–42.2%, respectively, of the plasma viral genomes in 27 (12.3%) of the 220 study participants.[13]
- HIV-1 isolates with the K65R mutation from two patients also harboured the M184V mutation, as did isolates with the K103N mutation from another two patients; isolates from the remaining 23 patients harboured only single mutations. After 24 weeks' treatment, 21 of the 27 patients with minor quasispecies had HIV-1 RNA levels of <50 copies/mL; of the remaining six patients, HIV-1 RNA levels of <50 copies/mL were not achieved in two patients (probably because of noncompliance with the treatment regimen) and the other four patients were lost to follow-up.[13] After treatment, eight of ten patients with detectable quasispecies of K103N variants had received emtricitabine/tenofovir DF in combination with a boosted PI.
- In an *in vitro* study, HIV-1 isolates with a K65R and M184V genotype developed under maximum selection pressure at the highest concentration(s) of emtricitabine (and tenofovir) tested.[12] HIV-1 isolates with the M184V or M184I reverse transcriptase mutation with high-level resistance to emtricitabine were readily selected *in vitro* in cultures of emtricitabine, and the combination of emtricitabine and tenofovir. In both the culture with tenofovir alone or with emtricitabine plus tenofovir, HIV-1 isolates with the K65R mutation resistant to tenofovir were observed. Also identified in the tenofovir cultures were S68N and S68K mutations, which had no detectable effect on resistance, suggesting a possibly compensatory activity in terms of viral fitness.
- The M184I mutation was the first mutation to appear in a subgroup of viruses, at low concentrations of emtricitabine and tenofovir; the K65R mutation was the next mutation to appear with low and intermediate concentrations of both drugs.[12] At intermediate concentrations, viruses were identified harbouring double mutations at K65N and K70R, which, at high emtricitabine concentrations, led to the development of K65R and M184V/I double mutations.[12]

2. Pharmacokinetic Profile

Most data on the pharmacokinetic profiles of emtricitabine and tenofovir DF, administered orally as individual agents or as emtricitabine/tenofovir DF, are derived from multiple- or single-dose studies in healthy adult volunteers and from the manufacturer's prescribing information.[6,7,19,20]

Absorption and Distribution

- After administration of a single 200 mg dose, emtricitabine is rapidly (time [t_{max}] to maximum plasma concentration [C_{max}] 1–2 hours) and well absorbed, with a median fasted oral bioavailability of 92%.[6] Similarly, absorption of tenofovir is rapid (t_{max} approximately 1 hour after administration of a single 300 mg dose), although median fasted oral bioavailability (25%) is less than that for emtricitabine.[6] Steady-state absorption parameters of emtricitabine and tenofovir, administered alone or in combination (table I), are similar to parameters reported after single-dose administration.
- After single-dose administration of emtricitabine/tenofovir DF (200 mg/300 mg) to 39 evaluable healthy adult volunteers, mean C_{max} and area under the plasma concentration-time curve (AUC) values were 2.13 mg/L and 10.6 mg • h/L; corresponding values for tenofovir were 0.25 mg/L and 1.96 mg • h/L.[20]

Table I. Pharmacokinetic parameters (at steady state: mean values) of emtricitabine (FTC) 200 mg once daily and tenofovir disoproxil fumarate (TDF) 300 mg once daily in 17 healthy volunteers after multiple-dose (7 days') administration of each drug alone or in combination (administered with or within 30 minutes of food intake)[19]

Parameter	Single administration		Combined administration	
	FTC	TDF	FTC	TDF
C_{max} (mg/L)	1.77	0.279	1.69	0.288
C_{min} (mg/L)	0.064	0.054	0.075	0.054
AUC (mg • h/L)	10.2	2.84	10.7	2.80
t_{max} (h)	3.02	2.43	2.98	2.40
$t_{1/2}$ (h)	10.6	15.3	10.7	15.9
CL/F (mL/min)	340	837	316	829

AUC = area under the plasma concentration-time curve; $\mathbf{C_{max}}$ = maximum plasma concentration; $\mathbf{C_{min}}$ = minimum plasma concentration; **CL/F** = apparent total body clearance; $\mathbf{t_{max}}$ = time to C_{max}; $\mathbf{t_{1/2}}$ = apparent plasma half-life.

