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Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate

Triple Combination Tablet

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Contents

Abstract

▲ A new formulation combining fixed doses of the nucleoside reverse transcriptase inhibitors emtricitabine (200mg) and tenofovir disoproxil fumarate (tenofovir DF; 300mg) with the non-nucleoside reverse transcriptase inhibitor efavirenz (600mg) represents the first once-daily, one-tablet antiretroviral regimen.

▲ Co-formulated efavirenz/emtricitabine/tenofovir DF demonstrated bioequivalence to concomitant administration of the individual agents in a pharmacokinetic trial in healthy volunteers (n = 48).

▲ Co-formulated efavirenz/emtricitabine/tenofovir DF has not been evaluated in clinical trials. However, a once-daily regimen of efavirenz, emtricitabine and tenofovir DF (administered as individual agents) was superior to once-daily efavirenz plus twice-daily co-formulated lamivudine/zidovudine in terms of virological suppression, immunological recovery and adverse events resulting in discontinuation of the study medications in a randomised, multicentre, noninferiority study in treatment-naive patients with HIV infection (n = 517). Both regimens are currently recommended as initial antiretroviral therapy.

▲ Preliminary data suggest that co-formulated efavirenz/emtricitabine/tenofovir DF, like the individual agents in combination with other antiretroviral drugs, is generally well tolerated. CNS adverse events, primarily headache and dizziness, were the most common treatment-emergent, drug-related adverse events in the pharmacokinetic study involving the co-formulation.

Features and properties of the efavirenz (EFV)/emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) triple combination tablet (Atripla™)	
Indication	
HIV infection	
Mechanism of action	
Antiviral	Non-nucleoside reverse transcriptase inhibitor (EFV) combined with two nucleoside reverse transcriptase inhibitors (FTC and TDF)
Dosage and administration	
Dosage in clinical trials	EFV 600mg/FTC 200mg/TDF 300mg
Route of administration	Oral
Frequency of administration	Once daily (one tablet)
Pharmacokinetic parameters (mean or median steady-state values) for FTC, tenofovir and EFV following once-daily administration of oral doses of FTC 200mg, TDF 300mg and EFV 600mg separately in HIV-infected patients	
Peak plasma concentration	EFV 12.9 μmol/L, FTC 1.72 μg/mL, tenofovir 0.33 μg/mL
Area under the plasma concentration-time curve	EFV 184 μmol • h/L, FTC 8.0 μg • h/mL, tenofovir 3.0 μg • h/mL
Elimination half-life	EFV 40–55h (200–400mg doses), FTC 8.2h, tenofovir 14.4h
Adverse events with co-formulated EFV/FTC/TDF (healthy volunteers)	
Mostly mild, transient and consistent with the known tolerability profiles of the individual agents	

Antiretroviral therapy, although noncurative, has nonetheless dramatically improved the prognosis of patients with HIV/AIDS, both in terms of quality and quantity of life.[1] Since complete eradication of HIV is not possible with existing antitretroviral drug regimens, one of the primary aims of therapy is to maximally and durably suppress the plasma HIV RNA load.[2] To achieve this goal in previously untreated (antiretroviral-naive) adult or adolescent patients, current US[2,3] and UK[4] guidelines favour triple combination therapy consisting of two nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTIs) plus either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a boosted protease inhibitor (PI).

In the US, emtricitabine or lamivudine plus tenofovir disoproxil fumarate (tenofovir DF) or zidovudine[2,3] (or didanosine[3]) form the dual NRTI backbone in preferred[2] or recommended[3] NNRTI- and PI-based regimens. Efavirenz is the NNRTI of choice (except in women who are in the first trimester of pregnancy or who wish to become pregnant[2]),[3] while ritonavir-boosted lopinavir[2,3] (or low-dose ritonavir with atazanavir, saquinavir or indinavir[3]) are the PIs of choice. Of interest, recent results from the INITIO study[5] indicated that an NNRTI (efaviranz)/2-NRTI regimen was better than a PI (nelfinavir)/2-NRTI regimen (as well as an NNRTI/PI/2-NRTI regimen) as initial therapy for HIV infection. However, the dual NRTI backbone assessed in this trial (stavudine plus didanosine) is no longer recommended.[2]

Among the factors that should be taken into account when selecting an initial antiretroviral regimen are the convenience of, and potential adherence to, treatment.[2] Suboptimal adherence (<90–95%) is common, and is also the main reason that patients do not achieve sustained suppression of viral replication, which is crucial in reducing HIV-related morbidity and mortality.[2,6] It also leads to the emergence of drug-resistant HIV.[2]

Strategies aimed at improving adherence include simplifying antiretroviral regimens (which are often complex) by, for example, reducing the number of pills and the dose administration frequency.[2] In this respect, NNRTI-based regimens generally have the advantage of a lower pill burden compared with most PI-based regimens.[2] In particular, efavirenz is the only NNRTI approved by the US FDA for once-daily administration,[7] a dose administration schedule strongly preferred by patients.[8]

Related advances in terms of the dual NRTI backbone include the advent of single-pill, fixed-dose combinations of lamivudine/zidovudine (Combivir®),[1] which is administered twice daily, and emtricitabine/tenofovir DF (Truvada®), which is administered once daily. Single-pill, fixed-dose combinations of abacavir with zidovudine (Epizicom®), lamivudine (Kivexa®) and lamivudine/zidovudine (Trizivir®), are also available, although abacavir does not feature in preferred[2] or recommended[3] NNRTI- or PI-based regimens, and abacavir/lamivudine/zidovudine is only recommended when NNRTI- or PI-based regimens cannot or should not be used.[2]

The simplification of HIV therapy has continued with the recent development of a single-pill, fixed-dose combination of efavirenz 600mg/emtricitabine 200mg/tenofovir DF 300mg (efavirenz/emtricitabine/tenofovir DF; Atripla™) which, like the individual agents, is administered once daily.[9] Treatment with these three drugs is a preferred/recommended NNRTI-based regimen.[2,3] This profile focuses on data relevant to the use of the co-formulation in patients with HIV infection.

