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Short Communication: High Effectiveness of Etravirine in Routine Clinical Practice in Treatment-Experienced HIV Type 1-Infected Patients

José R. Santos,[1,2] Josep M. Llibre,[1,2] Pere Domingo,[2,3] Arkaitz Imaz,[2,4] Elena Ferrer,[5] Daniel Podzamczer,[5] Isabel Bravo,[1] Esteban Ribera,[2,4] Sebastià Videla,[1] and Bonaventura Clotet[1,6]

Abstract

The effectiveness of etravirine has not been thoroughly investigated in routine clinical practice, where adherence rates and the heterogeneous nature of patients differ from the clinical trial setting. We evaluated the effectiveness of rescue regimens containing etravirine and the factors associated with treatment response. Multicenter retrospective cohort of all consecutive patients was recruited in a routine clinical practice setting. Patients were taking rescue regimens containing etravirine plus an optimized background regimen. The primary endpoint was the percentage of patients with HIV-1 RNA <50 copies/ml at week 48. The secondary endpoints were those factors associated with treatment response to etravirine. Endpoints were evaluated using univariate and multivariate analysis. A total of 122 patients were included with a median viral load of 11,938 (1055–55,500) copies/ml at baseline. The most frequent drugs in the backbone were darunavir/ritonavir in 98 (80.3%) patients and raltegravir in 76 (62.3%). In the full dataset analysis, 73% (89/122; 95% CI, 64–81%) of patients responded to treatment at week 48; in the on-treatment analysis, 82% (89/109; 95% CI, 71–87%) responded. The factors associated with treatment failure to etravirine [HR (95% CI)] were baseline $CD4^+$ T cell count <200 cells/mm^3 [2.45 (1.17–5.16)] and use of raltegravir [0.47 (0.22–0.99)] and darunavir [0.45 (0.21–0.98)] as backbone drugs. Skin rash was the only adverse event directly related to etravirine and led to withdrawal in three patients (2.5%). In routine clinical practice, rescue ETR-containing regimens are well tolerated and achieve rates of virological suppression higher than those observed in its pivotal clinical trials, especially when combined with darunavir and raltegravir.

Introduction

The availability of new drugs, in both existing or novel antiretroviral classes, with expanded activity against triple-class resistant HIV-1 makes it possible to achieve sustained virologic suppression in multitreated patients in routine clinical practice. New agents have demonstrated superiority in all efficacy parameters in their pivotal salvage trials.[1–6] The combination of these drugs allows us to construct regimens with at least two—and preferably three—fully active drugs, even in very treatment-experienced individuals.[7,8] However, with the exception of the DUET-1 and DUET-2 studies,[2,3] no trials have compared the efficacy of the different combinations of these drugs to date. In the DUET studies, darunavir was combined with etravirine (ETR) in all patients, and neither raltegravir nor maraviroc was available. The efficacy of etravirine at 24 weeks rose to 66% in patients from DUET-1 and 80% from DUET-2. In both trials, patients achieved sustained virological suppression with regimens containing three or more active agents.[2,3] The safety and efficacy of ETR in combination with the remaining new antiretrovirals have not been evaluated outside the strictly controlled conditions of a clinical trial, although preliminary reports on the combination of these new drugs have shown promising results.[9–12]

We evaluated the effectiveness of rescue regimens containing ETR combined with all the available active agents in routine clinical practice. We also analyzed the relationship between the

[1]Lluita contra la SIDA, Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona, Spain.
[2]Universitat Autònoma de Barcelona, Barcelona, Spain.
[3]Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain.
[4]Service of Infectious Diseases, Hospital Universitari Vall d'Hebron, Barcelona, Spain.
[5]HIV Unit, Service of Infectious Diseases, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain.
[6]IrsiCaixa Foundation, Barcelona, Spain.

number of additional active drugs in the optimized regimen and other factors associated with the response to ETR.

Materials and Methods

We conducted a multicenter retrospective study of HIV-1-infected patients aged at least 18 years who started an antiretroviral rescue regimen containing ETR between June 2003 and November 2009. Patients were recruited at the HIV units of four acute-care university hospitals in Barcelona, Spain. Patients with virological failure (at least two successive HIV-1 plasma RNA measurements >50 copies/ml) who had started a rescue therapy were selected through a systematic search of the electronic files at each center. All patients were treatment experienced and had resistance to three antiviral classes: nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). Clinicians selected the backbone regimen according to genotyping results and treatment history, and ETR was started at doses of 200 mg orally twice daily. Demographic characteristics, treatment history, historical and current HIV-1 genotypic resistance test results, and tropism (Trofile; Monogram Biosciences, Inc., CA) were recorded. HIV-1 RNA (Roche HIV-1 RNA Ultrasensitive PCR assay; Hoffmann-La Roche, Basel, Switzerland) measurements and $CD4^+$ T cell counts were recorded at baseline and every 12 weeks thereafter.