- The fixed-dose combination of emtricitabine/tenofovir DF 200 mg/300 mg showed bioequivalence to emtricitabine 200 mg and tenofovir DF 300 mg administered as individual formulations in 39 fasting healthy volunteers in a single-dose crossover study.[3,6,20]
- Following administration of emtricitabine/tenofovir DF with a high-fat or light meal, emtricitabine C_{max} and AUC (systemic exposure) were unchanged compared with values reported for individuals who received the combination in the fasted state.[6] By contrast, tenofovir absorption parameters were affected by food intake: t_{max} increased by approximately 0.75 hours with mean increases in mean C_{max} and AUC of 15% and 35%.[6]
- At steady state, pharmacokinetic parameters for concomitantly administered emtricitabine and tenofovir DF were similar to those for the two drugs administered as single agents in 17 healthy volunteers in a randomized, 3-way, multiple-dose study, providing a pharmacokinetic rationale for the development of the fixed-dose combination tablet.[19] Study participants were randomized to receive emtricitabine 200 mg once daily, tenofovir DF 300 mg once daily or emtricitabine 200 mg once daily plus tenofovir DF 300 mg once daily for 7 days, without a washout period between the regimens. The results for emtricitabine and tenofovir at steady state, shown in table I, are consistent with those reported in other studies in healthy volunteers or patients with HIV-1 infection.[19]
- *In vitro*, emtricitabine is minimally (<4%) bound to human plasma proteins (independent of plasma concentration over the range 0.02–200 mg/L); plasma protein binding of tenofovir is <0.7% over the plasma concentration range 0.01–25 mg/L.[6] At C_{max}, emtricitabine partitions almost equally into plasma and blood cells. The mean concentration of emtricitabine in semen is about four-fold higher than that in the plasma.[3] High concentrations of tenofovir were attained in the genital tract in nine patients with HIV-1 infection after multiple doses of 300 mg once daily.[21] Concentrations of tenofovir in the genital tract were about 19-fold higher than those measured in the blood plasma.[21]

Metabolism and Elimination

- Emtricitabine does not undergo extensive metabolism and is primarily eliminated via the renal route. Approximately 86% of a dose of emtricitabine was recovered in the urine with 13% recovered as emtricitabine metabolites (including 3′-sulfoxide diastereomers and their glucuronic acid conjugate).[6] About 70–80% of a single intravenous dose of tenofovir is eliminated in the urine.[6] Apparent body clearance (steady state) values for emtricitabine and tenofovir, administered alone or in combination (multiple doses), are shown in table I.[19]
- Steady-state plasma half-life (mean) values of emtricitabine after multiple doses (table I) are similar to that after a single 200 mg dose (about 10 hours [median]).[6] The median terminal elimination half-life of tenofovir was about 17 hours after administration of a single 300 mg dose.[6] Both emtricitabine

and tenofovir are eliminated by a combination of active tubular secretion and glomerular filtration.[6]

Special Populations

- Available data, although limited for tenofovir DF, indicate that the pharmacokinetics of emtricitabine and tenofovir DF are not appreciably affected by race or sex. The pharmacokinetic profiles of emtricitabine and tenofovir DF have not yet been evaluated in elderly patients in formal studies and data are also unavailable for paediatric patients. No substantial changes in the pharmacokinetic parameters of tenofovir were observed in non-HIV-infected patients with moderate to severe hepatic impairment and changes in emtricitabine pharmacokinetics are unlikely as it is not metabolized via the cytochrome P450 (CYP) metabolic pathway.[6] By contrast, the pharmacokinetics of emtricitabine and tenofovir are affected in patients with renal impairment and dosage modification is required for the fixed-dose combination of emtricitabine/tenofovir DF in patients with a creatinine clearance (CL_{CR}) of 30–49 mL/min (1.8–2.94 L/h) [section 5]. Tenofovir DF should not be taken by patients with a CL_{CR} of <30 mL/min or by those on haemodialysis.[6,22]

Drug Interactions

Data on drug interactions with emtricitabine/tenofovir DF administered as a fixed-dose combination are currently limited, as no formal interaction studies have been performed. Therefore, data reviewed here are from studies of the two individual agents with the focus being on clinically relevant interactions. Of note, the pharmacokinetics of emtricitabine and tenofovir DF are not altered to a clinically relevant extent when they are coadministered.[1,3,6]