1. Pharmacodynamic Profile

The pharmacodynamic properties of emtricitabine[10] and tenofovir DF[11] (including co-formulated emtricitabine/tenofovir DF[12]) have been reviewed in detail elsewhere, as have those of efavirenz;[13] much of the following discussion is based on data derived from US prescribing information for these agents.[14-17]

- The mechanism of action of emtricitabine and tenofovir DF (the ester prodrug of tenofovir) in-

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

volves the intracellular conversion of these drugs to their active metabolites (emtricitabine 5′-triphosphate and tenofovir diphosphate, respectively) which, in turn, inhibit the activity of HIV reverse transcriptase (RT) by competing with endogenous substrates (2′-deoxycytidine 5′-triphosphate and deoxyadenosine 5′-triphosphate, respectively). Incorporation of emtricitabine 5′-triphosphate and tenofovir diphosphate into the viral DNA causes chain termination, thereby inhibiting viral replication.[10,11] The antiviral activity of efavirenz is mediated predominantly by noncompetitive inhibition of HIV RT.[16]

Antiviral Activity

- Emtricitabine, tenofovir and efavirenz have each demonstrated antiviral activity *in vitro* against clinical isolates and laboratory strains of HIV-1 in lymphoblastoid cell lines and peripheral blood mononuclear cells, as well as macrophage/monocyte cells (tenofovir and efavirenz only) and the MAGI CCR5 cell line (emtricitabine only).[14-16]
- In drug-combination studies, emtricitabine showed synergistic *in vitro* antiviral activity with tenofovir;[17] efavirenz demonstrated additive effects (without cytotoxicity) with emtricitabine and tenofovir.[16] In addition, emtricitabine, tenofovir and efavirenz demonstrated additive (efavirenz) or additive-to-synergistic (emtricitabine and tenofovir) *in vitro* antiviral activity with the NRTIs abacavir, didanosine (tenofovir and efavirenz only), lamivudine, stavudine, zalcitabine and zidovudine, the NNRTIs delavirdine and nevirapine, and the PIs amprenavir, indinavir (tenofovir and efavirenz only), lopinavir (efavirenz only), nelfinavir, ritonavir and saquinavir.[14-16] Efavirenz also showed additive *in vitro* effects (without cytotoxicity) with the fusion inhibitor enfuvirtide.[16]

Resistance

- HIV isolates with reduced susceptibility to emtricitabine, tenofovir and efavirenz have been selected for *in vitro* and have been recovered from patients receiving these agents.[14-16]
- A single amino acid substitution at position 184 (M184I/V) and position 65 (K65R) in the HIV RT gene is associated with resistance to emtricitabine and tenofovir, respectively,[10,11] whereas one or more substitutions at positions 98, 100, 101, 103, 106, 108, 188, 190, 225 and 227 have been observed in patients not responding to treatment with efavirenz in combination with other antiretrovirals.[16] In addition, HIV-1 isolates with reduced susceptibility to efavirenz have emerged rapidly under *in vitro* selection; genotypic characterisation of these viruses identified mutations resulting in single (L100I, V179D), double (L100I/V108I) and triple (L100I/V179D/Y181C) amino acid substitutions in RT.[16] K103N, the mutation most commonly selected for by efavirenz, is associated with high-level resistance to the drug.[16,18]
- In terms of cross resistance, emtricitabine-resistant isolates (M184V/I) also demonstrate reduced susceptibility to lamivudine, but remain sensitive to both tenofovir and efavirenz.[14] Tenofovir-resistant isolates (K65R) likewise show reduced sensitivity to emtricitabine and lamivudine (as well as abacavir and didanosine),[15] although they probably remain hypersusceptible to NNRTIs (e.g. efavirenz) and zidovudine.[18] HIV variants with an average of three zidovudine resistance-associated mutations (including either M41L or L210W) showed a 3-fold reduction in sensitivity to tenofovir.[15]
- In a pivotal clinical trial (Study 934;[19] see section 3 for further details), the proportion of HIV-infected, antiretroviral-naive adults without baseline resistance mutations to efavirenz who developed a resistance mutation of any kind was numerically lower among recipients of a once-daily regimen of efavirenz 600mg, emtricitabine 200mg and tenofovir DF 300mg concomitantly administered as individual agents (hereafter referred to as efavirenz + emtricitabine + tenofovir DF) than recipients of once-daily efavirenz 600mg plus twice-daily co-formulated lamivudine/zidovudine 150mg/300mg (hereafter referred to as efavirenz + lamivudine/zidovudine): 9 of 244 patients (4%) versus 17 of 243 patients (7%); statistical analysis not performed. A total of 35 patients (12 in the efavirenz + emtric-

itabine + tenofovir DF group; 23 in the efavirenz + lamivudine/zidovudine group) who had a plasma HIV RNA level ≥400 copies/mL at week 48 (includes both viral rebounds and virological failures) or at the time of earlier discontinuation were included in this resistance analysis.[19]

