

Etravirine combined with antiretrovirals other than darunavir/ritonavir for HIV-1-infected, treatment-experienced adults: Week 48 results of a phase IV trial

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Abstract

Objective: VIOLIN (TMC125IFD3002; NCT01422330) evaluated the safety, tolerability, and pharmacokinetics of etravirine with antiretrovirals other than darunavir/ritonavir in HIV-1-infected patients.

Methods: In a 48-week, phase IV, single-arm, multicenter study, patients on prior antiretroviral therapy (≥ 8 weeks) who needed to change regimen for virologic failure (viral load ≥ 500 copies/mL) or simplification/adverse events (viral load < 50 copies/mL) received etravirine 200 mg bid with ≥ 1 other active antiretroviral, excluding darunavir/ritonavir or only nucleoside/tide reverse transcriptase inhibitors.

Results: Of 211 treated patients, 73% ($n = 155$) had baseline viral load ≥ 50 copies/mL and 27% ($n = 56$) had baseline viral load < 50 copies/mL. Protease inhibitors were the most common background antiretrovirals (83%). Diarrhea was the most frequent adverse event (17%). Serious adverse events (no rash) occurred in 5% of patients; none were etravirine related. Overall, median etravirine AUC_{12h} was 5390 ng h/mL and C_{0h} was 353 ng/mL ($N = 199$). Week 48 virologic response rates (viral load < 50 copies/mL; Food and Drug Administration Snapshot algorithm) were 48% (74/155) (baseline viral load ≥ 50 copies/mL) and 75% (42/56) (baseline viral load < 50 copies/mL). Virologic failure rates were 42% and 13%, respectively. The most frequently emerging etravirine resistance-associated mutations in virologic failures were Y181C, E138A, and M230L. Virologic response rates for patients with baseline viral load ≥ 50 copies/mL were 38% (30/79) (non-adherent) versus 64% (44/69) (adherent subset).

Conclusion: Etravirine 200 mg bid in combination with antiretrovirals other than darunavir/ritonavir was well tolerated in the studied treatment-experienced HIV-1-infected population. The overall etravirine safety and tolerability profile and pharmacokinetics (specifically in those patients who were adherent) were similar to those previously observed for etravirine in HIV-1-infected adults. The relatively high level of non-adherence, also observed in the pharmacokinetic assessments, negatively impacted virologic response, especially in patients with ≥ 50 copies/mL at baseline.

Keywords

Etravirine, safety, efficacy, virology, pharmacokinetics

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Introduction

Management of HIV-1-infected patients with prior antiretroviral experience requires a range of regimen options across different therapeutic classes, to allow individual tailoring with active drugs. Important considerations in selection of an appropriate regimen for such patients are as follows: virus drug resistance profile, adherence and tolerability, and potential drug–drug interactions with concomitant medications.¹

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The non-nucleoside analogue reverse transcriptase inhibitor (NNRTI), etravirine, is indicated for treatment-experienced patients with viral strains resistant to other NNRTIs.² Etravirine 200 mg bid (with an optimized background regimen that also included darunavir/ritonavir (darunavir/r)) demonstrated durable efficacy and a favorable safety profile versus placebo (also with an optimized background regimen), in both phase III DUET trials in treatment-experienced, HIV-1-infected adults.^{3–5} Pharmacokinetic studies suggest that etravirine can also be combined, without dosage adjustment, with antiretrovirals other than darunavir/r, such as lopinavir/r and raltegravir.^{6,7}

The primary objective of this study was to evaluate the safety, tolerability, and pharmacokinetics of etravirine when combined with antiretrovirals other than darunavir/r in treatment-experienced, HIV-1-infected adults. We present the final 48-week results.

Methods

Patients

HIV-1-infected, treatment-experienced adults who received ≥ 8 weeks of stable antiretroviral therapy prior to screening were recruited. All patients required a change of regimen for virologic failure (VF) (screening viral load (VL): ≥ 500 HIV-1 RNA copies/mL), tolerability issues, or regimen simplification (screening VL < 50 copies/mL).

