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ORIGINAL RESEARCH

Efficacy of etravirine combined with darunavir or other ritonavir-boosted protease inhibitors in HIV-1-infected patients: an observational study using pooled European cohort data*

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Objectives

This observational study in antiretroviral treatment-experienced, HIV-1-infected adults explored the efficacy of etravirine plus darunavir/ritonavir (DRV group; $n = 999$) *vs*. etravirine plus an alternative boosted protease inhibitor (other PI group; $n = 116$) using pooled European cohort data.

Methods

Two international (EuroSIDA; EUResist Network) and five national (France, Italy, Spain, Switzerland and UK) cohorts provided data (collected in 2007–2012). Stratum-adjusted (for confounding factors) Mantel–Haenszel differences in virological responses (viral load < 50 HIV-1 RNA copies/mL) and odds ratios (ORs) with 95% confidence intervals (CIs) were derived.

Results

Baseline characteristics were balanced between groups except for previous use of antiretrovirals (≥ 10: 63% in the DRV group *vs*. 49% in the other PI group), including previous use of at least three PIs (64% *vs*. 53%, respectively) and mean number of PI resistance mutations (2.3 *vs*. 1.9, respectively). Week 24 responses were 73% *vs*. 75% (observed) and 49% *vs*. 43% (missing = failure), respectively. Week 48 responses were 75% *vs*. 73% and 32% *vs*. 30%, respectively. All 95% CIs around unadjusted and adjusted differences encompassed 0 (difference in responses) or 1 (ORs). While ORs by cohort indicated heterogeneity in response, for pooled data the difference between unadjusted and adjusted for cohort ORs was small.

Conclusions

These data do not indicate a difference in response between the DRV and other PI groups, although caution should be applied given the small size of the other PI group and the lack of randomization. This suggests that the efficacy and virology results from DUET can be extrapolated to a regimen of etravirine with a boosted PI other than darunavir/ritonavir.

Keywords: darunavir/ritonavir, efficacy, etravirine, HIV-1, protease inhibitor

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Introduction

Etravirine (ETR) is a nonnucleoside reverse transcriptase inhibitor (NNRTI) with a high intrinsic activity against both wild-type HIV type 1 (HIV-1) and strains harbouring NNRTI and other resistance-associated mutations (RAMs) [1,2]. Conditional marketing authorization in the European Union (EU) was received for ETR in August 2008 [3]. At that time, ETR 200 mg twice daily in combination with a boosted protease inhibitor (PI/r) and other antiretrovirals (ARVs) was indicated for the treatment of HIV-1 infection in ARV treatment-experienced adults. Full marketing authorization in the EU was received for ETR in November 2013. ETR at a bodyweight-determined dose is now also approved for use in paediatric patients ≥ 6 years of age who are ARV treatment experienced.

The indication of ETR in treatment-experienced adults is based on the results of the two DUET (TMC125-C206 and TMC125-C216; TMC125 to Demonstrate Undetectable viral load in patients Experienced with ARV Therapy) studies [4–7]. In these randomized, double-blind, placebo-controlled, phase III studies, ETR 200 mg twice daily demonstrated durable efficacy and had a similar tolerability profile compared to placebo when both were given with an optimized background regimen (OBR). The OBR included investigator-selected nucleoside reverse transcriptase inhibitors (NRTIs), with or without enfuviritide (ENF) and darunavir/ritonavir (DRV/r) as the only allowed boosted PI.

Additional clinical data were requested to determine the efficacy of ETR in combination with boosted PIs other than DRV/r. As a consequence of the limited availability of eligible patients for a prospective clinical study, this observational study was designed to determine if the virological response observed in patients receiving ETR in combination with DRV/r (the DRV group) was comparable to the response in patients receiving ETR and boosted PIs other than DRV/r (the other PI group), using existing cohort data.

Methods

Patient population

The main inclusion criteria were adult male or female HIV-1-infected patients at the start of treatment with ETR and a background regimen containing a boosted PI with or without NRTIs, ENF, raltegravir (RAL) and/or maraviroc (MVC) and who had a detectable viral load (above the limit of detection of the HIV-1 viral load assay used in the cohort). Patients who had previously failed an NNRTI were allowed. Exclusion criteria included any patients treated with investigational medications, and patients with a background regimen not including a boosted PI.

