Original article

Pharmacokinetics of once-daily etravirine without and with once-daily darunavir/ritonavir in antiretroviral-naive HIV type-1-infected adults

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Background: A pharmacokinetic trial was conducted to evaluate the potential for once-daily etravirine in antiretroviral regimens without and with darunavir/ritonavir.
Methods: During this multicentre, open-label, Phase IIa trial, treatment-naive patients aged ≥18 years with HIV type-1 (HIV-1) received etravirine 400 mg once daily with tenofovir disoproxil fumarate/emtricitabine 300/200 mg once daily from days 1–14; on days 15–28, darunavir/ritonavir 800/100 mg once daily was added. On day 29, etravirine was discontinued and patients continued with the other medications to day 42. Serial blood sampling for etravirine pharmacokinetics was performed over 24 h on day 14 and 28; patients fasted for ≥10 h prior to these visits.
Results: Of 23 enrolled patients (male 87%, Caucasian 39%), pharmacokinetic profiles for etravirine were available for 21 and 20 patients on day 14 and 28, respectively. The plasma concentration–time profile and pharmacokinetics for etravirine were unchanged with or without darunavir/ritonavir. The mean maximum plasma concentration (C_{max}) was reached 4 h after administration and was 790 and 801 ng/ml on day 14 and 28, respectively; mean area under the plasma concentration–time curve (AUC) from before administration to 24 h after administration was 10,410 ng•h/ml on day 14 and 10,720 ng•h/ml on day 28. In a post-hoc analysis, etravirine C_{max} was higher, minimum plasma concentration was lower and AUC was similar when compared with etravirine 200 mg twice daily.
Conclusions: Addition of darunavir/ritonavir to etravirine, all dosed once daily, did not have a clinically significant effect on the pharmacokinetics of etravirine. Findings support further investigation of etravirine 400 mg once daily in HIV-1-infected patients. (Trial registration number NCT00534352.)

Introduction

Etravirine (formerly TMC125) is a potent non-nucleoside reverse transcriptase inhibitor (NNRTI) active against wild-type HIV type-1 (HIV-1) and NNRTI-resistant HIV-1 that has been shown *in vitro* to have a higher genetic barrier to the development of resistance compared with available first-generation NNRTIs [1]. Etravirine is approved at a dose of 200 mg twice daily for use in treatment-experienced adult patients. Regimens with higher numbers of daily drug doses are associated with lower adherence than regimens with lower numbers of daily drug doses [2]. Therefore, many available antiretrovirals are also being investigated for once-daily dosing in an attempt to simplify regimens and increase adherence. Early formulations of etravirine required a relatively high pill burden to achieve good bioavailability, so etravirine was evaluated twice daily. However, etravirine has a long half-life (approximately 41 h) and recent formulation improvements have increased the oral bioavailability of the drug, thereby reducing pill burden and potentially allowing for once-daily dosing [3,4]. The current etravirine formulation is recommended to be

administered with food in order to optimize bioavailability [5]. A study assessing the pharmacokinetics of etravirine 400 mg once daily versus 200 mg twice daily in healthy volunteers demonstrated similar exposure between the regimens, as evaluated by area under the plasma concentration–time curves (a curve over 12 h after each twice-daily dose administration [$AUC_{12\ h\ \times 2}$] versus a curve over 24 h from administration [$AUC_{24\ h}$]), with a 44% increase in maximum concentration (C_{max}) and a 25% decrease in minimum concentration (C_{min}) when etravirine was dosed once daily relative to twice daily [6].

Darunavir, an HIV protease inhibitor, combined with a low dose of ritonavir has been shown to be an effective therapeutic option for both treatment-naive (800/100 mg once daily) and treatment-experienced (600/100 mg twice daily) HIV-1-infected patients [7–9]. The coadministration of darunavir/ritonavir 600/100 mg twice daily and etravirine 200 mg twice daily was previously evaluated in healthy volunteers and resulted in a 37% decrease in the etravirine AUC from before administration to 12 h after administration [10]. This interaction was not judged to be clinically relevant and subsequently two Phase III, double-blind, randomized studies (DUET-1 and DUET-2) with coadministration of darunavir/ritonavir and etravirine were conducted in treatment-experienced HIV-1-infected patients. The combination was shown to have a good safety and efficacy profile when administered with an investigator selected optimized background regimen [11–13]. Moreover, in these trials, no apparent relationship between etravirine pharmacokinetics and efficacy or safety was observed [5,14].

In order to explore the potential for once-daily use of etravirine, we examined the pharmacokinetics and short-term safety and efficacy of etravirine 400 mg once daily with tenofovir disoproxil fumarate/emtricitabine, and also investigated this dosing regimen in combination with darunavir/ritonavir 800/100 mg once daily. This trial was conducted in antiretroviral-naive HIV-1-infected adult patients; treatment-experienced patients were excluded to minimize the need for other active agents and to avoid any potential induction or inhibitory effects of prior antiretroviral use that could confound data interpretation.