Patients were required to harbor virus susceptible to etravirine and ≥ 1 antiretroviral in the background regimen. Susceptibility was based on resistance testing (PhenoSense GTTM, Monogram Biosciences, San Francisco, CA, USA) (screening VL ≥ 500 copies/mL) or on antiretroviral treatment history or prior resistance testing (screening VL < 50 copies/mL). Key exclusion criteria included a currently active AIDS-defining condition and pregnant or breastfeeding women.

Study design and treatment

VIOLIN (TMC125IFD3002; NCT01422330) was an open-label, single-arm, multicenter phase IV study conducted in 10 countries of South and North America, Africa, Europe, and the Russian Federation. The primary objective was to evaluate the safety, tolerability, and pharmacokinetics of etravirine combined with antiretrovirals other than darunavir/r. Secondary objectives included maintenance or achievement of viral suppression and immunological, genotypic, and phenotypic changes. The study consisted of a 6-week screening period, a 48-week treatment period, and a 4-week follow-up for patients with ongoing adverse events (AEs).

Patients were taking etravirine 200 mg bid following a meal, combined with an investigator-selected background regimen of ≥ 1 active antiretroviral, to ensure a regimen with ≥ 2 active antiretrovirals. However, if either raltegravir or

atazanavir/r were included in the regimen, then the background regimen had to include ≥ 2 active antiretrovirals. The use of darunavir/r or only nucleoside/tide reverse transcriptase inhibitors (NRTIs) in the background regimen was not permitted.

The trial protocol was reviewed and approved by independent ethics committees or institutional review boards prior to study start. The trial was conducted according to the International Conference on Harmonization guideline for Good Clinical Practice and principles of Good Clinical Practice and Declaration of Helsinki. All patients provided written informed consent.

Safety evaluations

Study visits were scheduled at weeks 2, 4, 8, 12, 24, 36, and 48, and AEs were monitored and reported using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 14.0). Vital signs were assessed and a physical examination performed at each visit, except follow-up. An electrocardiogram was performed at screening only. Fasting blood samples were taken at each visit for laboratory evaluations, and confirmatory tests were performed following reporting of a grade 3 or 4 laboratory abnormality. AEs and laboratory abnormalities were graded according to the Division of AIDS (DAIDS) grading table.⁸

Pharmacokinetic measurements

Sparse blood samples were collected for all patients at weeks 4, 8, 24, and 48, or at withdrawal. Plasma concentrations of the different antiretrovirals (as applicable) were determined by respective validated liquid chromatography-mass spectrometry/mass spectrometry methods; the lower limits of quantification were 2 ng/mL (etravirine), 10 ng/mL (lopinavir), 5 ng/mL (ritonavir), and 250 ng/mL (atazanavir). Individual etravirine pharmacokinetic parameters were derived by Bayesian feedback using a population pharmacokinetic model.

Efficacy and adherence assessments

VL was assessed at each visit using COBAS[®] AmpliPrep/COBAS[®] TaqMan[®] HIV-1 Test, V2.0 (Roche Diagnostics, Basel, Switzerland). The primary efficacy endpoint was the virologic response at week 48, defined as the percentage of patients with VL < 50 copies/mL by the Food and Drug Administration (FDA) snapshot algorithm (intent-to-treat (ITT), missing = failure analysis). CD4⁺ cell count was evaluated at each visit.

VF in the snapshot analysis was defined as (1) last VL ≥ 50 copies/mL in the week 48 window, or (2) earlier discontinuation because of lack or loss of virologic response, or (3) discontinuation for reasons other than an AE/death or lack or loss of virologic response and VL ≥ 50 copies/mL at

discontinuation, or (4) switching background regimen for reasons other than tolerability.