- The most common emergent mutations in Study 934 were those conferring resistance to efavirenz.[19] Of the 26 patients with any resistance mutation at week 48, only one (in the efavirenz + lamivudine/zidovudine group) did not have an efavirenz resistance-associated mutation. Furthermore, the K103N mutation developed in 21 (84%) of the 25 patients with efavirenz resistance-associated mutations. Only two patients in the efavirenz + emtricitabine + tenofovir DF group developed the M184V/I mutation compared with seven patients in the efavirenz + lamivudine/zidovudine group.
- No patient treated with efavirenz + emtricitabine + tenofovir DF in Study 934 had the K65R mutation at week 48.[19] This unexpected finding was in contrast to the results of a previous well designed trial (Study 903), in which 7 (2.3%) of 299 treatment-naive patients receiving concomitant efavirenz, lamivudine and tenofovir DF had K65R mutations at 48 weeks.[15,19] The K65R mutation subsequently occurred in one other concomitant efavirenz, lamivudine and tenofovir DF recipient in Study 903 (at 96 weeks), and was present in a total of eight patients after 144 weeks of follow-up in this trial.[15]

2. Pharmacokinetic Profile

This section presents pharmacokinetic (bioequivalence) data for the co-formulated efavirenz/emtricitabine/tenofovir DF tablet (available from a single study;[20] published as an abstract), as well as data for the individual agents or co-formulated emtricitabine/tenofovir DF (derived from previous reviews[10-13,21] or US prescribing information[14-17]). The dose recommendation for co-formulated efavirenz/emtricitabine/tenofovir DF in patients with renal impairment is contained in the US prescribing information,[22] which also provides details of concomitant agents that are not recommended or contraindicated.

- Co-formulated efavirenz/emtricitabine/tenofovir DF was bioequivalent to efavirenz + emtricitabine + tenofovir DF in a randomised, open-label, single-dose, crossover study in 48 fasting, healthy subjects.[20] For efavirenz 600mg, emtricitabine 200mg and tenofovir DF 300mg, the 90% confidence intervals (CIs) for the geometric mean ratio (co-formulation vs individual agent) for the peak plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) values were contained within 80–125%, thus meeting the predefined criteria for bioequivalence.[20]
- Steady-state absorption pharmacokinetic parameters for the individual agents, as assessed in patients with HIV infection,[10,11,16] are presented in the Features and Properties table.
- Pharmacokinetic parameter values for emtricitabine and tenofovir in HIV-infected individuals are similar to those in healthy volunteers;[14,15] the C_{max} of these NRTIs is reached within 1–2.3 hours after single- or multiple-dose oral administration.[10,11,14,15] The C_{max} of efavirenz occurs ≈3.5 hours following multiple-dose oral administration to patients with HIV infection.[16]
- Mean absolute oral bioavailability values are available for emtricitabine (92–93%[14,17]) and tenofovir (from tenofovir DF; ≈25%[15]), but not for efavirenz.[2]
- In the presence of food, C_{max} values relative to the fasting state were reduced by 29% for emtricitabine (capsules),[14] but increased by ≈14%,[15] 39%[16] and 79%[16] for tenofovir (tenofovir DF tablets), efavirenz (capsules) and efavirenz (tablets), respectively. AUC values were unaffected for emtricitabine,[14] but increased by ≈40%,[15] 22%[16] and 28%[16] for tenofovir (tenofovir DF tablets), efavirenz (capsules) and efavirenz (tablets), respectively. Whereas emtricitabine and tenofovir DF can be taken without regard to meals,[14,15] efavirenz should be taken on an empty stomach, preferably at bedtime.[16]
- Efavirenz is highly bound to human plasma proteins (>99%),[16] unlike emtricitabine (<4%)[14] and tenofovir (<0.7%), which are minimally bound.[15]

• Steady-state elimination half-life values for the individual agents, as assessed in patients with HIV infection,[10,11,16] are presented in the Features and Properties table. Both emtricitabine and tenofovir are primarily eliminated via the kidneys by a combination of glomerular filtration and active tubular secretion.[12,17]

Emtricitabine is not an inhibitor[14] and tenofovir is not a substrate[15] for cytochrome P450 (CYP) enzymes, unlike efavirenz, which is predominantly metabolised by the CYP3A4 and CYP2B6 isoenzymes in the liver to essentially inactive hydroxylated metabolites.[13,16] Approximately 14–34% of a radiolabelled dose of efavirenz 400mg was recovered in the urine in the form of metabolites, while 16–61% was excreted in the faeces as unchanged drug.[13,16]

Special Patient Populations

• The pharmacokinetics of emtricitabine, tenofovir and efavirenz appear unaffected by gender (all three agents[14-16]) and race (emtricitabine[14] and efavirenz;[16] tenofovir insufficiently studied[15]). The pharmacokinetics of tenofovir DF have not been assessed in elderly or paediatric patients,[15] while those of emtricitabine and efavirenz have not been fully evaluated in the elderly,[14,16] but appear to be similar in paediatric and adult patients (based on comparison of weight-adjusted dosages).[14,16]