Study design

This was a phase IV, retrospective observational study to determine if the ARV activity of ETR when combined with ARV background regimens containing DRV/r was comparable to the ARV activity of ETR when combined with background ARV regimens containing a boosted PI which is not DRV/r. ARVs were typically used as per local treatment guidelines, so for DRV/r, this would probably have been twice daily in line with the prescribing information for treatment-experienced patients. However, these data were not specifically collected. Safety data were also not collected as this was not an objective of this study. Reporting of serious adverse events during prospective patient treatment was the responsibility of the treating physician in accordance with local guidance. The study was conducted in accordance with the Declaration of Helsinki, and in compliance with the Guidelines for Good Pharmacoepidemiology Practices [8] and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist [9]. Those responsible for each cohort confirmed that they had made all legally required disclosures and possessed consents and/or competent institutional review board/ethics committee authorizations or permissions to provide the sponsor with the data. Patient confidentiality was maintained at all times.

Prior to the start of the study, all seven eligible cohorts [two international (EuroSIDA and EUResist Network) and five national (France, Italy, Spain, Switzerland and UK)] were given a data availability questionnaire to assess their suitability for meeting the study objectives. The feedback from the questionnaire was used to determine sample size estimates (data from 250 patients were expected in the other PI group, while 1500 patients were expected in the DRV group).

Each cohort provided its data in one of two ways: in the first scenario, 'individual de-identified' individual patient data were provided, allowing the sponsor to perform the analysis; in the second scenario, the cohort provided analysed data, with the analysis being conducted by one of the cohort's representatives (see Table 1 for more details). In both cases, the same pre-specified statistical analysis plan was used. The primary analysis of this study is on the pooled data set.

Data analyses

Efficacy evaluations

The virological response rate in the current study, defined as the proportion of patients who had a plasma viral load < 50 HIV-1 RNA copies/mL, based on observed and missing = failure (M=F) imputed data was compared for the

Table 1 Patient numbers by cohort

Cohort	DRV group	Other PI group	Type of data
National Agency for AIDS Research (ANRS) (Paris, France)	302	28	Analysed
Tor Vergata University (Rome, Italy)	29	7	Individual
Chelsea & Westminster (London, UK)	66	4	Individual
EUResist Network (multinational)	188	17	Individual
EuroSIDA (multinational)	204	27	Analysed
Fundació Lluita Contra la SIDA (Barcelona, Spain)	48	10	Individual
Swiss HIV Cohort Study	162	23	Analysed
Total	999	116	

DRV, darunavir; PI, protease inhibitor.

DRV group *vs*. the other PI group at weeks 12, 24, 48 and 96 from starting the ETR-based regimen.

The observed virological response is based on a denominator of only patients with available viral load data. Patients contributing data at one time-point were not necessarily contributing to the data at any other time-points. The M=F-imputed virological response is based on a denominator of all patients within a given treatment group or subgroup. Any patients with missing viral load data at a specific time-point were considered nonresponders at that time-point. Although data were collected at four time-points, the subanalyses on virological response rates by baseline genotypic sensitivity score (GSS) and ETR weighted genotypic score (WGS) focus on weeks 12 and 24, given the low number of patients for the observed analysis at later time-points. The virological failure (VF) rate was defined as the percentage of patients either with a viral load > 50 copies/mL or who had stopped ETR prior to the considered time-point for reasons other than an adverse event and with a last viral load > 50 copies/mL.

The GSS was defined as the number of sensitive ARV drugs in the background regimen at baseline, as determined by genotype and calculated by summing the scores for each ARV used. ETR was excluded from the GSS calculation. For PIs and NRTIs, the GSS was calculated based on the National Agency for AIDS Research (ANRS) HIV-1 genotypic drug resistance interpretation algorithm [10]. A PI or NRTI with a score of 0 means that the mutations detected confer genotypic resistance to that PI/NRTI; a score of 0.5 indicates possible genotypic resistance, and a score of 1 indicates that the virus is sensitive. Because of the lack of genotypic data in regions outside of the reverse transcriptase and protease domains, ENF, RAL and MVC were counted as sensitive (scored as 1) if not used previously.

The ETR WGS was calculated by adding together the individual weight factors for each ETR RAM from a list of 20 ETR RAMs [11,12]. A score of 0–2 is associated with a high virological response, 2.5–3.5 with an intermediate response and ≥4 with a reduced response [11]. Although ETR activity was not assessed using the ANRS algorithm used for the other ARVs, the ETR WGS was shown to provide similar results compared to the ANRS score [13].