- As neither emtricitabine nor tenofovir DF is metabolized by CYP enzymes, they have a limited potential to interact with coadministered drugs that are metabolized via this pathway.[7] Minor (6%) inhibition of CYP1A metabolism and no inhibition of other tested CYP enzymes (CYP3A4, CYP2D6, CYP2C9 or CYP2E1) was observed in an *in vitro* study.[3]
- No clinically relevant interactions have been reported for emtricitabine in combination with indinavir, zidovudine, famciclovir or stavudine (single-dose studies). Similarly, tenofovir DF has not been shown to interact to a clinically relevant extent with indinavir, nelfinavir, saquinavir, abacavir, lopinavir/ritonavir, adefovir dipivoxil, entecavir, efavirenz or lamivudine.[6] No clinically relevant pharmacokinetic drug interactions between emtricitabine/tenofovir DF and tacrolimus were observed when these drugs were coadministered to healthy volunteers in a randomized, nonblind, crossover study.[23]
- Because both emtricitabine and tenofovir are predominantly excreted by the kidneys, coadministration of emtricitabine/tenofovir DF with drugs that are eliminated by active tubular secretion (e.g. aciclovir, adefovir dipivoxil, ganciclovir, cidofovir, valaciclovir and valganciclovir) should be avoided as such combinations may result in increased concentrations of emtricitabine, tenofovir and/or the concomitantly administered drug.[6] Plasma/serum concentrations of emtricitabine and/or tenofovir may increase when these drugs are administered with drugs that decrease renal function; however, interactions with drugs that compete for renal excretion have not been reported.[6]
- When coadministered with tenofovir DF, AUC, C_{max} and minimum plasma concentration (C_{min}) values of (boosted) atazanavir decreased by 25%, 28% and 23%, respectively; tenofovir AUC, C_{max} and C_{min} values increased by 24%, 14% and 22%, respectively, when coadministered with non-boosted atazanavir.[1,6] Similarly, tenofovir AUC, C_{max} and C_{min} increased by 22%, 24% and 37% when tenofovir DF was taken with boosted darunavir.[1] In addition, when tenofovir DF and lopinavir/ritonavir were coadministered, tenofovir AUC increased by 32%[6] and C_{min} increased by 51%.[6]
- Administration of tenofovir DF with didanosine (buffered or enteric-coated formulation) resulted in clinically significant increases in didanosine C_{max} and AUC values, thereby increasing the potential development of serious adverse reactions associated with didanosine (e.g. pancreatitis and neuropathy);[6] the mechanism for this interaction is not

yet known, although it has been suggested that tenofovir may be implicated in the intracellular deactivation of the active metabolite of didanosine.[10] The dose of didanosine should therefore be reduced to 250 mg for adults weighing >60 kg when it is administered with emtricitabine/tenofovir DF.[6] The prescribing information should consulted for further information on dosage modification for didanosine.

3. Therapeutic Efficacy

The efficacy of emtricitabine/tenofovir DF as a dual NRTI backbone in combination with a boosted PI has been evaluated in numerous randomized, multicentre, comparative clinical trials in antiretroviral therapy-naive adults with HIV-1 infection. Of these trials, the HEAT (Head-to-Head Epzicom and Truvada) study (reported in abstracts[24,25]) is the first large prospective trial designed to directly compare the efficacy of emtricitabine/tenofovir DF with that of the fixed-dose combination of abacavir/lamivudine, each in combination with lopinavir/ritonavir. Preliminary results of another study (ACTG [AIDS Clinical Trial Group] 5202) comparing emtricitabine/tenofovir DF with abacavir/lamivudine (each in combination with a boosted PI or an NNRTI) have also been reported.[26] Emtricitabine/tenofovir DF was also used as the dual NRTI backbone in several well designed trials that compared the virological efficacy of different boosted PIs.[16,17,27-30] Emtricitabine/tenofovir DF has also been studied in non-comparative trials, including the fully published BATON trial.[14]

Emtricitabine/tenofovir DF in combination with a boosted PI has also been compared with abacavir/lamivudine in treatment-experienced patients with HIV-1 infection in a single, well designed, noninferiority trial.[31]

In several of the trials referred to in this section, patients received either a boosted PI or an NNRTI; however, data pertaining to the PI rather than NNRTI treatment groups are, where possible, the focus of this section.

Antiretroviral Therapy-Naive Patients

Comparisons of Emtricitabine/Tenofovir Disoproxil Fumarate (DF) with Abacavir/Lamivudine in Combination with a Protease Inhibitor

The HEAT Study

The HEAT study is a phase IV, randomized, double-blind, placebo-matched, multicentre, 96-week, noninferiority trial in antiretroviral therapy-naive patients with baseline HIV-1 RNA levels of ≥1000 copies/mL.[24,25] Results at 48[24] and 96[25] weeks have been reported. At baseline, study participants were stratified according to viral load (<100 000 copies/mL or ≥100 000 copies/mL) but not by CD4+ cell count and were randomized to receive once-daily fixed-dose combinations of either emtricitabine/tenofovir DF 200 mg/300 mg (n = 345) or abacavir/lamivudine 600 mg/300 mg (n = 343) in a blinded manner in combination with nonblind once-daily lopinavir/ritonavir.[24,25] The mean age of enrolled patients was 38 years; 18% were female.[25] At baseline, median plasma HIV-1 RNA levels were 4.84 and 4.90 $\log_{10}$ copies/mL for the emtricitabine/tenofovir DF and abacavir/lamivudine treatment groups.[24]

The primary efficacy endpoint in the 48-week analysis was defined as the proportion of patients with HIV-1 RNA levels of <50 copies/mL at week 48 for the intent-to-treat (ITT) population (missing = failure, switch included analysis) [switching of therapy within drug classes was permitted for patients experiencing toxicity].[24] In the 96-week analysis, the primary objective was the evaluation of tolerability and safety at week 96 (section 4). Noninferiority of abacavir/lamivudine compared with emtricitabine/tenofovir DF could be established if at week 48 the lower limit of the two-sided 95% CI for the difference in the proportions of patients with an HIV-1 RNA level of <50 copies/mL was ≥–12%.[24] Virological failure was defined in the study protocol as the failure to attain an HIV-1 RNA level of <200 copies/mL by week 24 or confirmed viral rebound to ≥200 copies/mL following the confirmed decrease in viral load to <50 copies/mL by week 24.