• The presence of hepatic impairment does not substantially alter the pharmacokinetics of tenofovir[15] and is expected to have limited impact on the pharmacokinetics of emtricitabine (although this has not been studied).[14] In contrast, caution is necessary when administering efavirenz to individuals with hepatic impairment, as the pharmacokinetics of this drug (which is metabolised in the liver) have not been adequately studied in this patient group.[16]

• Conversely, the presence of renal impairment alters the pharmacokinetics of tenofovir[15] and emtricitabine,[14] but is expected to have minimal impact on the pharmacokinetics of efavirenz (although this has not been studied).[16] C_{max} and AUC values for tenofovir and emtricitabine were increased in adult patients with creatinine clearance <50 mL/min or with end-stage renal disease requiring dialysis; co-formulated efavirenz/emtricitabine/tenofovir DF should not be administered to patients with a creatinine clearance <50 mL/min.[22]

Drug Interactions

• Studies with the individual agents did not reveal any clinically significant pharmacokinetic interactions when the recommended once-daily doses of tenofovir DF (300mg) and either emtricitabine (200mg) or efavirenz (600mg) were coadministered in healthy volunteers.[14,15] The effect of emtricitabine on the pharmacokinetics of efavirenz (and vice-versa) has not been investigated.[14]

• No clinically significant pharmacokinetic interactions occur between emtricitabine and the following antiviral agents: zidovudine; indinavir; famciclovir; and stavudine.[14]

• Similarly, no potentially clinically relevant pharmacokinetic interactions have been reported between tenofovir DF and abacavir, indinavir, lamivudine, nelfinavir, ribavirin or adefovir dipivoxil.[11] However, didanosine C_{max} and AUC values were increased by 28–64% and 44–60%, respectively, when didanosine 400mg enteric-coated capsules or buffered tablets, but not 250mg enteric-coated capsules, were coadministered with tenofovir DF.[15] This interaction may be of clinical significance, notwithstanding these agents do not form a recommended NRTI backbone for initial NNRTI- or PI-based regimens.

• Coadministration of tenofovir DF with ritonavir-boosted lopinavir or ritonavir-boosted saquinavir resulted in increased tenofovir and saquinavir levels, respectively, while coadministration of tenofovir DF with atazanavir with or without ritonavir boosting resulted in decreased atazanavir levels and increased tenofovir levels.[11,15] Co-administration of co-formulated efavirenz/emtricitabine/tenofovir DF with atazanavir is not recommended.[22]

• Emtricitabine and tenofovir have a low interaction potential with drugs metabolised by CYP enzymes,[14,15] although coadministration of emtricitabine, tenofovir DF or co-formulated emtricitabine/tenofovir DF with drugs that are eliminated

by active tubular secretion may result in increased serum concentrations of emtricitabine, tenofovir and/or the coadministered agent.[12,17] Similarly, coadministration of emtricitabine, tenofovir DF or co-formulated emtricitabine/tenofovir DF with drugs that decrease renal function (e.g. cidofovir, ganciclovir) may cause increased serum concentrations of the NRTIs.[14,17]

- Efavirenz induces CYP3A4 activity *in vivo* (resulting in induction of its own metabolism), but inhibits this isoenzyme (as well as the 2C9 and 2C19 isoenzymes) *in vitro*.[13,16] As such, coadministration of efavirenz with inducers of CYP3A4 activity (e.g. rifampicin) is expected to result in lowered plasma concentrations of efavirenz, while coadministration of efavirenz with drugs primarily metabolised by CYP3A4, 2C9 and 2C19 may result in altered plasma concentrations of the coadministered drug.[13,16] In particular, concurrent administration of efavirenz[16] (and hence also co-formulated efavirenz/emtricitabine/tenofovir DF[22]) with astemizole, cisapride, midazolam, triazolam or ergot derivatives is contraindicated, as competition for CYP3A4 by efavirenz could inhibit the metabolism of these drugs, creating the potential for serious and/or life-threatening adverse events.

- Mean steady-state AUC values for efavirenz 200–600mg administered once daily were unchanged during coadministration with indinavir, azithromycin, cetirizine, clarithromycin, rifabutin, ethinylestradiol, paroxetine and sertraline, reduced during coadministration with nelfinavir (↓12%), saquinavir (soft gelatinous capsules [SGC]; ↓12%), lopinavir (with ritonavir boosting; ↓16%) and rifampicin (↓26%), and increased during coadministration with fluconazole (↑16%), ritonavir (↑21%) and voriconazole (↑44%).[16]

- AUC values for cetirizine, lorazepam, paroxetine, fluconazole, ritonavir (after afternoon dose), azithromycin, zidovudine and lamivudine were unchanged during coadministration with efavirenz, whereas those for voriconazole, atazanavir (400mg once daily × 20 days), saquinavir SGC, methadone, indinavir (after morning, afternoon and evening doses), clarithromycin, sertraline, rifabutin and lopinavir (with ritonavir boosting) were reduced by 77%, 74%, 62%, 52%, 33–46%, 39%, 39%, 38% and 19%, respectively, and those for ritonavir (after morning dose), nelfinavir and ethinylestradiol were increased by 18%, 20% and 37%, respectively.[16] Concurrent administration of efavirenz[16] (and hence also co-formulated efavirenz/emtricitabine/tenofovir DF[22]) with voriconazole is contraindicated.