Statistical evaluations

To account for the impact of potential prognostic factors, differences in response rates [and odds ratios (ORs)] were calculated, together with their 95% confidence intervals (CIs). These were adjusted for confounding factors: cohort of enrolment, drugs in the background regimen, baseline viral load, baseline GSS and ETR WGS. For each prognostic factor, response rates were determined within different strata and observed differences in response rates between the two groups were weighted according to the size of the strata (stratum-adjusted Mantel–Haenszel proportions). This resulted in an overall adjusted difference in response rates (and OR) giving more importance to differences observed in larger strata. Heterogeneity in virological response rates between the different cohorts was determined using Zelen's exact test of homogeneity of ORs.

The observed change from baseline in CD4 cell count (cells/μL) was analysed descriptively at weeks 12, 24, 48 and 96.

Results

Patient disposition and baseline characteristics

Data were retrieved and pooled for 1115 HIV-1-infected patients within a time period from 2007 to 2012 (999 patients in the DRV group and 116 patients in the other PI group). Three of the seven cohorts transferred analysed data (Table 1).

The demographic and baseline disease characteristics were generally balanced between the DRV group and the other PI group (Table 2). The mean (standard deviation [SD]) age of the patients overall was 46.2 (9.03) years, and the majority were male (79%) and/or white (77%). The mean (SD) time since HIV diagnosis was 15.4 (5.9) years.

Sixty-two per cent of all patients had previously used ≥ 10 ARVs, but more patients in the DRV group than in the other PI group were PI treatment experienced, with 64% and 53% of patients, respectively, having previously used at least three PIs. A higher proportion of patients in the DRV group than in the other PI group had previously used ENF (Table 2).

At baseline, the proportion of patients with GSS > 2 was 29% in the DRV group and 24% in the other PI group. The proportion of patients who had a sensitive ETR WGS was 72% *vs*. 75%, respectively.

Table 2 Baseline demographics and disease characteristics

	DRV group (*n* = 999)	Other PI group (*n* = 116)
Baseline demographics		
Age (years)	*n* = 697	*n* = 88
Mean (SD)	46.6 (9.1)	43.5 (8.6)
Sex [*n* (%)]	*n* = 997	*n* = 116
Male	800 (80)	79 (68)
Race [*n* (%)]	*n* = 585	*n* = 76
Asian	9 (2)	0 (0)
Black	79 (14)	14 (18)
Hispanic	11 (2)	1 (1)
White	459 (78)	53 (70)
Other	27 (5)	8 (11)
Disease characteristics		
Baseline viral load (log_{10} copies/mL)	*n* = 997	*n* = 116
Mean (SD)	3.8 (1.1)	3.7 (1.1)
Baseline CD4 count (cells/μL)	*n* = 987	*n* = 115
Mean (SD)	299 (245)	305 (183)
Duration of HIV infection (years)	*n* = 513	*n* = 63
Mean (SD)	15.7 (5.9)	13.4 (5.3)
Previously used ARVs [*n* (%)]		
Any ARV	*n* = 994	*n* = 115
<4	96 (10)	13 (11)
4–9	269 (27)	46 (40)
≥10	629 (63)	56 (49)
PIs	*n* = 999	*n* = 116
<3	357 (36)	54 (47)
3–5	434 (43)	39 (34)
>5	208 (21)	23 (20)
Other ARVs	*n* = 999	*n* = 116
ENF	285 (29)	22 (19)
RAL	105 (11)	9 (8)
MVC	23 (2)	2 (2)
Mean (SD) number of RAMs	*n* = 828	*n* = 97
IAS-USA NRTI RAMs [14]	3.6 (2.3)	3.1 (2.2)
NNRTI RAMs [15]	1.7 (1.7)	1.6 (1.5)
ETR RAMs [11,12]	0.8 (1.0)	0.7 (0.9)
IAS-USA primary PI RAMs [14]	2.3 (1.9)	1.9 (1.8)
IAS-USA DRV RAMs [14]	1.2 (1.4)	1.3 (1.2)
IAS-USA LPV RAMs [14]	5.0 (3.4)	3.7 (2.9)
IAS-USA ATV RAMs [14]	6.5 (4.1)	5.1 (3.6)
GSS [10] [*n* (%)]	*n* = 822	*n* = 97
>2	236 (29)	23 (24)
1.5–2	382 (46)	46 (47)
0–1	204 (25)	28 (29)
ETR WGS [11,12]		
Sensitive	589 (72)	73 (75)
Intermediate	156 (19)	18 (19)
Resistant	77 (9)	6 (6)

DRV, darunavir; PI, protease inhibitor; ARV, antiretroviral; SD, standard deviation; ENF, enfuviritide; RAL, raltegravir; MVC, maraviroc; IAS-USA, International AIDS Society USA; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; ETR, etravirine; RAM, resistance-associated mutation; LPV, lopinavir; ATV, atazanavir; GSS, genotype sensitivity score; WGS, weighted genotypic score.