- Virological noninferiority was demonstrated between the two treatment regimens at week 48, with

67% of emtricitabine/tenofovir DF and 68% of abacavir/lamivudine recipients (ITT populations) achieving HIV-1 RNA levels of <50 copies/mL (95% CI –6.63, 7.40); corresponding proportions of patients with HIV-1 RNA levels of <400 copies/mL were 71% and 75% (95% CI –2.71, 10.56). Corresponding time to loss of virological response (TLOVR) results were 61% and 63%, and for the observed patient populations were 87% and 84%. The results were robust to multiple analyses, including counting patients who switched therapy as treatment failures.[24]

- For patients with baseline HIV-1 RNA levels of <100 000 copies/mL, plasma HIV-1 RNA levels of <50 copies/mL were achieved in 69% of emtricitabine/tenofovir DF and 71% of abacavir/lamivudine recipients at week 48; corresponding results in patients with HIV-1 RNA levels of ≥100 000 copies/mL were 65% and 63%.[24]
- Virological efficacy was sustained at week 96, with plasma HIV-1 RNA levels of <50 copies/mL achieved in 58% and 60% of emtricitabine/tenofovir DF and abacavir/lamivudine recipients (95% CI –5.41, 9.32).[25] Results were similar for patients stratified on the basis of viral load at baseline. Virological failure occurred in 14% of patients in both treatment groups. Increases from baseline in median CD4+ cell counts in both treatment groups were also observed at 48 and 96 weeks.[25]

The ACTG 5202 Study

The ACTG 5202 study is an ongoing phase IIIB, randomized, partially-blinded, four-arm, multicentre, equivalence study comparing emtricitabine/tenofovir DF with abacavir/lamivudine (each taken in combination with open-label boosted atazanavir or efavirenz; patient numbers not reported) in treatment-naive patients aged ≥16 years with HIV-1 infection (plasma HIV RNA levels >1000 copies/mL);[26,32] 1858 patients were enrolled and patients were stratified on the basis of viral load (<100 000 or ≥100 000 copies/mL) at screening: preliminary results have been reported for 797 patients with screening plasma HIV-1 RNA levels of ≥100 000 copies/mL.[26] At baseline, the mean plasma HIV-1 RNA level was 5.1 $\log_{10}$ copies/mL and the CD4+ count was 181 cells/μL. The primary efficacy endpoint was time to virological failure (defined as a confirmed HIV-1 RNA level of 1000 copies/mL at weeks 16–24 or a level of 200 copies/mL at week 24); other primary endpoints were the time to the first grade 3/4 adverse event (section 4) or laboratory abnormality at least 1 grade higher than at baseline or time to treatment discontinuation.[26,32]

- Significant differences between the emtricitabine/tenofovir DF and abacavir/lamivudine treatment groups in virological efficacy for patients with screening HIV-1 RNA levels of ≥100 000 copies/mL were identified (by the Data Safety Monitoring Board) and resulted in the subsequent unblinding of this high viral load stratum arm. The Data Safety Monitoring Board requested data be combined and analysed as two arms (abacavir/lamivudine vs emtricitabine/tenofovir DF). Preliminary results (ITT; median follow-up 60 weeks) for the 797 patients (85% men) with high viral load (HIV-1 RNA level of ≥100 000 copies/mL) at screening showed that the time to virological failure was significantly shorter for the recipients of abacavir/lamivudine than for the patients who received emtricitabine/tenofovir DF (hazard ratio 2.33; 95% CI 1.46, 3.72; p = 0.0003). Virological failure occurred in more than twice as many patients in the abacavir/lamivudine group than in the emtricitabine/tenofovir DF group (57 vs 26 patients).[26]
- A systematic MEDLINE review of 12 prospective trials of boosted PIs with an NRTI backbone as first-line treatment for 4896 patients with HIV-1 infection (published between January 2000 and March 2008; trials included the HEAT study and the ACTG 5202 study) suggested that emtricitabine/tenofovir DF was more effective than abacavir/lamividine when treatment efficacy was determined on the basis of plasma HIV-1 RNA levels of <50 copies/mL, using the US FDA TLOVR algorithm in which most treatment failures were discontinuations for non-virological reasons (e.g. adverse events) [reported as a poster].[33] The apparent efficacy advantage for emtricitabine/tenofovir DF was evident for patients with baseline HIV-1 RNA levels above and below 100 000 copies/mL. Factors

possibly influencing the apparent differences in treatment included different adverse event or adherence management strategies.[33]