- Concomitant use of efavirenz[16] (or co-formulated efavirenz/emtricitabine/tenofovir DF[22]) and St John's wort-containing products is not recommended.

3. Therapeutic Efficacy

Efficacy trials with co-formulated efavirenz/emtricitabine/tenofovir DF have not been conducted. Accordingly, this section focuses on two supporting studies (Study 934 [published in full[19]] and COMET [Combination of Efavirenz and Truvada; reported in an abstract/poster[23]]) which evaluated efavirenz + emtricitabine + tenofovir DF (Study 934[19]) or efavirenz plus co-formulated emtricitabine/tenofovir DF (hereafter referred to as efavirenz + emtricitabine/tenofovir DF; COMET) in adults with HIV infection.

Additional randomised studies supporting the efficacy of efavirenz,[16,24,25] emtricitabine[10,14] and tenofovir DF[11,15] as individual agents in combination with other antiretroviral drugs have been presented and/or reviewed elsewhere, and are not considered here.

Study 934 was a 48-week, randomised, open-label, multicentre, noninferiority comparison of efavirenz + emtricitabine + tenofovir DF versus efavirenz + lamivudine/zidovudine.[19] A total of 517 antiretroviral-naive adults (men and women aged ≥18 years) with HIV infection (plasma HIV RNA level >10 000 copies/mL; no minimum CD4 cell count required) were randomised at 67 sites across Europe and the US; those in the efavirenz + emtricitabine + tenofovir DF arm received their study medications without regard to meals.

The primary endpoint in Study 934 was the proportion of patients without baseline resistance muta-

tions to efavirenz in whom the plasma HIV RNA level was <400 copies/mL after 48 weeks of therapy;[19] efavirenz + emtricitabine + tenofovir DF was considered to be noninferior to efavirenz + lamivudine/zidovudine if the lower limit of the 95% CI for the between-group difference (efavirenz + emtricitabine + tenofovir DF − efavirenz + lamivudine/zidovudine) in the proportion of patients with a plasma HIV RNA level <400 copies/mL was no lower than −13%. Similar noninferiority analyses were performed in respect of the secondary endpoints of viral suppression to <50 copies/mL and changes in the CD4+ cell count after 48 weeks.

The maintenance of sustained viral suppression in Study 934[19] was based on the FDA time to loss of virological response (TLOVR) algorithm,[26] which requires confirmation of response (two consecutive values) or no response (missing data or early study discontinuation counted as failure).

The COMET study, a 24-week noncomparative, multicentre, phase IV trial based in the US, assessed the effect of switching antiretroviral-experienced patients with HIV infection who were stable (i.e. virologically suppressed) on efavirenz + lamivudine/zidovudine to efavirenz plus co-formulated emtricitabine/tenofovir DF (hereafter referred to as efavirenz + emtricitabine/tenofovir DF). A total of 411 patients were enrolled, all of whom had received lamivudine/zidovudine for ≥8 weeks and had a viral load <400 copies/mL (prior to switching). Study endpoints included viral suppression to <400 and <50 copies/mL and changes in the CD4+ cell count.[23]

Treatment-Naive Patients

Five hundred and eleven of the 517 patients randomised in Study 934 received study medication, including two treatment-experienced patients in the efavirenz + emtricitabine + tenofovir DF arm who were subsequently excluded from all efficacy populations (but were included in the safety population; see section 4).[19]

Treated eligible patients (hereafter referred to as the intent-to treat [ITT] population) in the efavirenz + emtricitabine + tenofovir DF and efavirenz + lamivudine/zidovudine arms (n = 255 and 254, respectively) had a median age of 36 and 37 years, respectively, a median baseline plasma HIV RNA level of 5.0 and 5.0 $\log_{10}$ copies/mL, respectively, and a median baseline CD4+ cell count of 233 and 241 /mm^3, respectively. Eleven patients in each group had baseline resistance mutations to efavirenz; hence, the primary analysis populations consisted of 244 and 243 patients, respectively.[19]

- Figure 1 summarises the patient disposition after 48 weeks of therapy in Study 934. Using the FDA TLOVR algorithm, efavirenz + emtricitabine + tenofovir DF was noninferior and, furthermore, superior to efavirenz + lamivudine/zidovudine in respect of the primary endpoint of the proportion of patients with sustained viral suppression to <400 copies/mL after 48 weeks (84% vs 73%; 95% CI for the between-group difference 4, 19; p = 0.002) as well as the secondary endpoint of the proportion of patients with sustained viral suppression to <50 copies/mL after 48 weeks (80% vs 70%; 95% CI 2, 17; p = 0.02).[19]

- Similar results and conclusions regarding these virological endpoints emerged in analyses of the ITT population: viral suppression to <400 copies/mL (efavirenz + emtricitabine + tenofovir DF, 81% vs efavirenz + lamivudine/zidovudine, 70%; 95% CI for the between-group difference 3, 18; p = 0.005); and viral suppression to <50 copies/mL (77% vs 68%; 95% CI 1, 16; p = 0.03).[19]

- Likewise, efavirenz + emtricitabine + tenofovir DF satisfied the criteria for noninferiority to, and also demonstrated superiority over, efavirenz + lamivudine/zidovudine with regard to the additional secondary endpoint of the mean increase from baseline in CD4+ cell count (190 vs 158 /mm^3; 95% CI for the between-group difference 9, 55; p = 0.002).[19] The median increase from baseline in CD4+ cell percentage was also slightly, but significantly, higher in the efavirenz + emtricitabine + tenofovir DF arm than in the efavirenz + lamivudine/zidovudine arm (11% vs 10%; p = 0.02).