Methods

Study design

The primary objective of this multicentre, open-label, single-arm, Phase IIa trial was to determine the pharmacokinetic profile of etravirine 400 mg once daily without and with darunavir/ritonavir 800/100 mg once daily. Secondary objectives included assessment of the short-term safety and tolerability of this dosing regimen and evaluation of short-term changes in fasting lipid profiles, insulin and glucose during the treatment period. Following a 4 week screening period, patients received etravirine 400 mg once daily with tenofovir disoproxil fumarate/emtricitabine 300/200 mg once daily from days 1–14 (treatment A); on days 15–28, darunavir/ritonavir 800/100 mg once daily was added to the regimen (treatment B). On day 29, etravirine was discontinued and patients continued on tenofovir disoproxil fumarate/emtricitabine and darunavir/ritonavir to day 42 (treatment C). All doses were administered following a meal. Patients with adherence of <90% to darunavir, etravirine or ritonavir, using a 4 day recall assessment, on two separate clinic visits during the first 42 days were discontinued from the study. After completion of the 42-day study period, patients could choose to continue into an open-label extension phase of the trial consisting of treatment with darunavir/ritonavir 800/100 mg once daily and tenofovir disoproxil fumarate/emtricitabine 300/200 mg once daily for up to 48 weeks. Here we report only the results through to day 42, with a focus on pharmacokinetic analyses [15].

This study was conducted in line with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The research protocol received ethical approval from all study sites and written, informed consent was provided by all patients. This trial is registered at clinicaltrials.gov (NCT00534352).

Study population

Antiretroviral treatment-naive men and women aged ≥18 years with documented HIV-1 infection and a life expectancy ≥6 months were eligible for the study. Patients were required to have no antiretroviral resistance based on screening or historical resistance assays. Exceptions were made for patients with isolated mutations that did not affect susceptibility to any of the study drugs. Susceptibility to etravirine was defined as presence of fewer than three etravirine resistance-associated mutations (list of 13; virco® TYPE HIV-1 version 4.1.01, Virco Lab Inc. USA, Titusville, NJ, USA) [16]. Predicted fold-change values for etravirine were not available at the time of screening.

Key exclusion criteria included previous or current use of antiretrovirals, including non-antiretrovirals with known anti-HIV activity or those that could potentiate antiretroviral activity (for example, hydroxyurea); use of concomitant medications that might interact with darunavir, emtricitabine, etravirine, ritonavir or tenofovir disoproxil fumarate; the presence of any currently active AIDS-defining illness, chronic hepatitis B and/or C coinfection or acute viral hepatitis; diabetes mellitus or hyperlipidaemia requiring lipid-lowering therapy; and any grade 3 or 4 laboratory abnormality, as defined by the Division of AIDS grading tables. Additionally, patients were excluded if they had any condition or

clinically significant active disease that, in the opinion of the investigator, could compromise the patient's safety, protocol adherence or the outcome of the study. Women were excluded if pregnant or breastfeeding, or were of childbearing potential without the use of effective non-hormonal birth control methods.

Assessments

Serial blood sampling for pharmacokinetics was performed over 24 h on day 14 for etravirine and day 28 for etravirine, darunavir and ritonavir. Patients fasted for at least 10 h prior to clinic visits on days 14 and 28. Blood samples were taken 10 min before drug administration and 1, 2, 3, 4, 6, 9, 12 and 24 h after administration. Plasma concentrations of etravirine, darunavir and ritonavir were determined using liquid chromatography with tandem mass spectrometry methods that had been previously validated [10]; the lower limits of quantification for etravirine, darunavir and ritonavir were 2.00 ng/ml, 5.00 ng/ml and 5.00 ng/ml, respectively.

Adverse events (AEs) were assessed and recorded throughout the trial only in the phase where it first emerged and not in subsequent phases. On days 1, 8, 14, 22, 28 and 42, a physical examination was performed, vital signs recorded and blood samples collected for laboratory safety assessments (biochemistry and haematology) and efficacy evaluations. Plasma HIV-1 RNA levels were determined using Roche AMPLICOR HIV-1 MONITOR® Test (v1.5; Roche Molecular Systems Inc, Branchburg, NJ, USA) and immunological changes were determined by absolute changes in $CD4^+$ T-cell count. On days 1, 14, 28 and 42, 10-h fasted blood samples were collected for assessment of a lipid panel (triglycerides, total cholesterol, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol), glucose and insulin. Discontinuations from the trial were recorded and final evaluations conducted unless the patient withdrew consent.