Sixty-seven per cent of patients (670 of 999) in the DRV group and 47% of patients in the other PI group (55 of 116) received RAL or ENF/MVC. The proportion of patients who also used an NRTI(s) in their background regimen was 58% (583 of 999) in the DRV group and 68% (79 of 116) in the other PI group. The proportion of patients in the other PI group who received lopinavir/ritonavir (LPV/r) was 65.5% (76 of 116), with 24% (28 of 116) receiving atazanavir/ritonavir (ATV/r). Other boosted PIs (amprenavir, fosamprenavir, indinavir, saquinavir and tipranavir) were used by fewer than 10 patients.

Efficacy

Virological response

Virological response rates are presented in Fig. 1, which shows results of both the observed method and the M=F imputation. Virological response rates were comparable between treatment groups based on both methods. Observed virological response rates were higher at week 24 (73% of 662 patients with viral load data available in the DRV group *vs*. 75% of 67 patients in the other PI group), week 48 (75% of 422 patients *vs*. 73% of 48 patients, respectively) and week 96 (80% of 265 patients *vs*. 73% of 33 patients, respectively) than at week 12 (65% of 741 patients *vs*. 68% of 75 patients, respectively). M=F-imputed responses were lower at later time-points than at weeks 12 and 24 (Fig. 1). However, week 96 results must be interpreted with caution because of the small sample size of the other PI group.

The virological failure rate was 29% of 999 patients in the DRV group and 28% of 116 patients in the other PI group at week 12. Corresponding figures were 22% and 25%, respectively, at week 24 and 17% and 26%, respectively, at week 48.

Stratum-adjusted Mantel–Haenszel differences in response rates

Stratum-adjusted differences in response rates are shown in Table 3. There were no significant differences between treatment groups at weeks 12 and 24 in M=F-imputed and observed virological response rates. All 95% CIs around the unadjusted and adjusted differences encompassed 0 for the difference in response rates and encompassed 1 for ORs. ORs by cohort indicated heterogeneity in virological response rates between the different cohorts (Fig. 2) (P value = 0.0353 from Zelen's exact test of homogeneity of ORs, for week 24 observed data). The net effect on the overall pooled result, however, was small. Data presented in Table 3 show that the unadjusted ORs and those adjusted for cohort were similar.

Virological response by baseline resistance

Virological response rates at weeks 12 and 24 were similar in the two treatment groups in patients with a sensitive baseline ETR WGS (Table 4). The results of the comparison between treatment groups using M=F-imputed data were consistent with those using observed data. Taking the low

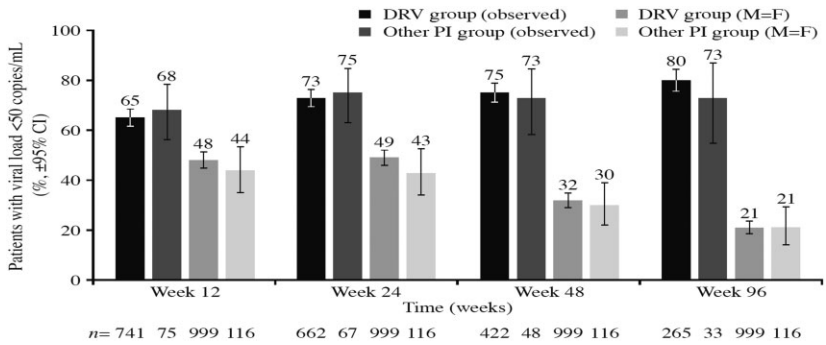

Fig. 1 Virological response rates at weeks 12, 24, 48 and 96. DRV, darunavir; PI, protease inhibitor; M = F, missing = failure; CI, confidence interval.