Emtricitabine/Tenofovir DF as the 'Backbone' in Comparative Trials of Protease Inhibitors

Emtricitabine/tenofovir DF was the dual NRTI backbone in numerous fully published randomized trials of various design (most were noninferiority trials) comparing the efficacy of various boosted PIs, including atazanavir, darunavir, fosamprenavir, and saquinavir,[16,28-30] or different regimens of fixed-dose boosted lopinavir formulations[17,27] (table II) and in two noncomparative trials[14,34] in antiretroviral therapy-naive patients with HIV infection (table II). The primary endpoint for most of the trials shown in table II was the proportion of patients with plasma HIV-1 RNA levels of <50 copies/mL (ITT: missing/discontinuation = failure analysis).

- Emtricitabine/tenofovir DF was effective as the dual NRTI backbone in the trials comparing the efficacy of boosted PIs. Across these trials, plasma HIV-1 RNA levels of <50 copies/mL were achieved in 64–84% of patients (table II). Improvements in immunological status were also seen, as evidenced by increases in CD4+ cell counts across all studies (table II).
- In the largest of these trials, the CASTLE study, the antiviral efficacy of boosted atazanavir was noninferior to that of a fixed-dose combination of lopinavir/ritonavir in patients also receiving emtricitabine/tenofovir DF 200 mg/300 mg once daily, with mean increases in CD4+ cell counts similar for the two groups, at week 48. Mean CD4+ cell counts at this timepoint were 203 and 219 for patients enrolled into the boosted atazanavir and lopinavir/ritonavir groups, respectively (table II).[28] In addition, rates of virological failure were the same (6%) with both treatment regimens. The investigators concluded that the results of this trial support the use of boosted atazanavir as a first-line therapy as a component of a HAART regimen.[28]
- Similarly, at 48 weeks, the antiviral efficacy of boosted darunavir was noninferior to that of a fixed-dose combination of lopinavir/ritonavir (each in combination with emtricitabine/tenofovir DF) in the ARTEMIS study.[16] Preliminary long-term results of this study (reported in an abstract)[35] showed that the efficacy of both treatment regimens was sustained at 96 weeks with plasma HIV-1 RNA levels of <50 copies/mL achieved in 79% of the boosted darunavir recipients and 71% of the lopinavir/ritonavir recipients demonstrating non-inferiority (95% CIs 2, 15). Subsequent statistical testing showed that the boosted darunavir regimen had antiviral efficacy superior ($p = 0.012$) to that of the lopinavir/ritonavir regimen.[35]
- Emtricitabine/tenofovir DF in combination with boosted atazanavir also showed efficacy in the BATON trial (table II) and good adherence to treatment was reported.[14]
- In addition, first-line treatment with emtricitabine/tenofovir DF in combination with a boosted PI or an NNRTI for 48 weeks also produced beneficial effects in 395 HIV-1-infected patients (median baseline plasma viral load of 5.0 $\log_{10}$ copies/mL and a median CD4+ count of <211 cells/μL) in a 'real life' clinical practice study that enrolled outpatients from 50 centres in Germany.[34] At week 48, viral load was <50 copies/mL in 82% of evaluated patients and a median increase in CD4+ count of 406 cells/μL was reported.[34]

Antiretroviral Therapy-Experienced Patients

Data are currently limited on the efficacy of emtricitabine/tenofovir DF in combination with a PI in patients with HIV-1 infection, with the only study reported to date[31,37] including only a small proportion of patients receiving this type of combination regimen. Patients with HIV-1 infection with virological suppression (HIV-1 RNA levels of <200 copies/mL) who had been previously treated with lamivudine-containing HAART (including a second NRTI) for at least 6 months were enrolled in the randomized, non-blind, noninferiority 'switch' BICOMBO trial (conducted in Spain).[31,37] In this trial, patients (for whom neither tenofovir DF nor abacavir were contraindicated) received emtricitabine/tenofovir DF 200 mg/300 mg once daily ($n = 166$) or the fixed-dose formulation of abacavir/lamivudine 600 mg/300 mg once daily ($n = 167$).[31]

Table II. Efficacy of ritonavir-boosted protease inhibitor (PI) highly active antiretroviral treatment regimens containing the fixed-dose combination of emtricitabine/tenofovir disoproxil fumarate (200 mg/300 mg once daily [od]) as the dual nucleoside/nucleotide reverse transcriptase inhibitor (RTI) backbone: results of randomized, comparative fully published trials (and a single noncomparative [nc] trial) in antiretroviral therapy-naive patients (pts) with HIV-1 infection