Statistical analyses

Results from previous studies showed that the intrasubject variability on the $\log_{10}$-transformed C_{max} and $AUC_{12\ h}$ from administration of etravirine was ≤40% [14]. Therefore, it was estimated that with complete data from 20 patients, the 90% confidence interval (CI) of the true ratio of the means for the above parameters would be contained within 81–124% of the observed ratio of the means.

All safety analyses were performed on the intent-to-treat (ITT) population, which included all patients who received at least one dose of study medication, and all efficacy analyses were performed on the ITT-observed population. All pharmacokinetic analyses were performed on the on-protocol population, which included all patients from the ITT population with post-baseline pharmacokinetics measurements and no major pharmacokinetic-related protocol deviations during the trial. Baseline demographics, safety assessments and pharmacokinetic parameters for darunavir, ritonavir and etravirine are presented using descriptive statistics. Pharmacokinetic parameters were determined using a non-compartmental model with extravascular input. The following parameters were calculated: time to maximum plasma concentration, C_{max}, pre-dose plasma concentration, C_{min} and AUC_{24h}. Pharmacokinetic and statistical analyses were performed by Kinesis Pharma B.V. (Breda, the Netherlands) using a validated computer program WinNonlin® Professional (version 4.1; Pharsight Corporation, Mountain View, CA, USA). Statistical analysis was performed comparing treatment A versus treatment B. The primary pharmacokinetic parameters were AUC_{24h}, C_{min} and C_{max} on the logarithmic scale. The least-squares means (LSM) of the primary parameters for the test and the reference treatments were estimated with a linear mixed-effects model, controlling for treatment as fixed effects and subject as a random effect, and included all available data. A 90% CI was constructed around the difference between the LSM of test and reference. Both the difference between the LSM and the 90% CIs were retransformed to the original scale.

Results

Patient characteristics

Of the 23 patients that were enrolled from four sites across the USA, 20 (87.0%) completed day 42 of the study (Table 1); 2 patients were discontinued by the investigator because of non-adherence with study medication (treatment A, n=1; treatment C, n=1) and 1 patient was lost to follow up (treatment A). The majority of patients were male (87%) and had a baseline viral load (VL) <100,000 copies/ml (87%). The study population was racially diverse (61% non-Caucasian), with a median age of 35 years (range 20–77 years). Eight patients with evidence of antiretroviral resistance on current or past resistance assays were granted exemption to enter the study because they did not have evidence of resistance to any of the study drugs. According to mutation count available at the time of screening and the current lower clinical cutoff for etravirine of 3.2 (virco® TYPE HIV-1 version 4.3.00), all 23 patients were susceptible to etravirine at baseline.

Pharmacokinetics

Full pharmacokinetic profiles for etravirine were available for 21 patients on day 14 and profiles for etravirine, darunavir and ritonavir were available for 20 patients on day 28.

Table 1. Patient demographics and baseline characteristics

Characteristic	Value
Patients, *n*	23
Median age, years (range)	35 (20–77)
Male, *n* (%)	20 (87.0)
Median BMI, kg/m^2 (range)	25.9 (17.0–38.4)
Race/ethnicity	
Black, *n* (%)	9 (39.1)
Caucasian, *n* (%)	9 (39.1)
Hispanic, *n* (%)	5 (21.7)
Median viral load, $\log_{10}$ copies/ml (range)	4.3 (2.8–5.9)
Baseline viral load category	
Viral load <100,000 HIV RNA copies/ml, *n* (%)	20 (87.0)
Viral load ≥100,000 HIV RNA copies/ml, *n* (%)	3 (13.0)
Median CD4$^+$ T-cell count, cells/mm^3 (range)	403 (144–895)
Baseline CD4$^+$ T-cell count category	
CD4$^+$ T-cell count <200 cells/mm^3, *n* (%)	3 (13.0)
CD4$^+$ T-cell count ≥200 cells/mm^3, *n* (%)	20 (87.0)
Etravirine fold change[a] ≤3.2, *n* (%)	23 (100)
Darunavir fold change[a] ≤10, *n* (%)	23 (100)
Patients with predicted reduced response[b]	
Nelfinavir, *n* (%)	4 (17.4)
Zidovudine, *n* (%)	2 (8.7)
Lamivudine, *n* (%)	1 (4.3)
Didanosine, *n* (%)	1 (4.3)
Tipranavir/ritonavir, *n* (%)	1 (4.3)
Number of reverse transcriptase mutations	
Median IAS-USA NRTI RAMs (range)[c]	0 (0–0)
Median IAS-USA NNRTI RAMs (range)[c]	0 (0–1)
Median etravirine RAMs 2007 (range)[d]	0 (0–1)
Median etravirine RAMs 2008 (range)[e]	0 (0–1)
Number of protease mutations	
Median IAS-USA primary PI mutations (range)[c]	0 (0–0)
Median IAS-USA PI RAMs (range)[c]	3 (0–7)
Median darunavir RAMs 2007 (range)[f]	0 (0–0)
Baseline lipid and glucose	
Median glucose, mg/dl (range)	91.0 (75.0–107.0)
Median HDL, mg/dl (range)	41.0 (30.0–60.0)
Median insulin, µU/ml (range)	5.00 (1.90–23.00)
Median LDL, mg/dl (range)	92.0 (59.0–139.0)
Median TC/HDL ratio (range)	3.67 (2.20–4.95)
Median TC, mg/dl (range)	145.0 (110.0–222.0)
Median triglycerides, mg/dl (range)	70.0 (35.0– 249.0)