Adherence to treatment was assessed based on antiretroviral plasma concentration data combined with etravirine pill count. A patient was considered non-adherent if treatment adherence by pill count was <95% and/or observed plasma concentrations for etravirine or, if applicable, other antiretrovirals (lopinavir and atazanavir) were below the detection limit at any visit during the trial.

Virology assessments

VF patients who were on study at week 12 were classified either as rebounders when having confirmed VL ≥ 50 copies/mL or VL ≥ 50 copies/mL on last on-treatment assessment after having confirmed VL < 50 copies/mL (time-to-loss of virologic response (TLOVR) non-VF censored), or as non-responders when having never achieved two consecutive VL < 50 copies/mL.

Samples for resistance testing were taken at all timepoints. Genotype and phenotype testing (PhenoSense GT™) was performed at screening, baseline, and the final visit for patients with VL ≥ 500 copies/mL. Resistance testing could be requested at any other timepoint for patients with VL ≥ 500 copies/mL.

Drug resistance to NRTIs, NNRTIs, and protease inhibitors (PIs) was assessed using predefined mutation listings.⁹ In particular, a list of 50 NNRTI resistance-associated mutations (RAMs) was compiled (including G190T) for analysis of NNRTI resistance.^{9–11}

Data analyses

The sample size was calculated as ≥ 200 patients to assess safety and tolerability. When the true incident rate of an AE is 1%, the probability of observing at least one such AE in a sample of 200 patients is more than 85%.

The primary (final) analysis was conducted once all patients had completed the final week 48 or withdrawal visit and follow-up visit. All analyses were done for the ITT population (defined as all patients who were enrolled in the study and received ≥ 1 dose of etravirine).

Baseline, efficacy, pharmacokinetic, and adherence data are also presented for the two subpopulations of patients with baseline VL ≥ 50 copies/mL or < 50 copies/mL. In addition, subgroup analyses were conducted to evaluate the effect on virologic outcome of age, sex, race, adherence, HIV-1 subtype, use of PIs, etravirine baseline phenotype, and genotype and phenotypic susceptibility of antiretrovirals in the background regimen.

Results

Patient disposition and baseline characteristics

The study began on 26 August 2011 and ended 11 November 2013. Of the 528 patients screened, 211 were enrolled and treated. Most of the 317 screening failures were related to

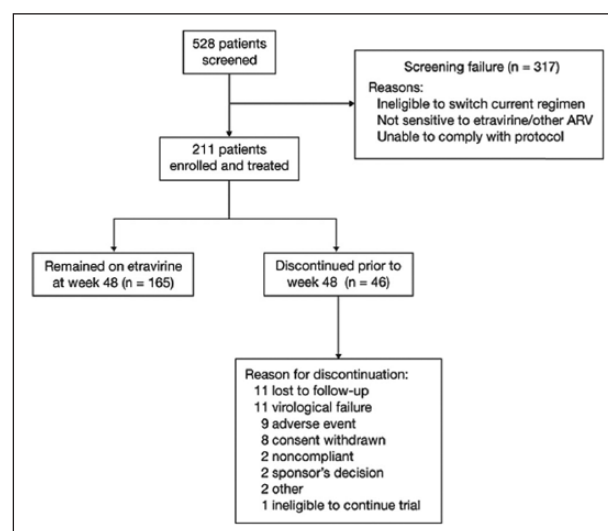


Figure 1. ARV: antiretroviral. Patient disposition through 48 weeks.

ineligibility of reasons for switching or to harboring virus that was not sensitive to antiretrovirals in the regimen (Figure 1).

In all, 78% (165/211) of patients completed the study. The most common reasons for discontinuation were loss to follow-up ($n=11$, 5%), reaching a virologic endpoint ($n=11$, 5%), AEs ($n=9$, 4%), and withdrawal of consent ($n=8$, 4%) (Figure 1). The majority of participants were from South Africa (51%) and the United States (17%) and were black or African American (61%) (Table 1). There was an even distribution of women (55%) and men (45%).