Study [trial design]	Treatment regimen (mg) [time of assessment]	No. of pts (ITT[a])	Baseline		Pts with plasma HIV-1 RNA levels <50 copies/mL (%) [primary endpoint]	CD4+ count: mean increase from baseline (cells/μL)
			mean plasma HIV-1 RNA level ($\log_{10}$ copies/mL)	mean CD4+ count (cells/μL)		
Comparisons of various ritonavir-boosted PIs						
Molina et al.[28] (CASTLE)	ATV[b] 300 od [48 wk]	440	5.01 (med)	205 (med)	78[c]	203
[nb, mc, noninferiority]	LPV/r 400/100 bid [48 wk]	443	4.96 (med)	204 (med)	76[c]	219
Smith et al.[29] (ALERT)	FOS[b] 1400 od [48 wk]	53	4.9 (med)	176	75	170
[nb, mc]	ATV[b] 300 od [48 wk]	53	4.9 (med)	205	83	183
Ortiz et al.[16] (ARTEMIS)	DRV[b] 800 od [48 wk][d]	343	4.86	228 (med)	84[e]	137 (med)
[nb, mc, noninferiority]	LPV/r 800/200 od or 400/100 bid [48 wk][d]	346	4.84	218 (med)	78[e]	141 (med)
Walmsley et al.[30,36] (GEMINI)	SQV[b] 1000 bid [48 wk]	167	5.20	142 (med)	64.7[f]	178 (med)
[nb, multinational, mc]	LPV/r 400/100 bid [48 wk]	170	5.17	142 (med)	63.5[f]	204 (med)
Comparisons of ritonavir-boosted lopinavir regimens						
Johnson et al.[17]	LPV/r[g] 800/200 od [48 wk]	115	4.8 (med)	214 (med)	70	185
[nb, mc, noninferiority]	LPV/r[g] 400/100 bid [48 wk]	75	4.6 (med)	232 (med)	64	196
Gathe et al.[27] (study M05-730)	LPV/r[h] 800/200 od [48 wk]	333	4.93	216.2	77[i]	186
[nb, mc, noninferiority]	LPV/r[h] 400/100 bid [48 wk]	331	5.05	214.7	76[i]	198
The BATON trial						
Elion et al.[14] [nc, mc]	ATV[b] 300 od [48 wk]	100	4.8 (med)	256 (med)	81	217 (med)

a For the primary endpoint assessments.

b Boosted with ritonavir 100 mg.

c Between-group difference 1.7%; 95% CI –3.8, 7.1: noninferiority established. Predefined noninferiority margin was –10%.

d The study was conducted over 192 wk; fully published 48-wk results reported.

e Results for the per-protocol population; TLOVR (primary endpoint). ITT result was identical. Estimated between-group difference 5.6%; 95% CI –0.1, –11; p < 0.001: noninferiority established. Predefined noninferiority margin was –12%.

f Estimated difference in proportion for noninferiority 1.14%, 96% CI –9.6, 11.9; p < 0.012: noninferiority established. Predefined noninferioriy margin –12%.

g Administered as the capsule formulation.

h Administered as the tablet formulation.

i For the difference in response rates, 95% CIs –5, 8 confirming noninferiority. Predefined noninferiority margin was –12%.

ATV = atazanavir (ritonavir-boosted); **bid** = twice daily; **DRV** = darunavir (ritonavir-boosted); **FOS** = fosamprenavir (ritonavir-boosted); **ITT** = intent-to-treat; **LPV/r** = ritonavir-boosted lopinavir (administered as a fixed-dose combination formulation); **mc** = multicentre; **med** = median; **nb** = nonblind; **SQV** = saquinavir (ritonavir-boosted); **TLOVR** = time to loss of virological response.

All patients also received a PI (10% in each treatment group) or an NNRTI (90%). The primary endpoint was the proportion of patients with treatment failure (for any reason, including virological rebound to >200 copies/mL, loss to follow-up, death) at week 48; the noninferiority of emtricitabine/tenofovir DF compared with abacavir/lamivudine was demonstrated if the upper limit of the 95% CI for the between-group difference in primary endpoint results was <12.5.[31] Results are not yet available for the subgroups of patients who received a PI or an NNRTI.

- Emtricitabine/tenofovir DF 200 mg/300 mg once daily (n = 166) was an effective treatment for previously treated patients with HIV-1 infection. At week 48, the noninferiority endpoint was not met, with treatment failure reported for 13% and 19% of emtricitabine/tenofovir DF and abacavir/lamivudine recipients, respectively (95% CI −2, 14).[31] The between-group difference in efficacy was largely attributed to treatment discontinuation among some abacavir/lamivudine recipients because of suspected abacavir hypersensitivity.[31]

- For virological efficacy assessments, a secondary efficacy endpoint defined as the proportion of patients with virological failure (HIV-1 RNA levels ≥200 copies/mL at week 48), noninferiority criteria were met, with 0% and 2.4% of emtricitabine/tenofovir DF and abacavir/lamivudine recipients, respectively, experiencing virological failure (95% CI 0.05, 6).[31] All four patients with virological failure were receiving an NNRTI rather than a PI. By contrast, there was a significant (p = 0.032) between-group difference in favour of abacavir/lamivudine in terms of changes in CD4+ cell counts (secondary endpoint) with CD4+ count changes of −2.7 and +44 cells/μL reported for the emtricitabine/tenofovir DF and abacavir/lamivudine recipients, respectively, at week 48.