[a]Represent lower cutoffs of predicted fold change in protein binding adjusted 50% effective concentration in cell-based assays according to reanalysis with virco® TYPE HIV-1 version 4.3.00 (Virco Lab Inc. USA, Titusville, NJ, USA). [b]virco® TYPE HIV-1 version 4.2.01. Refer to [c]Johnson *et al.* 2007 [20], [d]Vingerhoets *et al.* 2007 [16], [e]Vingerhoets *et al.* 2008 [21] and [f]De Meyer *et al.* 2008 [22]. BMI, body mass index; HDL, high-density lipoprotein; IAS, International AIDS Society; LDL, low-density lipoprotein; NRTI, nucleoside reverse transcriptase inhibitor; RAM, resistance-associated mutation; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TC, total cholesterol.

Etravirine

The plasma concentration–time profile of etravirine (Figure 1A) and pharmacokinetic parameters (Table 2) were unchanged with coadministration of darunavir/ritonavir 800/100 mg once daily. On both day 14 and 28, the mean C_{max} was reached 4 h after administration. The mean pre-dose plasma concentration was comparable to that observed 24 h after administration, which suggests steady-state conditions (Figure 1A). Etravirine exposure was well above the threshold level for the average protein binding adjusted 50% effective concentration (EC_{50}) in cell-based assays for wild-type virus of 4 ng/ml. Mean C_{min} for etravirine dosed once daily was >50-fold higher than the protein binding adjusted EC_{50} for wild-type HIV (4 ng/ml), without (233 ng/ml, range 58–480 ng/ml) and with (236 ng/ml, range 56–738 ng/ml) coadministration of darunavir/ritonavir once daily. Additionally, each patient had a C_{min} for etravirine >10-fold higher than the protein binding adjusted EC_{50} for wild-type HIV.

Intersubject variability (percentage coefficient of variation) in etravirine plasma concentrations on days 14 and 28 was 36% and 41% for C_{max}, respectively, and 56% and 71% for C_{min}, respectively. The individual plasma concentration–time profiles showed some small and inconsistent differences between the profiles taken on days 14 and 28, which resulted in similar mean plasma concentration–time profiles.