Two patients were included in the study with screening VLs between 50 and 500 copies/mL; both were classed as protocol violators. A further four patients who had screening VL < 50 copies/mL and 13 with screening VL ≥ 500 copies/mL had a baseline VL between 50 and 500 copies/mL. For the analysis, these 19 patients were included in the baseline VL ≥ 50 copies/mL subpopulation. Most patients (73%; 155/211) had baseline VL ≥ 50 copies/mL (Table 2). Overall, 42% ($n=88$) of patients were Centers for Disease Control and Prevention category C. Only 4% of patients had previously received ≥ 2 NNRTIs and 1% had received > 5 PIs (Table 2).

Of the patients with genotypic data available, most patients who continued into the treatment period had ≥ 1 NNRTI RAM (75.5% (114/151)),^{9–11} ≥ 1 IAS-USA NRTI RAM (65% (98/151)),⁹ and ≥ 1 IAS-USA PI RAM (99% (150/151))⁹ but had no IAS-USA primary PI mutations (87% (131/151)) at baseline⁹ (Table 2). The most frequently observed baseline etravirine RAMs were G190A (18/151), V90I (15/151), A98G (10/151), and K101E (9/151) (Supplementary Figure 1).

Of the patients with phenotypic data available at baseline, 36% (54/151) were sensitive to efavirenz and 34% (52/151) were sensitive to nevirapine, whereas 96% (145/151) were fully susceptible to etravirine (five patients were partially

Table 1. Patient baseline demographics.

	All patients (N=211)
Female, n (%)	116 (55)
Median age, years (range)	41 (19–65)
Race, n (%)	
Black or African American	129 (61)
White	53 (25)
American Indian or Alaska Native	17 (8)
American Indian or Alaska Native and White	10 (5)
Not allowed to ask due to local regulations	2 (1)
Asian	0
Other	0
Ethnicity, n (%)	
Hispanic or Latino	49 (23)
Not Hispanic or Latino	151 (72)
Not allowed to ask due to local regulations	11 (5)

susceptible and one patient was resistant resulting in deviations from the study entry criteria). Most patients, 95% (145/151) and 74% (112/151), respectively, were sensitive to ≥ 6 PIs and ≥ 4 NRTIs. Patients were considered sensitive to enfuvirtide (100%), raltegravir (97%), or maraviroc (99%) if not used in previous therapy.

Concomitant antiretroviral use

Most patients received ≥ 2 active background antiretrovirals; 45% received two and 25% received three active background antiretrovirals; 30% received one active agent.

The most common background antiretrovirals were PIs (83%), including lopinavir/r (62%), atazanavir/r (9%), and unboosted atazanavir (3%). Most patients received NRTIs (78%), mainly tenofovir (56%) and/or emtricitabine (25%). Other agents used were raltegravir (9%) or maraviroc (1%). In general, PIs were mostly used together with one or two NRTIs (61%) although 20% of patients received a PI combined solely with etravirine.

Adherence

Only 49% (99/201) of patients were considered adherent to treatment, as determined by etravirine pill count $>95\%$ combined with no undetectable antiretroviral plasma concentrations at any of the pharmacokinetic visits. Adherence was lower in patients with baseline VL ≥ 50 copies/mL than <50 copies/mL (47% (69/148) vs 57% (30/53), respectively).

Safety and tolerability

The overall median duration of etravirine exposure was 48.1 weeks (range: 0.6–54.1 weeks). Most AEs were grade 1 or 2 in severity (Table 3). Serious AEs occurred in 5% of

patients but none were rash AEs or considered related to etravirine. AEs leading to discontinuation of etravirine occurred in nine patients (4%), most commonly due to pregnancy (five patients).

The most common treatment-emergent AE regardless of causality was diarrhea in 17% of patients (Table 3). Other common AEs were reported in $<10\%$ of patients (Table 3). The most common laboratory events were increased total cholesterol (34% (71/211)) and hyperuricemia (27% (58/211)). Most laboratory abnormalities were grade 1 or 2, with grade 3 or 4 events occurring in $\leq 5\%$ of patients (Table 3).