Table 3 Stratum-adjusted differences in response rates at weeks 12, 24, 48 and 96

	Difference* in response rates [% (95% CI)]		Odds ratio† (95% CI)	
	Observed	M = F imputed	Observed	M = F imputed
Week 12				
Unadjusted difference	2.8 (−8.4–14.0)	−4.4 (−14.0–5.2)	1.14 (0.68–1.89)	0.84 (0.57–1.23)
Difference adjusted for				
Cohort	2.3 (−9.0–13.6)	−3.8 (−13.1–5.4)	1.11 (0.66–1.85)	0.85 (0.57–1.27)
Background regimen	4.4 (−6.3–15.1)	−1.3 (−10.4–7.9)	1.24 (0.73–2.11)	0.95 (0.63–1.42)
Baseline viral load	1.6 (−9.5–12.8)	−4.3 (−13.9–5.3)	1.08 (0.64–1.81)	0.84 (0.57–1.24)
Baseline GSS	0.6 (−11.8–13.1)	−7.8 (−18.2–2.6)	1.03 (0.60–1.77)	0.73 (0.48–1.12)
Baseline etravirine WGS [11,12]	0.9 (−10.7–12.6)	−8.0 (−18.5,−2.5)	1.04 (0.60–1.83)	0.72 (0.47–1.11)
Week 24				
Unadjusted difference	1.2 (−9.8–12.2)	−5.5 (−15.1–4.0)	1.07 (0.60–1.90)	0.80 (0.54–1.18)
Difference adjusted for				
Cohort	1.1 (−10.3–12.5)	−7.1 (−16.2–2.1)	1.06 (0.60–1.87)	0.75 (0.51–1.11)
Background regimen	1.8 (−9.6–13.3)	−3.3 (−12.9–6.3)	1.10 (0.62–1.96)	0.87 (0.59–1.30)
Baseline viral load	1.9 (−9.0–12.8)	−5.6 (−15.2–4.0)	1.11 (0.61–2.01)	0.80 (0.54–1.18)
Baseline GSS	0.6 (−11.8–12.9)	−6.5 (−17.0–4.0)	1.03 (0.56–1.87)	0.77 (0.51–1.18)
Baseline etravirine WGS [11,12]	0.0 (−11.2–11.3)	−5.6 (−16.1–4.9)	1.00 (0.54–1.85)	0.80 (0.52–1.22)
Week 48				
Unadjusted difference	−2.4 (−15.8–10.9)	−1.7 (−10.5–7.2)	0.88 (0.45–1.73)	0.93 (0.61, 1.41)
Difference adjusted for				
Cohort	−1.9 (−15.9–12.2)	−4.9 (−13.2–3.4)	0.91 (0.46–1.79)	0.77 (0.49–1.21)
Background regimen	−1.6 (−15.4–12.3)	−2.0 (−11.0–7.0)	0.92 (0.47–1.82)	0.91 (0.60–1.39)
Baseline viral load	−2.5 (−16.0–10.9)	−1.6 (−10.5–7.3)	0.87 (0.44–1.72)	0.93 (0.61–1.41)
Baseline GSS	−1.8 (−17.1–13.5)	−2.5 (−12.3–7.3)	0.91 (0.44–1.90)	0.89 (0.56–1.41)
Baseline etravirine WGS	–†	−2.0 (−14.6–10.7)	–†	0.92 (0.55–1.54)
Week 96				
Unadjusted difference	−7.3 (−23.4–8.9)	−0.5 (−8.4–7.3)	0.86 (0.35–2.10)	0.97 (0.60–1.56)
Difference adjusted for				
Cohort	−9.6 (−25.9–6.8)	−4.6 (−12.0–2.9)	0.58 (0.25–1.35)	0.74 (0.44–1.23)
Background regimen	−7.2 (−22.7–8.4)	−1.1 (−9.2–7.0)	0.67 (0.29–1.54)	0.94 (0.58–1.51)
Baseline viral load	−7.8 (−24.4–8.9)	−0.5 (−8.4–7.5)	0.65 (0.28–1.48)	0.97 (0.61–1.56)
Baseline GSS	−6.0 (−24.0–12.1)	+0.3 (−8.6–9.2)	0.70 (0.28–1.77)	1.02 (0.61–1.70)
Baseline etravirine WGS	−7.3 (−24.9–10.2)	−4.9 (−16.7–7.0)	0.65 (0.25–1.65)	0.80 (0.46–1.39)

CI, confidence interval; M = F, missing = failure; GSS, genotypic sensitivity score; WGS, weighted genotypic score; PI, protease inhibitor; DRV, darunavir.
*Response rate for other PI group – response rate for DRV group.
†Response rate for other PI group/response rate for DRV group.
†At week 48, no observations were available for the resistant stratum. Therefore, the difference and odds ratio could not be calculated.

number of patients with a resistant ETR WGS into consideration, virological response rates appeared higher in patients with a sensitive ETR WGS than in patients with a resistant ETR WGS in both treatment groups.