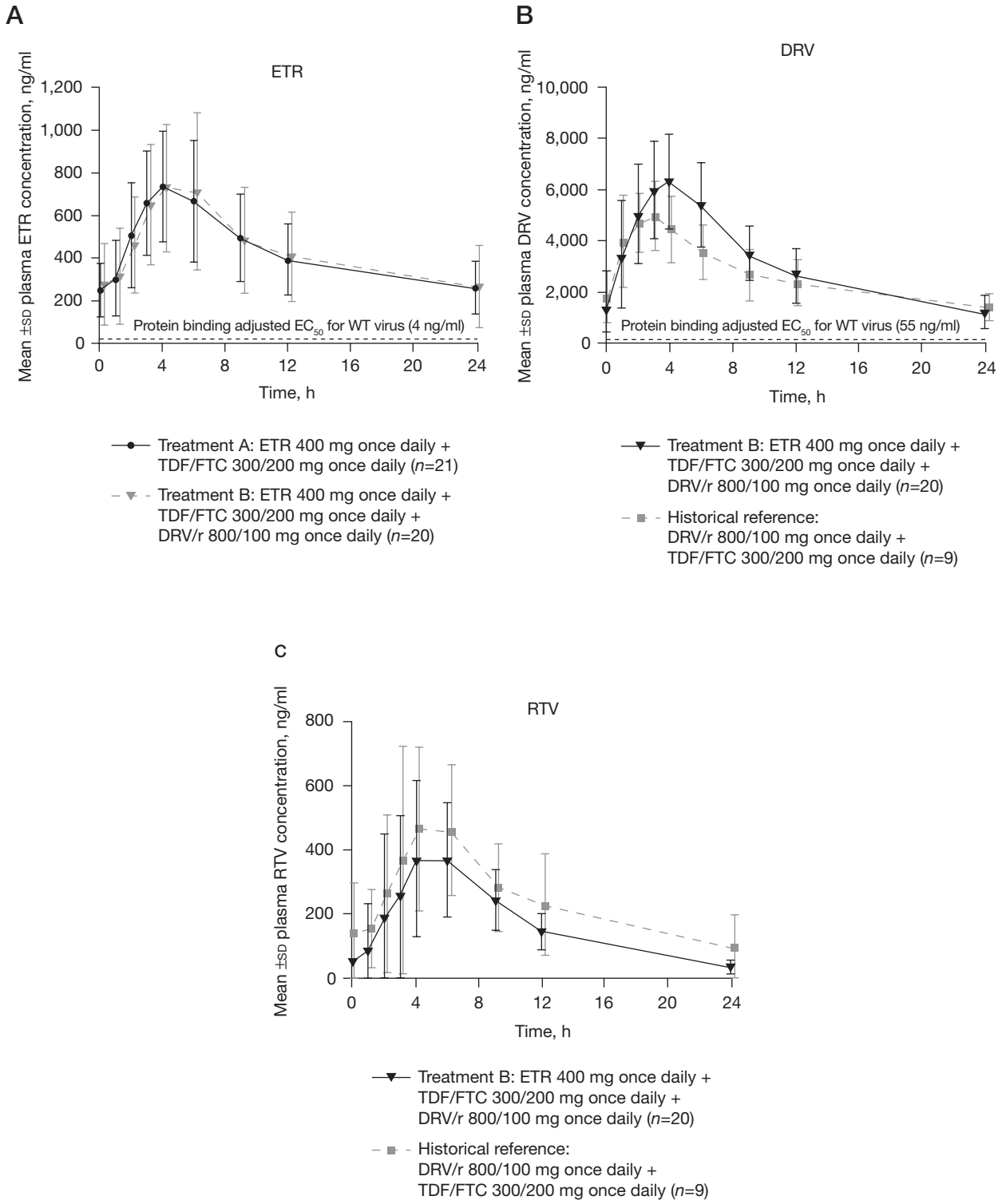
A post-hoc analysis was performed to compare the pharmacokinetics of etravirine 400 mg once daily at day 14 in the current study with the pharmacokinetics of etravirine 200 mg twice daily at week 4 in a substudy of the DUET trials [17]. In general, etravirine C_{max} was higher, C_{min} was lower and AUC was similar when comparing once-daily dosing in the current study with twice-daily dosing in the historical control (DUET pharmacokinetic substudy; Table 3).

Darunavir/ritonavir

The mean (range) pre-dose plasma concentration for darunavir was 1,335 (68–4,180) ng/ml. The median time to maximum plasma concentration for darunavir was approximately 4 h after administration (Table 2). Plasma concentration–time profiles for darunavir illustrate that darunavir exposures were above the threshold level for the average protein binding adjusted EC_{50} for wild-type virus of 55 ng/ml. Mean C_{min} for darunavir (1,049 ng/ml, range 67.5–2,330 ng/ml) was approximately 19-fold higher than the protein binding adjusted EC_{50} for wild-type HIV.

The mean (range) pre-dose plasma concentration for ritonavir was 53 ng/ml (8–327). The median time to maximum plasma concentration for ritonavir was approximately 6 h after administration (Table 2). LSM (90% CI) data for darunavir and ritonavir parameters

Figure 1. Plasma concentration–time profiles



(A) Etravirine (ETR) 400 mg once daily with or without darunavir/ritonavir (DRV/r) 800/100 mg once daily. **(B)** Darunavir (DRV) 800 mg once daily (as part of a DRV/r 800/100 mg once-daily regimen) with or without ETR 400 mg once daily compared with historical controls (ARTEMIS week 4 pharmacokinetic substudy [*n*=9]; TNK, unpublished observations) [8]. **(C)** Ritonavir (RTV) 100 mg once daily (as part of a DRV/r 800/100 mg once-daily regimen) with or without ETR 400 mg once daily compared with historical controls (ARTEMIS week 4 pharmacokinetic substudy [*n*=9]; TNK, unpublished observations) [8]. FTC, emtricitabine; EC_{50}, 50% effective concentration in cell-based assays; TDF, tenofovir disoproxil fumarate; WT, wild type.

Table 2. Pharmacokinetics of etravirine, darunavir and ritonavir

Parameter	Etravirine			Darunavir		Ritonavir	
	Day 14 (reference; *n*=21)	Day 28 (test; *n*=20)	LSM ratio[a] (90% CI)	Day 28 (*n*=20)	LSM ratio[b] (90% CI)	Day 28 (*n*=20)	LSM ratio[b] (90% CI)
Mean C_{max}, ng/ml (SD)	790 (287)	801 (327)	1.03 (0.93–1.13)	7,008 (1,514)	1.28 (1.09–1.51)	465 (231)	0.76 (0.52–1.10)
Mean C_{min}, ng/ml (SD)	233 (130)	236 (168)	0.95 (0.83–1.10)	1,049 (616)	0.75 (0.45–1.25)	27 (21)	0.36 (0.21–0.59)
Median t_{max}, h (range)	4.00 (1.97–6.05)	4.03 (2.97–9.02)	–	3.99 (1.97–6.08)	–	5.99 (1.97–9.12)	–
Mean AUC_{24h}, ng•h/ml (SD)	10,410 (4,186)	10,720 (5,459)	0.99 (0.89–1.10)	76,130 (22,080)[c]	1.18 (0.96–1.47)	4,128 (1,854)[c]	0.72 (0.52–0.99)