Virologic response

Week 48 virologic responses (VL <50 copies/mL; snapshot analysis) were 55% (116/211) overall, 48% (74/155) for patients with baseline VL ≥ 50 copies/mL, and 75% (42/56) for patients with baseline VL <50 copies/mL (Figure 2(a)). VF (snapshot analysis) occurred in 34%, 42%, and 12.5% of patients, respectively. ITT-TLOVR virologic responses were 53% (111/211), 45% (69/155), and 75% (42/56), respectively. Virologic response (non-completer=failure (NC=F) analysis) for patients with baseline VL ≥ 50 copies/mL was 54% (83/155) at week 24 and 48% (75/155) at week 48.

Lack of treatment adherence had a marked impact on virologic outcome, especially in patients with baseline VL ≥ 50 copies/mL; week 48 virologic responses (snapshot analysis) were 64% (44/69) versus 38% (30/79) for adherent versus non-adherent patients, respectively (Figure 2(b)). Non-adherence in patients with baseline VL ≥ 50 copies/mL seemed to be potentially related to pill burden because virologic response was highest in patients receiving the lowest number of background antiretrovirals. Genotypic and phenotypic susceptibility and composition of the background antiretroviral regimen had no significant effect on virologic response. For the 36% (25/69) of patients for whom there were no signs of non-adherence and who were non-responders, high baseline VL was an important prognostic factor of non-response, with 3/25 having baseline VL $\geq 20,000$ to $<50,000$ copies/mL and 9/25 having baseline VL $\geq 50,000$ copies/mL.

For the other baseline factors evaluated (age, sex, race, HIV-1 subtype, use of boosted PIs, baseline etravirine fold change and weighted genotypic score, and number of sensitive background antiretrovirals), there were no consistent effects on virologic response (data not shown). However, numbers in the subgroups were low and the study was not powered to make comparisons, so no firm conclusions could be drawn.

Immunologic response

The mean 48-week increase from baseline in CD4⁺ cell count in patients with baseline VL <50 copies/mL was 32 cells/mm³ (standard error (SE): 17 cells/mm³; NC=F analysis) versus 65 cells/mm³ (SE: 11.4 cells/mm³) in patients with baseline VL ≥ 50 copies/mL.

Table 2. Patient baseline disease characteristics and resistance.

	Baseline VL < 50 copies/mL subpopulation (n = 56)	Baseline VL ≥ 50 copies/mL subpopulation (n = 155)	All patients (N = 211)
Median log ₁₀ VL, copies/mL (range)	1.28 (1.3–1.7)	4.42 (1.7–6.5)	3.74 (1.3–6.5)
Median CD4 ⁺ cell count, cells/mm ³ (range)	411 (157–1050)	238 (2–1059)	270 (2–1059)
Median duration of known HIV infection, years (range)	7.1 (0.5–26.7)	7.3 (0.4–27.2)	7.3 (0.4–27.2)
Previous use of, n (%)			
NNRTIs			
0	11 (20)	28 (18)	39 (18.5)
1	43 (77)	120 (77)	163 (77)
≥ 2	2 (4)	7 (5)	9 (4)
NRTIs			
0	0	1 (<1)	1 (<1)
≤ 5	54 (96)	145 (94)	199 (94)
> 5	2 (4)	9 (6)	11 (5)
PIs			
0	28 (50)	82 (53)	110 (52)
≤ 3	24 (43)	69 (44.5)	93 (44)
> 5	1 (2)	1 (<1)	2 (1)
Enfuvirtide	1 (2)	0	1 (<1)
Individual antiretrovirals used at study entry, n (%)			
NNRTIs			
Efavirenz	22 (39)	68 (44)	90 (43)
Nevirapine	4 (7)	18 (12)	22 (10)
Rilpivirine	0	1 (<1)	1 (<1)
NRTIs			
Lamivudine	32 (57)	95 (61)	127 (60)
Tenofovir	31 (55)	59 (38)	90 (43)
Zidovudine	8 (14)	47 (30)	55 (26)
Emtricitabine	14 (25)	33 (21)	47 (22)
Stavudine	9 (16)	23 (15)	32 (15)
Abacavir	5 (9)	16 (10)	21 (10)
Didanosine	2 (4)	6 (4)	8 (4)
PIs			
Ritonavir (low dose)	18 (32)	54 (35)	72 (34)
Lopinavir	10 (18)	31 (20)	41 (19)
Atazanavir	6 (11)	16 (10)	22 (10)
Saquinavir	1 (2)	6 (4)	7 (3)
Fosamprenavir	2 (4)	5 (3)	7 (3)
Darunavir	3 (5)	3 (2)	6 (3)
Tipranavir	0	1 (<1)	1 (<1)
Raltegravir	3 (5)	3 (2)	6 (3)
Maraviroc	1 (2)	0	1 (<1)
Number of baseline RAMs, median (range)			
Patients with baseline genotype data, n	3	148	151
ETR RAMs	0	0 (0–4)	0 (0–4)
NNRTI RAMs ^a	0 (0–1)	2 (0–6)	2 (0–6)
Primary PI mutations ^b	0	0 (0–6)	0 (0–6)
PI RAMs ^b	4 (1–5)	5 (0–14)	5 (0–14)
NRTI RAMs ^b	0	1 (0–5)	1 (0–5)