Baseline GSS appeared to have little influence on the observed virological response. Only small differences in the proportion of responders according to baseline GSS were observed (especially for the categories GSS 0–1 and 1.5–2).

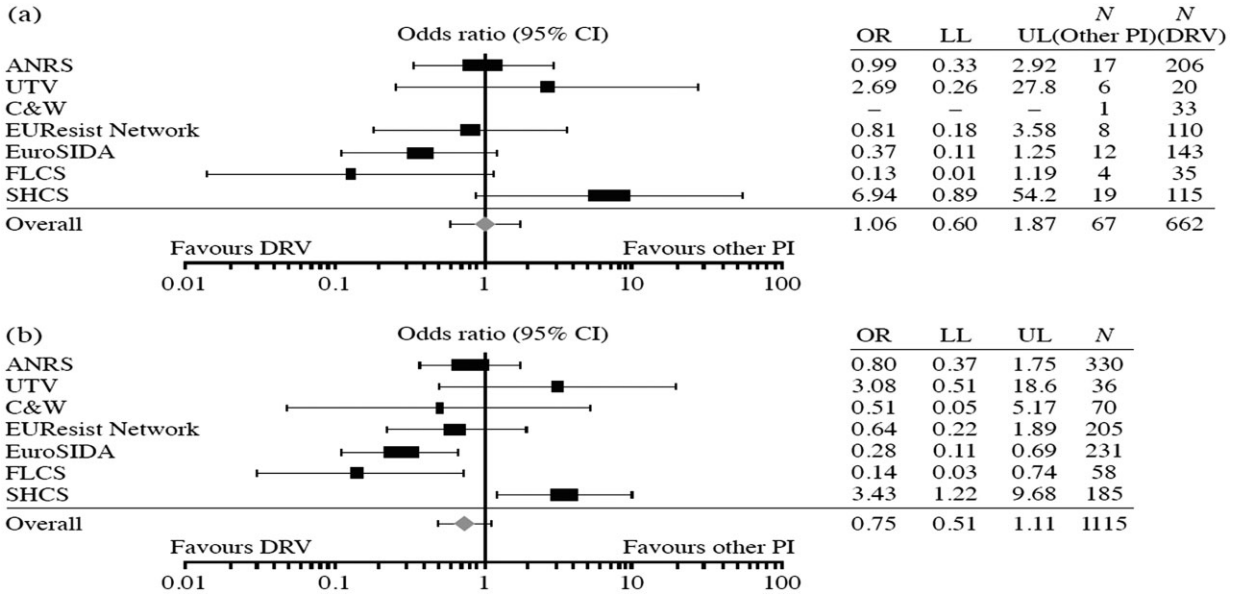

Fig. 2 Odds ratios at week 24 by cohort for (a) observed case analysis and (b) missing = failure analysis. CI, confidence interval; OR, odds ratio of response rate for other PI group/response rate for DRV group; LL, lower limit; UL, upper limit; PI, protease inhibitor; DRV, darunavir; ANRS, National Agency for AIDS Research; UTV, Tor Vergata University; C&W, Chelsea & Westminster; FLCS, Fundació Lluita Contra la SIDA; SHCS, Swiss HIV Cohort Study.

Table 4 Virological response rates by baseline etravirine weighted genotypic score and baseline genotypic sensitivity score (GSS)