[a]Test/reference. [b]Day 28/historic control (ARTEMIS week 4 pharmacokinetic substudy; TNK, unpublished observations) [8]. [c]*n*=19. AUC_{24h}, area under the plasma concentration–time curve from pre-dose to 24 h post-dose; CI, confidence interval; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; LSM, least-squares mean; $t_{max,}$ time to maximum plasma concentration.

Table 3. Pharmacokinetics of etravirine in HIV-infected patients following once- and twice-daily dosing; current study versus historical control

Parameter	Current study[a] (*n*=21)	DUET 1 and 2[b] (*n*=25)
Median C_{min}, ng/ml (range)	197 (58–480)	195 (109–3,900)
Median C_{max}, ng/ml (range)	765 (254–1,410)	525 (285–4,980)
Median t_{max}, h (range)	4 (2–6)	4 (0–6)
Median AUC_{12h}, ng•h/ml (range)	–	4,307 (2,284–53,870)
Median AUC_{24h}, ng•h/ml (range)	9,778 (3,364–18,650)	–

[a]Etravirine 400 mg once daily, treatment-naive patients at day 14. [b]Etravirine 200 mg twice daily, treatment-experienced patients at week 4. AUC_{12h}, area under the plasma concentration–time curve from pre-dose to 12 h post-dose; AUC_{24h}, area under the plasma concentration–time curve from pre-dose to 24 h post-dose; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; t_{max}, time to maximum plasma concentration.

from this trial compared with historical controls (TNK, unpublished observations) [8] are presented in Table 2.

In a post-hoc analysis, C_{max} and $AUC_{24\,h}$ were slightly higher for darunavir and C_{min}, C_{max} and AUC_{24h} were slightly lower for ritonavir than those observed in historical controls consisting of nine patients in a pharmacokinetic substudy at week 4 of the ARTEMIS (AntiRetroviral Therapy with TMC114 ExaMined In Naive Subjects) trial, in which darunavir/ritonavir (800/100 mg) was administered once daily with a fixed dose background regimen of tenofovir disoproxil fumarate 300 mg once daily and emtricitibine 200 mg once daily (Figure 1B and C; TNK, unpublished observations) [8]. The LSM ratios for C_{min}, C_{max} and AUC_{24h} for historical controls versus results obtained in the current study were 0.75, 1.28 and 1.18, respectively, for darunavir and 0.36, 0.76 and 0.72, respectively, for ritonavir.

Antiviral activity

Over the course of the study, the median decline in VL was 1.7 $\log_{10}$ copies/ml at day 14 (*n*=21), 1.8 $\log_{10}$ copies/ml at day 28 (*n*=20) and 1.9 $\log_{10}$ copies/ml at day 42 (*n*=20). Seventeen patients (85%) had achieved VL <400 copies/ml at day 42, with seven of these (35%) achieving a virological response of <50 copies/ml. The median increase in $CD4^+$ T-cell count from baseline was 56 cells/mm^3 at day 42 (*n*=19).

Safety

Regardless of causality, which was determined by the investigator, AEs were reported in 14 patients (60.9%) during treatment A, 10 (47.6%) during treatment B and 4 (19.0%) during treatment C; all AEs were grade 1 or 2 in severity (Table 4). No grade 3 or 4 AEs, serious AEs or deaths were reported and no AE led to discontinuation. The most common AEs were nausea, headache and pruritus (Table 4). Treatment-emergent AEs considered at least possibly related to etravirine were reported for seven patients during each of treatment periods A and B. The most common were nausea (*n*=4; 17.4%), headache (*n*=3; 13.0%), rash (*n*=2; 8.7%) and flatulence (*n*=2; 8.7%). Treatment-emergent AEs considered at least possibly related to darunavir were reported for nine patients (42.9%) during treatment B; none were reported during treatment C. The most common AEs at least possibly related to darunavir were nausea (*n*=3, 13.0%) and rash (*n*=2, 8.7%). No lipid-, glucose metabolism-, liver- or cardiac-related AEs were reported during this