- Mean adherence to treatment (determined on the basis of pill counts) was slightly, but significantly, improved in the efavirenz + emtricitabine + te-

nofovir DF arm compared with the efavirenz + lamivudine/zidovudine arm (90% vs 87%; p = 0.04).[19]

Treatment-Experienced Patients

Preliminary results are available for 217 of the 411 treatment-experienced patients enrolled in the COMET Study who, at the time of this analysis, had either completed 24 weeks of therapy (n = 198) or discontinued the study prior to completing 24 weeks of therapy (n = 19).[23] These individuals had a median age of 42 years; most (86%) were men. They had received co-formulated lamivudine/zidovudine (or the individual components) for a median of 4 years; most (89%) had received co-formulated lamivudine/zidovudine for >1 year.

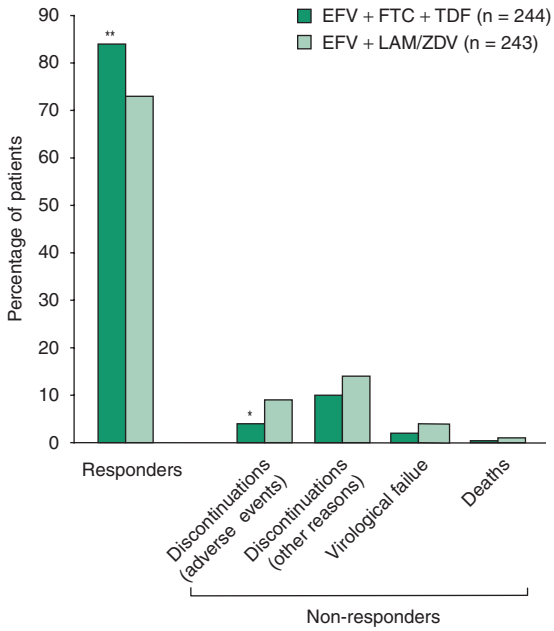

Fig. 1. Comparative virological efficacy of a once-daily regimen of efavirenz 600mg, emtricitabine 200mg and tenofovir disoproxil fumarate 300mg administered as individual agents (EFV + FTC + TDF) versus once-daily efavirenz 600mg plus twice daily co-formulated lamivudine/zidovudine 150mg/300mg (EFV + LAM/ZDV) in antiretroviral-naive adults with HIV infection. Responders (patients achieving and maintaining confirmed [two consecutive values] suppression of plasma HIV RNA load to <400 copies/mL after 48 weeks of treatment) versus nonresponders in a randomised, open-label, multicentre trial (Study 934[19]). The primary endpoint was the proportion of patients with viral suppression to <400 copies/mL after 48 weeks; results shown are for patients without baseline resistance mutations to EFV. Virological failure includes confirmed viral rebound and failure to achieve confirmed viral suppression to <400 copies/mL after 48 weeks. 'Other reasons' for discontinuation include noncompliance, loss to follow-up, consent withdrawal, pregnancy and unspecified events. * p = 0.02, ** p = 0.002 vs EFV + LAM/ZDV.

- Ninety-four percent of patients switched from efavirenz + lamivudine/zidovudine to efavirenz + emtricitabine/tenofovir DF maintained viral suppression to <400 copies/mL at week 24 (n = 189). Moreover, the proportion of patients with viral suppression to <50 copies/mL increased significantly from 59% before the switch to 76% 24 weeks after the switch (p < 0.001; n = 189).[23]

4. Tolerability

The following tolerability profile of co-formulated efavirenz/emtricitabine/tenofovir DF is based on adverse event data following administration of the co-formulated tablet[20] or concomitant administration of the components (e.g. efavirenz + emtricitabine + tenofovir DF in Study 934[19] and efavirenz + emtricitabine/tenofovir DF in COMET[23,27]). Additional information regarding the safety of the components as individual agents in combination with other antiretroviral drugs is derived from US prescribing information[14-17] and recent reviews.[10-12,24,28]

- A single dose of co-formulated efavirenz/emtricitabine/tenofovir DF was generally well tolerated in the only study involving the triple combination tablet, a bioequivalence study in healthy volunteers[20] (section 2). CNS adverse events were the most common treatment-emergent, drug-related adverse events; headache and dizziness affected 24% of volunteers receiving co-formulated efavirenz/emtricitabine/tenofovir DF versus 29% of those receiving efavirenz + emtricitabine + tenofovir DF. Most adverse events (in either treatment group) were mild, transient and consistent with the known tolerability profiles of the individual agents. However, two serious adverse events (both spontaneous abortions in the first trimester of pregnancy) were reported.[20]

- Sixty-three percent of efavirenz + emtricitabine + tenofovir DF recipients in Study 934 experienced

adverse events of grade 2–4 severity (modified Common Toxicity Criteria). Adverse events of grade 2–4 severity that occurred in ≥5% of patients treated with this regimen were dizziness, nausea, diarrhoea, fatigue, headache and rash (see figure 2).[19]

- Four percent of efavirenz + emtricitabine + tenofovir DF recipients in Study 934 discontinued therapy because of adverse events (see figure 1).[19] Whereas emtricitabine-associated skin discolouration (reported by seven patients receiving this NRTI) did not cause the individuals affected to cease their treatment, NNRTI-associated rash prompted the withdrawal of two patients. Tenofovir DF has previously been associated with renal impairment (including Fanconi's syndrome) in mostly high-risk individuals;[11] however, renal safety was similar in the two arms of Study 934 and no patient discontinued their study medication due to renal adverse events.[19]

- Fifty-six percent of efavirenz + emtricitabine + tenofovir DF recipients in Study 934 experienced laboratory abnormalities of grade 2–4 severity, including elevations of amylase (17%), triglycerides (13%) and creatinine phosphokinase (12%) [see figure 2].