	DRV group	Other PI group	DRV group	Other PI group
Total *n*	999	116		
n with available resistance data	814	97		
Baseline etravirine weighted genotypic score	**Observed response (%)**		**M = F imputed response (%)**	
Week 12	*n* = 638	*n* = 64	*n* = 814	*n* = 97
Sensitive [*n*/total (%)]	313/447 (70)	34/44 (77)	313/583 (54)	34/73 (47)
Intermediate [*n*/total (%)]	68/127 (54)	7/14 (50)	68/156 (44)	7/18 (39)
Resistant [*n*/total (%)]	32/64 (50)	1/6 (17)	32/75 (43)	1/6 (17)
Week 24	*n* = 565	*n* = 60	*n* = 814	*n* = 97
Sensitive [*n*/total (%)]	305/395 (77)	35/43 (81)	305/583 (52)	35/73 (48)
Intermediate [*n*/total (%)]	74/115 (64)	5/13 (38)	74/156 (47)	5/18 (28)
Resistant [*n*/total (%)]	34/55 (62)	4/4 (100)	34/75 (45)	4/6 (67)
Total *N*	999	116		
N with available resistance data	808	97		
Baseline GSS	**Observed response (%)**		**M = F imputed response (%)**	
Week 12	*n* = 634	*n* = 64	*n* = 808	*n* = 97
GSS 0–1 [*n*/total (%)]	98/153 (64)	11/19 (58)	98/198 (49.5)	11/28 (39)
GSS 1.5–2 [*n*/total (%)]	197/304 (65)	25/34 (73.5)	197/380 (52)	25/46 (54)
GSS > 2 [*n*/total (%)]	118/177 (67)	6/11 (54.5)	118/230 (51)	6/23 (26)
Week 24	*n* = 561	*n* = 59	*n* = 808	*n* = 97
GSS 0–1 [*n*/total (%)]	102/143 (71)	12/16 (75)	102/198 (51.5)	12/28 (43)
GSS 1.5–2 [*n*/total (%)]	180/262 (69)	24/32 (75)	180/380 (47)	24/46 (52)
GSS > 2 [*n*/total (%)]	130/156 (83)	7/11 (64)	130/230 (56.5)	7/23 (30)

DRV, darunavir; PI, protease inhibitor; M = F, missing = failure.

These differences were independent of the use of DRV *vs*. other PIs (Table 4).

Immunological response

The mean (standard error) change in CD4 cell count from baseline was +68.5 (5.1) cells/μL in the DRV group and +65.4 (14.7) cells/μL in the other PI group at week 12, +74.8 (5.8) cells/μL *vs*. +105.8 (18.9) cells/μL, respectively, at week 24 and +96.7 (9.6) cells/μL *vs*. 166.2 (37.3) cells/μL, respectively, at week 48. The CD4 cell count continued to increase into week 96 but the sample size was low so the results should be interpreted with caution.

Discussion

This retrospective, observational study was designed to compile available cohort data on the use of ETR in combination with boosted PIs other than DRV/r. The hypothesis was that the virological response achieved by patients in the other PI group would be comparable to that achieved by patients in the DRV group in an unselected group of HIV-positive patients seen for care in Europe.

The number of patients in this observational study was higher than that estimated to be obtainable from conducting a prospective clinical trial. Another strength of this retrospective, observational study design is that collaborators leading the various cohorts are experienced in systematically collecting data specifically designed for HIV research.

The results of the current study give an overview of how ETR is used in clinical practice, with the majority of patients treated with ETR also receiving DRV/r as a boosted PI in their background regimen (90%), potentially in combination with an NRTI, RAL or ENF/MVC. Our results suggest that there is no difference in observed and M=F-imputed virological response rates between patients treated with ETR in combination with a background regimen containing DRV/r or another boosted PI. This comparison should be interpreted with caution given the relatively small sample size of the other PI group and possible influence of confounding factors. For example, baseline characteristics indicate that patients in the DRV group were more ARV treatment experienced than patients in the other PI group, but at the same time, the proportion of patients with a baseline GSS > 2 was higher in the DRV group than in the other PI group. Imbalances were observed for other measured factors such as drugs used in the background regimen. However, the calculated stratum-adjusted Mantel–Haenszel results also did not indicate that there were differences in response rates between the treatment groups. All 95% CIs around the unadjusted and adjusted differences encompassed 0 for difference in response rates (other PI group – DRV group) or encompassed 1 for ORs (other PI group/DRV group). Nevertheless, we cannot rule out further confounding caused by unmeasured factors. At weeks 12 and 24, numerical differences were positive (and ORs > 1) for the observed response rates and negative (and ORs < 1) for the M=F-imputed response rates. However, this latter observation should be interpreted cautiously as it is a result of more missing data because of stopping ETR or missing data at a specific time-point in the other PI group. As expected, M=F-imputed response rates declined over time as less viral load data were available at later time-points. Also as expected, with the observed method, response rates increased over time because patients remaining on treatment later on tended to be those who responded best. Mean increases in CD4 cell counts occurred in both treatment groups over time. The increase appeared more pronounced in the other PI group than in the DRV group with longer treatment duration, although sample size in the other PI group was small.