Table 4. Summary of adverse events and laboratory abnormalities

Parameter	Treatment A[a]	Treatment B[b]	Treatment C[c]
At least 1 AE	14 (60.9)	10 (47.6)	4 (19.0)
Serious AEs	0	0	0
Grade 3 or 4 clinical AEs	0	0	0
AEs leading to discontinuation	0	0	0
AEs reported in >1 patient in any treatment phase[d]			
Nausea	2 (8.7)	3 (14.3)	0
Headache	2 (8.7)	1 (4.8)	0
Pruritus	2 (8.7)	0	0
Infections and infestations	3 (13.0)	3 (14.3)	2 (9.5)
Rash/maculo-papular rash	1 (4.3)	2 (9.5)	0
Laboratory parameters[e]			
General biochemistry			
Hypoalbuminaemia	0	1 (4.8)	0
Hypokalaemia	2 (9.5)	1 (4.8)	0
Hyponatraemia	4 (19.0)	0	2 (10.0)
Lipids and glucose			
Hyperglycaemia	2 (9.5)	2 (9.5)	1 (5.0)
Hypoglycaemia	0	3 (14.3)	0
LDL direct	0	0	2 (10.0)
Total cholesterol	0	0	2 (10.0)
Liver function			
ALT	0	0	1 (5.0)
AST	1 (4.8)	0	1 (5.0)
Hyperbilirubinaemia	0	1 (4.8)	0
Hematology			
Platelet count	1 (4.8)	0	0
WBC count	1 (4.8)	0	0
Neutrophils	2 (9.5)	1 (4.8)	0
Change from baseline to end of respective treatment period[f] in lipid/glucose parameters			
Median glucose, mg/dl (range)	-2.0 (-36.0–42.0)	-2.0 (-31.0–12.0)	-1.5 (-22.0–43.0)
Median HDL, mg/dl (range)	0.0 (-12.0–17.0)	-2.0 (-26.0–14.0)	-1.0 (-30.0–8.0)
Median insulin, µU/ml (range)	-0.79 (-13.30–11.30)	0.00 (-16.00–20.00)	0.00 (-10.00–32.21)
Median LDL, mg/dl (range)	-8.0 (-43.0–29.0)	-6.0 (-36.0–32.0)	1.5 (-39.0–49.0)
Median TC/HDL ratio (range)	-0.05 (-1.00–0.72)	0.10 (-0.58–4.82)	0.36 (-0.38–7.65)
Median TC, mg/dl (range)	-3.0 (-45.0–44.0)	1.0 (-51.0–47.0)	11.0 (-64.0–58.0)
Median triglycerides, mg/dl (range)	1.0 (-124.0–103.0)	24.0 (-80.0–104.0)	32.5 (-88.0–166.0)

Results displayed as *n* (%) unless otherwise stated. [a]Etravirine + tenofovir disoproxil fumarate/emtricitabine (*n*=23 for adverse advents, *n*=21 for laboratory parameters and *n*=21 for lipid/glucose parameters). [b]Etravirine + tenofovir disoproxil fumarate/emtricitabine + darunavir/ritonavir (*n*=21 for adverse advents, *n*=21 for laboratory parameters and *n*=21 for lipid/glucose parameters). [c]Tenofovir disoproxil fumarate/emtricitabine + darunavir/ritonavir (*n*=21 for adverse advents, *n*=20 for laboratory parameters and *n*=20 for lipid/glucose parameters). [d]Regardless of severity and causality. [e]All events grade 1 or 2, except for one case of grade 3 decreased neutrophils during treatment A. [f]Treatment A, day 14; treatment B, day 28; and treatment C, day 42. AE, adverse event; ALT, alanine transaminase; AST, aspartate aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; WBC, white blood cell.

trial. No consistent or clinically relevant changes over time in vital signs were observed during the trial.

Laboratory assessments

No laboratory abnormalities were considered clinically relevant; thus none were reported as AEs during the trial. The most common treatment-emergent graded laboratory abnormalities were hyponatraemia and hypoglycaemia (Table 4), all of which were grade 1 or 2 in severity. All cases of hyponatraemia were grade 1, defined as serum sodium levels of 130–135 mmol/l (normal adult range 136–145 mmol/l). All other treatment-emergent graded laboratory abnormalities were observed in two or fewer patients per treatment phase. Low-density lipoprotein and total cholesterol abnormalities were small and only reported during treatment C (Table 4). Only one grade 3 event was reported: transient grade 3 neutropenia occurred during the initial

14-day treatment period (treatment A) with etravirine and tenofovir disoproxil fumarate/emtricitabine. No treatment-emergent grade 4 laboratory abnormalities were reported. The most common treatment-emergent, non-graded laboratory abnormalities were high-density lipoprotein below the normal range and insulin above the normal range (ED *et al.*, data not shown).

Lipids and glucose

At the end of each treatment period, changes from baseline in lipid and glucose parameters were small and not considered clinically relevant (Table 4).