VL: viral load; NNRTI: non-nucleoside analogue reverse transcriptase inhibitor; NRTI: nucleoside/tide reverse transcriptase inhibitor; PI: protease inhibitor; RAM: resistance-associated mutation; ETR: etravirine.

^aBased on a list of 50 NNRTI RAMs.^{9–11}

^bBased on International AIDS Society-USA lists.⁹

Table 3. Safety and tolerability summary.

Incidence, n (%)	All patients (N = 211)
Any AE	145 (69)
Any AE at least possibly related to etravirine	49 (23)
Serious AEs	11 ^a (5)
Grade 3 or 4 AEs ^b	28 (13)
AEs leading to discontinuation of etravirine	9 ^c (4)
AEs any grade, regardless of causality (in $\geq 5\%$ of patients)	
Diarrhea	35 ^d (17)
Upper respiratory tract infection	17 (8)
Bronchitis	13 (6)
Influenza	12 (6)
Nasopharyngitis	11 (5)
Urinary tract infection	11 (5)
AEs of special interest ^e	
Hepatic	12 (6)
Rash (any type)	9 (4)
Neuropsychiatric	7 (3)
Treatment-emergent grade 3–4 ^b laboratory abnormalities (in ≥ 5 patients)	
Hyperbilirubinemia	10 ^f (5)
Hypophosphatemia	9 (4)
Increased low-density lipoprotein-cholesterol	6 (3)

AE: adverse event; NNRTI: non-nucleoside analogue reverse transcriptase inhibitor.

^aApproximately, half of serious AEs were grade 2. Two patients each experienced grade 3 menorrhagia and cholelithiasis, and four patients each experienced grade 4 pneumonia, tuberculosis, appendicitis, and angioedema.

^bAs defined by the Division of AIDS grading scheme.

^cPregnancy in five patients; the remaining four discontinuations occurred as a result of grade 4 tuberculosis which was considered serious, and, in three patients, an AE that was considered possibly related to etravirine (grade 1 paresthesia, grade 3 rash, and grade 2 weight loss following appendicitis).

^dOf the 35 patients with diarrhea, 31 received lopinavir/r in the investigator-selected background regimen.

^eWell-described AEs associated with NNRTIs.

^fOf the 10 patients with grade 3 or 4 hyperbilirubinemia, 6 received atazanavir/r in the investigator-selected background regimen.