The primary endpoint was the proportion of patients with an HIV-1 viral load <50 copies/ml at 48 weeks. Secondary endpoints included the relationship between treatment response and the number of active antiretrovirals at baseline, CDC stage, $CD4^+$ T cell count and viral load ≥100,000 copies/ml at baseline, number of previous lines of treatment, number of previous antiretrovirals, number of NNRTIs/NRTIs/PIs, previous failure or interruption with efavirenz or nevirapine, adverse events leading to discontinuation of therapy, and changes in $CD4^+$ T cell counts. Treatment failure was defined as a confirmed viral load >50 copies/ml before week 48 or early discontinuation of ETR for any reason. The number of active drugs was calculated using the HIV Drug Resistance Database, Stanford (version 6.0.8). We assigned 1, 0.5, or 0 points to drugs with scores of <15, 15–59, and ≥60 points, respectively. Enfuvirtide and raltegravir were considered active in those patients using the drugs for the first time. Maraviroc was considered active in those patients who had CCR5 tropism.

The primary endpoint was measured in all patients who started treatment (full dataset). The last observation carried forward was used if no information was available at week 48. Quantitative variables are expressed as mean (±SD) or median and interquartile range, and qualitative variables as percentages. Normally distributed variables were compared using the *t* test; nonnormally distributed variables were compared using the Wilcoxon rank sum test. The relationship between treatment response, clinical characteristics, and number of active drugs at baseline was assessed using univariate and multivariate (Cox regression) analysis. The hazard ratio and its 95% confidence interval (95% CI) were also calculated. All statistical analyses were performed using SPSS version 15.0 for Windows (SPSS, Chicago, IL). Statistical significance was set at $p < 0.05$.

Results

A total of 122 patients with virological failure started a rescue regimen containing ETR. Patients had received a median of 8 (4–10) antiretroviral regimens over a mean of 11.9 (4.2) years and had a median HIV-1 RNA of 11,938 (1055–55,500) copies/ml. When rescue therapy was started, 82 (67.2%) and 67 (54.9%) patients had experienced failure or interruption of previous regimens with nevirapine or efavirenz, respectively. Darunavir and raltegravir were the most frequent drugs in the backbone regimens, and were taken by 98 (80.3%) and 76 (62.3%) patients, respectively. Only 11 (9%) patients took maraviroc, 8 (6.6%) lopinavir/ritonavir, and 5 (4.1%) atazanavir/ritonavir. Baseline characteristics are shown in Table 1.

Of the 122 patients included in the study, 89 (73%, 95% CI: 64–81%) achieved virological suppression in the full dataset analysis and 33 (27%, 95% CI: 19–35%) experienced treatment failure at 48 weeks. Of these, 17 (51.5%) had confirmed virological failure, 11 (33.3%) were lost to follow-up, 3 (9.1%) experienced a toxicity-limiting adverse event with ETR, and 2 (6%) stopped treatment. These last two patients had achieved complete viral suppression when they voluntarily decided to discontinue. As a result, the proportion of patients who achieved treatment response at week 48 in the on-treatment analysis was 89/109 (82 %).

Factors found to predict treatment failure at 48 weeks in the univariate analysis were baseline $CD4^+$ T cell count <200 cells/mm^3 [(HR = 2.148; 95% CI, 1.029–4.483); $p = 0.042$], use of raltegravir [(HR = 0.452; 95% CI, 0.225–0.908); $p = 0.026$] and darunavir [(HR = 0.380; 95% CI, 0.184–0.783); $p = 0.009$] as backbone drugs, and time on antiretroviral treatment (risk per year) [(HR = 0.921; 95% CI, 0.851–0.998); $p = 0.043$]. In the multivariate analysis, only the baseline $CD4^+$ T cell count <200 cells/mm^3 [(HR = 2.458; 95% CI, 1.170–5.166); $p = 0.018$] and use of raltegravir [(HR = 0.459; 95% CI, 0.214–0.985); $p = 0.046$] and darunavir [(HR = 0.474; 95% CI:0.226–0.994), $p = 0.048$] were identified as predictors of treatment response. The factors not identified as predictors of treatment response in the univariate analysis were a viral load >100,000 copies/ml (HR = 1.056, 95% CI, 0.406–2.751), overall time since HIV-1 diagnosis, prior interruption or failure on regimens containing nevirapine and efavirenz, and number of previous antiretroviral regimens, number of fully active drugs (≥3 at baseline), and number of previous PIs/NRTIs/NNRTIs (Table 2).

According to the Stanford HIVDB score (version 6.0.8), ETR was fully active in 56/122 (45.9%) patients, intermediate in 49/122 (40.2%), and resistant in 8/122 (6.6%). The baseline genotyping result was not available in 9/122 (7.4%) patients.