Discussion

In this study of HIV-infected patients, the addition of darunavir/ritonavir to etravirine, all dosed once daily, did not have a clinically significant impact on the pharmacokinetics of etravirine. Previous assessments in HIV-negative subjects have suggested decreases in the mean ratio of etravirine pharmacokinetic parameters (C_{max} 0.68, C_{min} 0.51, AUC 0.63) when etravirine 200 mg twice daily was coadministered with darunavir/ritonavir 600/100 mg twice daily at steady state [10]. Etravirine had no effect on darunavir pharmacokinetics [10]. Differences in results from previous studies and those presented here might relate to potential disparities in the study populations and doses being studied. In particular, the increased dose of ritonavir in the previous study – 200 mg total over 24 h, compared with the current regimen of ritonavir 100 mg total over 24 h – may account for some of the observed differences in interactions. Ritonavir has been shown to induce various drug-metabolizing enzymes, including uridine diphosphate-glucuronosyltransferase, CYP2C9 and CYP2C19 [18], that are partly responsible for etravirine metabolism. The lower dose of ritonavir in this study may have led to less induction of these enzymes, resulting in less of an interaction compared with previous studies.

In general, and as expected when comparing once-daily etravirine in treatment-naive patients in combination with tenofovir disoproxil fumarate/emtricitabine with twice-daily etravirine in treatment-experienced patients in combination with darunavir/ritonavir in DUET, C_{max} was higher, C_{min} was lower and AUC was similar for etravirine once daily [17]. Mean C_{min} for once-daily etravirine was 58–59-fold higher than the protein binding adjusted EC_{50} for wild-type HIV without and with coadministration of once-daily darunavir/ritonavir. In the DUET studies, no relationship between etravirine pharmacokinetics and efficacy or safety was observed [14]. While acknowledging the limitations of cross-study comparisons, data from the DUET studies and the current study suggest similar pharmacokinetic exposure for once- and twice-daily etravirine. Therefore, a once-daily etravirine regimen might be a viable treatment option for antiretroviral-naive patients. However, larger studies are needed to confirm the efficacy and safety of etravirine in this population.

Darunavir C_{max} and $AUC_{24\ h}$ were slightly higher and C_{min} was slightly lower in the present trial when compared with the limited substudy data from the ARTEMIS trial in treatment-naive patients (TNK, unpublished observations) [8]. However, in both trials, C_{min} was well above protein binding adjusted EC_{50} for wild-type virus. For ritonavir, C_{min}, C_{max} and $AUC_{24\ h}$ were all lower compared with data from the ARTEMIS trial (TNK, unpublished observations) [8]. The alternative dosing schedule of etravirine may have affected the pharmacokinetic parameters of darunavir and/or ritonavir. Although exposure ($AUC_{12\ h\ x2}$ versus AUC_{24h}) is similar between etravirine 200 mg twice daily and 400 mg once daily, C_{max} is approximately 44% higher when dosed once daily [6]. In this study, higher levels of etravirine at the intestinal level might have contributed to greater CYP3A inhibition in the case of darunavir and CYP2C9 and/or CYP2C19 induction in the case of ritonavir, leading to the slightly higher darunavir exposures and lower ritonavir exposures. The current study was not designed to assess the pharmacokinetics of darunavir or ritonavir because these parameters had been studied previously and no relevant effect of etravirine on darunavir or ritonavir pharmacokinetics has previously been demonstrated [10]. The small variability in pharmacokinetic parameters may also be related to the small sample size in each study; however, as previously reported in treatment-experienced patients [19], these differences are not expected to result in clinically relevant changes in safety or efficacy outcomes for darunavir/ritonavir, or to require dose adjustments during coadministration.

Once-daily etravirine was associated with good short-term safety and tolerability in the current trial. No deaths, serious AEs or AEs leading to treatment discontinuation were reported during the main treatment phase of this trial and all AEs were mild to moderate in severity. No consistent or clinically relevant changes over time in laboratory parameters, including lipid and glucose assessments, or vital signs were observed. Efficacy data for the current trial are limited by the lack of a comparator arm; however, changes from baseline in VL and $CD4^+$ T-cell counts by day 42 are favourable and warrant further investigation in larger trials.

Conclusion

This clinical trial demonstrates that the pharmacokinetic parameters of etravirine are not significantly affected by the addition of darunavir/ritonavir and tenofovir disoproxil fumarate/emtricitabine in a once-daily treatment regimen. Furthermore, the study shows that these antiretroviral combinations are generally

safe and well tolerated when administered once daily to antiretroviral-naive HIV-1-infected patients. These findings, combined with the short-term efficacy data, support further clinical investigation of etravirine 400 mg once daily in HIV-1-infected patients.

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Results from this trial have previously been presented at the *Ninth International Congress on Drug Therapy in HIV Infection*, 9–13 November 2008, Glasgow, UK: Lalezari J, DeJesus E, Osiyemi O, *et al*. Pharmacokinetics (PK) of once-daily etravirine (ETR) without and with once-daily darunavir/ritonavir (DRV/r) in antiretroviral-naive HIV-1 infected adults.

Disclosure statement

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