- Efavirenz + emtricitabine + tenofovir DF was better tolerated than efavirenz + lamivudine/zidovudine in Study 934 in terms of the number of patients discontinuing their study medications due to adverse events (see figure 1). In particular, no efavirenz + emtricitabine + tenofovir DF recipient compared with 6% of efavirenz + lamivudine/zidovudine recipients withdrew from treatment because of anaemia ($p < 0.001$). The overall incidences of adverse events and laboratory abnormalities of grade 2–4 severity were similar in the two treatment groups.[19]

- Mean increases in fasting lipid parameters after 48 weeks of therapy theoretically favoured efavirenz + emtricitabine + tenofovir DF recipients over efavirenz + lamivudine/zidovudine recipients with regard to total (+0.54 vs +0.91 mmol/L; $p < 0.001$) and low-density lipoprotein (+0.34 vs +0.52 mmol/L; $p = 0.01$) cholesterol levels, whereas the opposite was true in respect of high-density lipoprotein cholesterol levels (+0.16 vs +0.23 mmol/L; p =

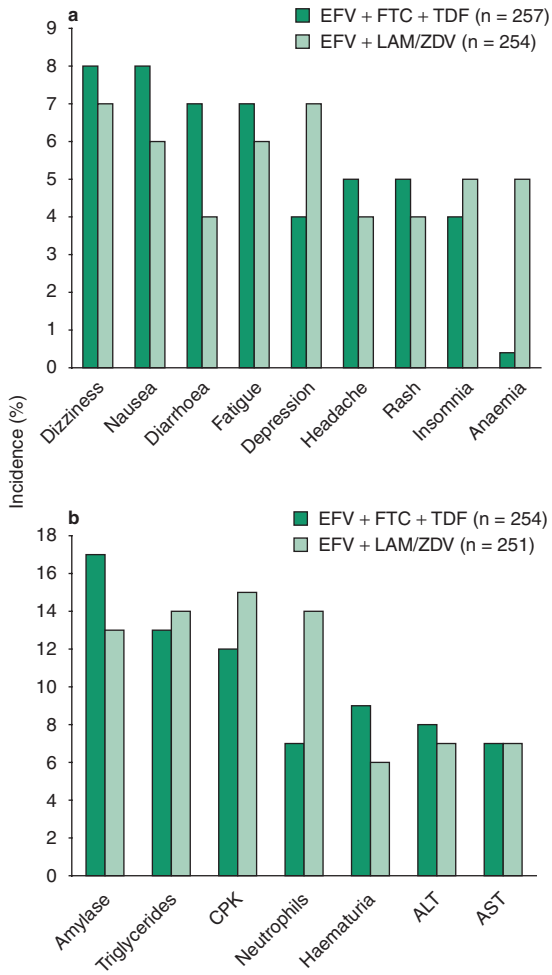

Fig. 2. Comparative tolerability profile of a once-daily regimen of efavirenz 600mg, emtricitabine 200mg and tenofovir disoproxil fumarate 300mg administered as individual agents (EFV + FTC + TDF) versus once-daily efavirenz 600mg plus twice-daily co-formulated lamivudine/zidovudine 150mg/300mg (EFV + LAM/ZDV) in antiretroviral-naive adults with HIV infection. **(a)** Adverse events and **(b)** laboratory abnormalities of grade 2–4 severity (modified Common Toxicity Criteria) occuring in ≥5% of patients in either the EFV + FTC + TDF or EFV + LAM/ZDV arm of a 48-week, randomised, open-label, multicentre trial (Study 934).[19] Laboratory abnormalities were defined as follows: amylase ≥132 U/L; triglycerides ≥400 mg/dL; creatinine phosphokinase (CPK) ≥499 (men) or ≥424 (women) U/L; neutrophils <1000 /mm^3; haematuria >10 red blood cells/high-power field; ALT ≥109 (men) or ≥86 (women) U/L; and AST ≥91 (men) or ≥86 (women) U/L.