Virology

In the virology analysis, of the 75 patients classified as VFs, 69 (44%) had baseline VL ≥ 50 copies/mL (49 non-responders and 20 rebounders) and 6 (11%) had baseline VL < 50 copies/mL (all rebounders).

Matched baseline and endpoint genotypic and phenotypic data were available for 49/75 VFs. An NNRTI RAM^{9–11} emerged in 29/49 VFs. The most frequently emerging etravirine RAMs (developing in ≥ 5 VFs) were Y181C (18/49), E138A (5/49), and M230L (5/49). The only other NNRTI RAM that emerged in ≥ 5 VFs was H221Y (6/49), which is not an etravirine RAM.^{12–14}

Other etravirine RAMs that each emerged in < 5 VFs were V90I, E138G, E138K, and E138Q. The median (range)

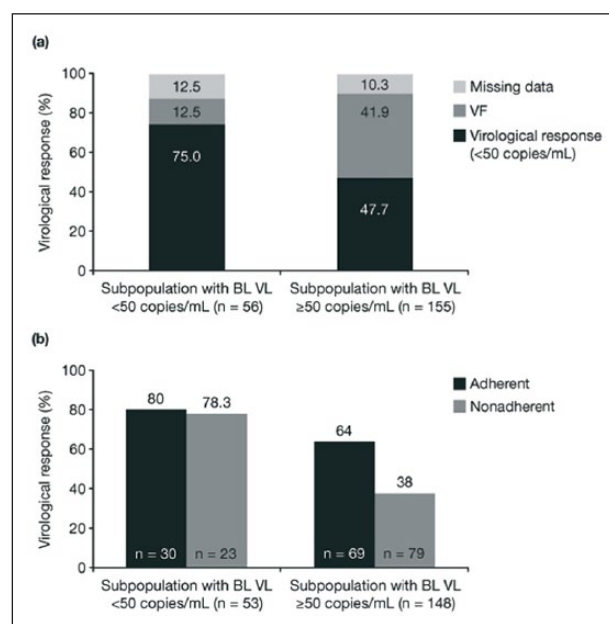


Figure 2. VF: virologic failure; BL: baseline; VL: viral load. (a) Virologic outcome at week 48 (snapshot analysis) according to baseline viral load category and (b) virologic response (VL < 50 copies/mL at week 48; snapshot analysis) according to adherence or non-adherence.^a

^aDefined using etravirine pill count data ($> 95\%$ or $\leq 95\%$, respectively) combined with pharmacokinetic sampling (undetectable antiretroviral plasma concentrations at any visit: no or yes, respectively).

etravirine fold change increased from baseline (0.84, 0.39–39) to endpoint (5.76, 0.50–217.84).

PI RAMs that emerged were L10I and A71T, each once (1/49). No emerging primary PI mutations were observed. Emerging NRTI RAMs were M41L, L74V, K219Q (1/49), D67N, M184I, T215Y (2/49), and M184V (3/49).

Pharmacokinetic analysis

For the overall population, the Bayesian estimates (median and range, n = 199) of etravirine AUC_{12h} and C_{0h} were 5390 (216–38,200) ng h/mL and 353 (4–3080) ng/mL, respectively. Median (range) etravirine AUC_{12h} by background regimen subgroup was 4865 (216–22,900) ng h/mL (etravirine plus lopinavir/r, n = 126), 6760 (981–38,200) ng h/mL (etravirine plus atazanavir/r, n = 17), 2660 (366–21,900) ng h/mL (etravirine plus other PIs, n = 25), and 8150 (1640–16,400) ng h/mL (no PIs, n = 31). Etravirine pharmacokinetic results were also impacted by drug adherence, both overall and by boosted PI subgroup (Supplementary Table 1 presents data by patient adherence).

Discussion

In this phase IV study, co-administration of etravirine 200 mg bid with antiretrovirals other than darunavir/r in a treatment-experienced, HIV-1-infected population had an overall safety

and tolerability profile and pharmacokinetics that were consistent with previously published data for etravirine.^{3–5,15–25} There were no new etravirine safety findings.