4. Tolerability

Tolerability data for emtricitabine/tenofovir DF in combination with a boosted PI have been reported in a number of clinical trials, including the randomized HEAT study (section 3) in treatment-naive patients with HIV-1 infection, for which 48-[24] and 96-week[25,38] adverse event data are available, and the ACTG 5202 study (see section 3 for study details).[26] Preliminary information on the tolerability of emtricitabine/tenofovir DF in combination with a PI (or an NNRTI) in treatment-experienced patients is also available.[31] Data on the safety profile of the fixed-dose combination of emtricitabine/tenofovir DF in the US prescribing information[6] are derived from trials where the combination was administered in combination with an NNRTI (rather than a PI) and therefore not reviewed in detail in this article.

- Emtricitabine and tenofovir DF, administered alone or in combination, are generally well tolerated by adults with HIV-1 infection (reviewed previously[3]). The most common adverse events with coadministered emtricitabine and tenofovir DF as separate agents were diarrhoea, nausea and vomiting.[3] Tenofovir DF has been associated with renal impairment and acute tubular necrosis; risk factors include pre-existing renal impairment and advanced HIV disease.[1]
- Adverse events reported in the HEAT study over the initial 96-week treatment period are shown in figure 1.
- The most common grade 2–4 treatment-related adverse events in patients treated with emtricitabine/tenofovir DF for 96 weeks in the HEAT study were diarrhoea and nausea (figure 1).[38]
- Over a 96-week treatment period, the tolerability profile of emtricitabine/tenofovir DF, in terms of drug-related adverse events and premature discontinuation of drug treatment, appeared to be similar to that of abacavir/lamivudine (each given in combination with lopinavir/ritonavir) in the HEAT study.[25,38]
- Premature discontinuation of treatment because of adverse events was reported for 21 (17%) emtricitabine/tenofovir DF and 20 (18%) abacavir/lamivudine recipients. [25] Drug-related grade 3–4 adverse events occurred in 52 (15%) of emtricitabine/

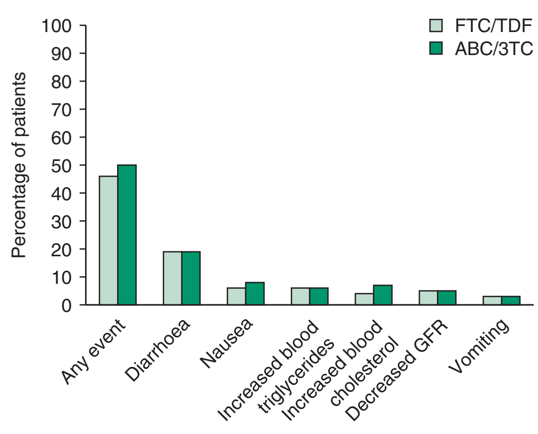

Fig. 1. Tolerability profile of emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) compared with that of abacavir/lamivudine (ABC/3TC) in the HEAT study in antiretroviral therapy-naive patients with HIV-1 infection with baseline HIV-1 RNA levels of ≥1000 copies/mL; all patients also received once-daily ritonavir-boosted lopinavir. Patients were randomized to receive either FTC/TDF 200 mg/300 mg once daily (n = 345) or ABC/3TC 600 mg/300 mg once daily (n = 343). The trial was double-blind, placebo-matched and multicentre in design. Treatment-related adverse events (grade 2–4) shown (incidence ≥3%) were reported at week 96.[38] **GFR** = glomerular filtration rate.

tenofovir DF and 50 (15%) of abacavir/lamivudine recipients; drug-related serious adverse events (excluding abacavir-associated hypersensitivity reaction) were documented in 6 (2%) of emtricitabine/tenofovir DF and 4 (1%) of abacavir/lamivudine recipients at week 96.[25]