When comparing across studies, differences in study design, patient populations, inclusion criteria and endpoints need to be taken into consideration. However, generally virological response rates in our meta-analysis compare well with those that have been observed both in the randomized, double-blind, phase III DUET studies [4–7] and in clinical practice [16–18]. In the pooled DUET trials [4–7], 47% (week 12), 61% (week 24) and 60% (week 48) of treatment-experienced, HIV-1-infected patients receiving ETR 200 mg twice daily in combination with DRV/r and investigator selected NRTIs, with or without ENF, achieved a virological response (viral load <50 copies/mL; intent-to-treat, time-to-loss of virological response algorithm). Corresponding observed response rates in the pooled DUET trials were 52% (week 12), 66% (week 24) and 75% (week 48) (Janssen data on file). In a US observational study of 587 treatment-experienced adults, week 24 observed virological response rates, determined using the primary endpoint of < 400 copies/mL, were similar for 340 patients receiving ETR in a regimen including DRV/r or in a regimen containing a PI/r other than DRV/r (n = 69) (79% *vs*. 81%, respectively) [16]. In a small Spanish study of 122 patients from a routine clinical practice, of the 11.5% who used ETR in combination with a boosted PI other than DRV/r, the week 48 virological response rate (<50 copies/mL, M=F) for the entire cohort was 73% [17].

Similar virological response rates were seen in the two treatment groups in patients with a sensitive ETR WGS. Responses were higher in patients with a sensitive ETR WGS than in patients with an intermediate or resistant ETR WGS. While this effect was observed in both treatment groups, it was more pronounced in the other PI group than in the DRV group, although sample sizes were small in

these subgroups. The observation that virological response appeared to be similar in the two treatment groups regardless of baseline GSS could be attributable to the high proportion of patients with a sensitive ETR WGS in those patients with a low GSS (data not shown) or differences in the intrinsic potency of the ARVs, which were not taken into account when calculating the GSS.

There are several limitations to this study. The study was not a randomized clinical trial and lacked power to make formal statistical comparisons between the other PI group and the DRV group. There was clear heterogeneity in virological response rates between the cohorts ($P = 0.0353$, Zelen's exact test of homogeneity of ORs, week 24 observed data). However, the net effect on the overall pooled result was small, as indicated by the small difference between the unadjusted and adjusted for cohort ORs for differences in virological response rates between treatment groups. The other PI group had a relatively low number of patients. This was initially estimated to be approximately 250 patients but in actuality it was 116 patients. The number of patients in the DRV group ($n = 999$) was also lower than expected ($n = 1500$). The reasons for this difference were the inclusion in the estimates of patients with an undetectable viral load at the start of ETR treatment, unavailability of core data (viral load and baseline genotype) for some patients, use of (combinations of) ARVs not allowed according to the protocol and the lack of permission to use data from individual sites contributing to particular cohorts. In view of this low sample size, any week 96 data are shown for information, but are not discussed here. As three of the seven cohorts transferred analysed data, this limited any subgroup comparisons that could be made and prevented complex statistical adjustment for confounding factors being made. As this was a retrospective study, subgroup comparisons by ARV treatment could be confounded by intrinsic (i.e. reflecting the disease stage) and extrinsic (e.g. ARV cost, reimbursement and availability) factors. There was a potential for duplicate information because smaller cohorts may have contributed data to multinational cohorts, and data were provided by cohorts in a de-identified format. Upon feedback from cohorts, the potential for this overlap was considered to be < 1%, and most cohorts confirmed the lack of overlap with other cohorts. Finally, the lack of safety and DRV/r dosing data are important limitations.

Despite the limitations of this retrospective, observational study, it enabled the compilation of European data on the use of ETR with boosted PIs other than DRV/r, which also represented daily clinical practice. There was no overall difference in virological response rates between the DRV group and other PI group, for a given set of measured confounding factors. All 95% CIs around the unadjusted and adjusted differences in response rates at weeks 12 and 24 encompassed 0 for the difference in response rates (or 1 for the ORs). ETR appears to contribute to regimen activity because observed responses were higher in patients with a sensitive than an intermediate or resistant ETR WGS. Overall, the results of this observational study indicate that it might be appropriate to extrapolate the efficacy and virology results of the DUET studies to a regimen of ETR with a boosted PI other than DRV/r, although caution should be applied because of the lack of randomization and the small sample size of the other PI group.

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