The overall observed etravirine exposures in this study were similar to those observed for etravirine 200 mg bid in the presence of darunavir/r in previous studies in HIV-1-infected, treatment-experienced patients.^{16,17,26} The etravirine pharmacokinetic assessments were impacted by suboptimal adherence, which was taken into account for the comparison with previously observed pharmacokinetic findings for etravirine. Mean etravirine exposure tended to be lower in patients receiving lopinavir/r, the most commonly used background PI, compared with other regimens including atazanavir/r or not including a PI. A drug–drug interaction with lopinavir/r has also been described in healthy volunteers,⁷ and was similar to that observed between etravirine and darunavir/r in healthy volunteers.²⁷ The higher observed median etravirine exposures with regimens including atazanavir/r or not including a PI are still within range of the exposures observed with darunavir/r in previous studies.^{7,15} The TEACH study showed that etravirine and atazanavir/r can be co-administered without the need for dosage adjustment.¹⁵ The observed differences in etravirine exposure by antiretrovirals in the background regimen are not considered clinically relevant and should be interpreted cautiously due to limited patient numbers in some subgroups.

This study enrolled a heterogeneous patient population with baseline VL < 50 or ≥ 50 copies/mL. The week 48 virologic response rate (snapshot analysis) (48%) for patients with baseline VL ≥ 50 copies/mL was lower than in some other studies that evaluated etravirine combined with antiretrovirals other than darunavir/r in treatment-experienced patients.^{5,20,21,25,28,29} This difference may be largely explained by the relatively high level of treatment non-adherence in the baseline VL ≥ 50 copies/mL subpopulation, which appeared potentially related to pill burden, as the virologic response rate was 64% in this subgroup for those who were considered adherent.

In previously reported studies of virologically suppressed patients experiencing AEs who then switched to an etravirine-based regimen not including darunavir/r, viral suppression was well maintained (range: 77%–100%).^{30–36} In this study, while patient numbers were low in patients with baseline VL < 50 copies/mL (N = 56), 75% of patients maintained virologic suppression at week 48. Poor adherence had minimal impact on virologic response in this subpopulation compared with the subpopulation with baseline VL ≥ 50 copies/mL.

The most frequently emerging etravirine RAMs, Y181C, E138A, and M230L (≥ 5 VFs) have also been observed previously in patients with VF in etravirine trials,^{12–14,37} as has the only other NNRTI RAM that emerged in ≥ 5 VFs, H221Y.¹⁴

Strengths of this study were the diverse patient population and the equal representation of women and men. A limitation

was that it was an open-label, single-arm study, so no direct comparison was made with etravirine-based regimens that include darunavir/r.

In conclusion, etravirine 200 mg bid with a background regimen other than darunavir/r was generally well tolerated for use in treatment-experienced patients. The overall etravirine safety and tolerability profile and pharmacokinetics (specifically in those patients that were adherent) were consistent with those for etravirine previously observed in HIV-1-infected adults. There was a relatively high level of non-adherence, also observed in the pharmacokinetic assessments that negatively impacted virological response, particularly in patients with baseline VL ≥ 50 copies/mL.

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Author contribution

All authors were involved in the development of the primary manuscript, interpretation of data, have read and approved the final version, and have met the criteria for authorship as established by the ICMJE. E.A., A.B., and R.S. all participated in recruiting significant numbers of patients as well as acquisition of data. H.C., L.L., L.T., B.V.B., S.V., and M.O. all had a significant involvement in the data analyses.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: H.C., L.T., S.V., and M.O. are full-time employees of Janssen. L.L. and B.V.B. are consultants at Janssen. E.A., A.B., and R.S. declare no conflicts of interest or financial disclosures.

Ethical approval

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Informed consent

Written informed consent was obtained from all patients before the study.

Trial registration

ClinicalTrials.gov identifier: NCT01422330.

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