- Proximal renal tubule dysfunction (not defined) was reported in 6 (2%) of the patients who received emtricitabine/tenofovir DF and in none of the abacavir/lamivudine recipients in the HEAT study. Suspected abacavir hypersensitivity reaction occurred in 14 (4%) patients treated with abacavir/lamivudine and in 3 (<1%) patients who received emtricitabine/tenofovir DF.[25]
- In the ACTG 5202 study in treatment-naive patients, those treated with abacavir/lamivudine 600 mg/300 mg once daily, compared with recipients of emtricitabine/tenofovir DF 200 mg/300 mg once daily, had a shorter time to the emergence of grade 3/4 adverse events (hazard ratio 1.89; 95% CI 1.43, 2.5; $p < 0.0001$), which were most commonly general body aches and increases in lipid levels. The incidence of suspected drug hypersensitivity was 7% in each NRTI group.[26]
- Emtricitabine/tenofovir DF was generally well tolerated when used as the dual NRTI backbone in randomized trials comparing the efficacy of different boosted PIs (atazanavir, darunavir and lopinavir) [section 3].[16,17,27,28] Similarly, the combination was usually well tolerated by treatment-experienced patients receiving concomitant treatment with PIs (or NNRTIs) in the BICOMBO trial.[31] In this trial, the rate of treatment discontinuation due to an adverse event was significantly lower with emtricitabine/tenofovir DF than with abacavir/lamivudine (5% vs 10%; $p = 0.004$).[31]

5. Dosage and Administration

In the US, the fixed-dose combination of emtricitabine/tenofovir DF, administered in combination with other antiretroviral agents such as PIs or NNRTIs, is indicated for the treatment of adults with HIV-1 infection. The use of emtricitabine/tenofovir DF in antiretroviral therapy-experienced patients should be guided by laboratory testing as well as the patient's treatment history.[6] Emtricitabine/tenofovir DF should not be used as a component of a triple NRTI regimen[6] and should not be coadministered with Atripla®, Emtriva®, Viread® or lamivudine-containing products.[6] In the EU, emtricitabine/tenofovir DF, in combination with other antiretroviral drugs, is approved for the treatment of adults with HIV-1 infection, based solely on the results of trials in antiretroviral therapy-naive patients with HIV-1 infection.[22]

The recommended dosage of emtricitabine/tenofovir DF is 200 mg/300 mg (one tablet) once daily with or without food (in the US[6]) or with food (in the EU[22]). As increased systemic exposure to the individual agents has been reported in patients with moderate to severe renal impairment (see section 2), dosage modification (one tablet every 48 hours) is required for patients with a baseline CL_{CR} of 30–49 mL/min (1.8–2.94 L/h).[6,22] Tenofovir DF should not be taken by patients with a CL_{CR} of <30 mL/min or by those on haemodialysis.[6,22]

In the US prescribing information,[6] there is an NRTI class boxed warning stating that lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. In addition, it states that emtricitabine/tenofovir DF is not approved for the treatment of patients with chronic hepatitis B infection and that severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus and HIV-1 and discontinue emtricitabine/tenofovir DF.[6]

Local prescribing information should be referred to for further information on warnings, precautions and contraindications.

6. Emtricitabine/Tenofovir DF in Combination with a Protease Inhibitor in HIV-1 Infection: Current Status

Emtricitabine/tenofovir DF as a dual NRTI backbone in combination with various boosted PIs has shown good efficacy in the treatment of antiretroviral therapy-naive adults with HIV-1 infection in randomized clinical trials. Preliminary data also suggest that emtricitabine/tenofovir DF in combination with a PI is effective for treatment-experienced patients with virological suppression switching from a lamivudine-containing regimen.[31,37]

Emtricitabine/tenofovir DF was usually well tolerated when used in combination with boosted PIs and rates of treatment discontinuation due to adverse events were low.[16,17,27,28] In addition, mutations conferring resistance to either emtricitabine or tenofovir DF were seldom observed in clinical isolates of HIV-1 from treatment-naive patients.

Of note, preliminary data from two head-to-head trials are inconsistent on the relative efficacy of emtricitabine/tenofovir DF and abacavir/lamivudine, each in combination with a boosted PI. In the HEAT study,[24,25] the noninferiority of abacavir/lamivudine compared with emtricitabine/tenofovir DF was established, whereas emtricitabine/tenofovir DF was more effective than abacavir/lamivudine for patients with high baseline viral loads (≥100 000 copies/mL) in ACTG 5202.[26] In this latter trial, patients received dual NRTI combinations with either a PI or an NNRTI.

As discussed previously, in the most recent US DHHS treatment guidelines, emtricitabine/tenofovir DF is the preferred dual NRTI backbone regimen for use as a component of PI-based regimens for antiretroviral therapy-naive patients.[1] In these guidelines, the fixed-dose combination of abacavir/lamivudine has been changed from a preferred to an alternative dual NRTI backbone because of reports from observational studies of an increased risk of myocardial infarction in patients with cardiovascular risk factors.[39] In addition, based on the results of ACTG 5202,[26] there are concerns about the efficacy of abacavir/lamivudine in the treatment of patients with high screening viral loads (≥100 000 copies/mL).[1]

In conclusion, emtricitabine/tenofovir DF, administered as a once-daily tablet, offers convenient dose administration, which may lead to good treatment adherence. Emtricitabine/tenofovir DF is an effective and well tolerated dual NRTI combination for first-line use as a backbone in PI-based HAART regimens for the treatment of antiretroviral therapy-naive adults with HIV-1 infection.

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