0.004). Mean increases in fasting triglyceride levels were similar in the two treatment groups.[19]

- The mean increase in bodyweight in efavirenz + emtricitabine + tenofovir DF recipients was numerically higher than that in efavirenz + lamivudine/zidovudine recipients (2.8% vs 1.5%).[19] In addition, total limb fat was significantly higher in efavirenz + emtricitabine + tenofovir DF recipients than in efavirenz + lamivudine/zidovudine recipients (8.9kg [n = 51] vs 6.9kg [n = 49]; p = 0.03), based on a non-randomised subgroup of patients who underwent dual-energy x-ray absorptiometry at week 48; this difference appeared to persist through 96 weeks of therapy (preliminary analysis).[19]

- After 24 weeks of therapy, 191 antiretroviral-experienced, stable patients who switched from efavirenz + lamivudine/zidovudine to efavirenz + emtricitabine/tenofovir DF in the COMET study had a median increase in haemoglobin level of + 0.6 g/dL ($p < 0.001$ vs baseline, i.e before the switch).[23,27] Of note, the proportion of patients who reported that they were very satisfied with their treatment was greater at week 24 than at baseline (85% vs 58%; $p < 0.001$), based on a subgroup (n = 172) who completed a Symptoms and Treatment Satisfaction questionnaire.[23,27]

- Emtricitabine and tenofovir DF, as individual agents in combination with other antiretroviral drugs, are generally well tolerated in patients with HIV infection.[10-12] The most commonly reported treatment-emergent adverse events with three-drug regimens containing these NRTIs were headache, diarrhoea, nausea, skin rash and asthenia of generally mild to moderate intensity.[10,11] Compared with stavudine, emtricitabine, as a component of efavirenz-based triple therapy, was associated with fewer treatment-limiting adverse events;[10] tenofovir DF was associated with a more favourable serum lipid profile.[11] Moreover, antiretroviral regimens containing both efavirenz and emtricitabine (plus didanosine) continued to be well tolerated after 3–4 years of treatment.[10]

- In common with all NRTIs, however, prescribing information for emtricitabine[14] and tenofovir DF[15] (as well as co-formulated emtricitabine/tenofovir DF[17] and efavirenz/emtricitabine/tenofovir DF[22]) carries a black box warning concerning the risk of lactic acidosis and severe hepatomegaly with steatosis associated with nucleoside analogues.

- Decreases in bone mineral density (BMD) and increases in biochemical markers of bone metabolism have been observed with tenofovir DF, although the clinical significance of these changes with regard to long-term bone health and future fracture risk is unknown.[15] At week 144 in one study, a significant difference between tenofovir DF and stavudine (each administered in combination with lamivudine and efavirenz) was evident in the decrease from baseline in BMD at the lumbar spine (mean −2.2% vs −1.0%; p = 0.001), but not at the hip (2.8% vs 2.4%).[11]

- Efavirenz also appears to be generally well tolerated as an individual agent in combination with other antiretroviral drugs.[24] The most common (and notable) adverse events in patients receiving efavirenz-containing antiretroviral regimens are CNS disturbances (e.g. headache, dizziness, insomnia, fatigue, abnormal dreams, impaired concentration and restlessness) and skin rash. In clinical trials, CNS symptoms and rash were reported by 53% and 26% of patients receiving efavirenz, respectively; the incidences of these events in patients receiving control regimens were 25% and 17%, respectively.[22] Typically, these occurrences are of mild to moderate intensity and short-term (2–4 weeks) duration.[24,28]

- Rash associated with blistering, moist desquamation or ulceration occurred in 0.9% of patients treated with efavirenz-containing antiretroviral regimens in controlled trials (n = 1008);[15] discontinuation of co-formulated efavirenz/emtricitabine/tenofovir DF is advised in individuals who develop severe cutaneous toxicity.[22]

- Serious psychiatric adverse experiences (e.g. severe depression [2.4%], suicidal ideation [0.7%], nonfatal suicide attempts [0.5%], aggressive behaviour [0.4%], paranoid [0.4%] or manic [0.2%] reactions) were reported among 1008 patients receiving efavirenz-containing antiretroviral regimens for, on average, 2.1 years in controlled trials. The inci-

dences of these events in patients treated with non-efavirenz-containing (control) regimens for a mean of 1.5 years were 0.9%, 0.3%, 0%, 0.5% 0.3% and 0.3%, respectively.[16]

- Efavirenz (and hence also co-formulated efavirenz/emtricitabine/tenofovir DF) is not recommended for use during the first trimester of pregnancy or in women planning pregnancy (or not using effective contraception methods) because of potential teratogenicity.[2,3,16] Co-formulated efavirenz/emtricitabine/tenofovir DF should be used during pregnancy only if the potential benefit justifies the potential harm to the fetus.[22]

5. Dosage and Administration

Co-formulated efavirenz/emtricitabine/tenofovir DF is indicated for use alone as a complete regimen or in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults.[22] The recommended dose of efavirenz 600mg/emtricitabine 200mg/tenofovir DF 300mg in adults is one tablet once daily taken orally on an empty stomach. Dose administration at bedtime may improve the tolerability of nervous system symptoms.[22] Co-formulated efavirenz/emtricitabine/tenofovir DF should not be prescribed for patients requiring dosage adjustment such as those with moderate or severe renal impairment (creatinine clearance <50 mL/min).[22]

Local prescribing information should be consulted for information regarding warnings and precautions relating to the use of this product.

6. Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate: Current Status

In July 2006, the US FDA approved co-formulated efavirenz/emtricitabine/tenofovir DF, alone or in combination with other antiretroviral products, for the treatment of HIV-1 infection in adults. As the first formulation to combine three preferred/recommended antiretroviral agents in a single once-daily tablet, co-formulated efavirenz/emtricitabine/tenofovir DF represents a simplified treatment option for HIV, with the aim of improving adherence to, and hence the success of, treatment.

Disclosure

During the peer review process, the manufacturers of the agent under review were offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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