As for the number of active antiretrovirals in the backbone regimen, 10 of the 17 patients who experienced virological failure (58.82%) had ≤2.5 active drugs and 7/17 (41.17%) had ≥3.0 active drugs. Of these, two patients who were on maraviroc, four on lopinavir/ritonavir, and two on atazanavir/ritonavir experienced virological failure despite taking ≥2.5 active drugs at baseline. In addition, according to their medical records, these six (35.29%) patients had poor adherence, which could explain their treatment failure, even though they were taking active drugs at baseline. Unfortunately, the design of the study and the heterogeneity of the medical records meant that it was not possible to correctly evaluate adherence in the remaining patients.

In addition to virological efficacy, rescue regimens containing ETR resulted in a significant overall increase in $CD4^+$

Table 1. Baseline Characteristics of HIV-1-Infected Patients Taking Rescue Regimens Containing Etravirine Plus an Optimized Antiretroviral Regimen[a]

Baseline characteristic	N = *122*
Male[b]	97 (79.5)
Age (years)[c]	44.5 (9.1)
HCV[b]	79 (64.8)
HBV[b]	7 (5.7)
CDC stage[b]	
A	24 (19.7)
B	17 (13.9)
C	54 (44.3)
Time since HIV diagnosis (years)[d]	15.5 (12.2–18.5)
Time on treatment (years)[c]	11.9 (4.2)
No. of previous antiretroviral regimens[d]	7 (4–10)
No. of previous antiretroviral drugs[c]	10.6 (3.7)
No. of previous NRTIs[d]	6 (5–7)
No. of previous NNRTIs[d]	1 (1–2)
No. of previous PIs[c]	3.5 (2.0)
Interruption/failure of previous NNRTIs[b]	
NVP	82 (67.2)
EFV	67 (54.9)
ARV at baseline[b]	
Darunavir/ritonavir	98 (80.3)
Lopinavir/ritonavir	8 (6.6)
Atazanavir/ritonavir	5 (4.1)
Saquinavir/ritonavir	1 (0.8)
Enfuvirtide	9 (7.4)
Raltegravir	76 (62.3)
Maraviroc	11 (9.0)
Tenofovir	62 (50.8)
Lamivudine	53 (43.4)
Zidovudine	10 (8.2)
Abacavir	9 (7.4)
Didanosine	8 (6.6)
Stavudine	5 (4.1)
Baseline active drugs[d]	2.5 (2–3)
≤1.5 active drugs[b]	18 (14.9)
2 active drugs[b]	21 (17.2)
2.5 active drugs[b]	39 (32)
3 active drugs[b]	19 (15.6)
≥3.5 active drugs[b]	24 (19.7)
CCR5 tropism[e] ($n = 36$)[b]	
CCR5	15 (41.6)
CXCR4 and D/M	10 (27.7)
Non-reportable	11 (30.5)
$CD4^+$ T cell count (cells/mm^3)[c]	274.4 (213.3)
Viral load (copies/ml)[d]	11,938 (1055–55,500)

[a]ARV, antiretroviral drugs; HCV, hepatitis C virus; HBV, hepatitis B virus; NRTIs, nucleoside reverse transcriptase inhibitors; NNRTIs, nonnucleoside reverse transcriptase inhibitors; PI, protease inhibitor; D/M, dual/mixed.
[b]*n* (%).
[c]Mean (standard deviation).
[d]Median (interquartile range).
[e]Measured by Trofile.

T cell count during follow-up*p* from 274 (213) cells/mm^3 at baseline to 417 (231) cells/mm^3 at week 48 ($p < 0.0001$).

There were no unexpected adverse events. Sixteen (13.11%) patients presented side effects associated with their antiretroviral treatment. Only three (2.5%) presented adverse events leading to discontinuation of therapy and the remaining 13 (10.65%) maintained their ETR-based regimens. Rash was the most frequent adverse event and was observed in eight (6.5%) patients, of whom only three were women ($p = 0.359$) and six were also using DRV in the backbone. Three of these eight patients presented a moderate diffuse rash[13] and discontinued ETR (two of them had started darunavir and ETR simultaneously at baseline), four had mild and transient ETR-related rash, and one experienced a confirmed darunavir-related rash after week 24 leading to discontinuation of darunavir, while ETR was maintained. NRTI-associated adverse events were reported in six patients (worsening of neuropathy in three, dizziness caused by emtricitabine in one, and anemia caused by zidovudine in two). Diarrhea due to boosted PI was reported in two patients.

Discussion

Rescue regimens containing ETR plus optimized antiretroviral drugs in heavily treatment-experienced individuals show higher effectiveness rates than those observed in pivotal ETR trials.[2,3,14] In our analysis, 73% of patients achieved a viral load of <50 copies/ml at 48 weeks in a restrictive full dataset analysis. This result is higher than the rates observed in the pooled DUET-1 and −2 trials, where 61% of patients receiving ETR achieved complete viral suppression.[15] This is contrary to what normally happens in treatment-naive patients, in whom the excellent response rates seen in clinical trials are difficult to match in routine clinical practice. This higher effectiveness of ETR, when prescribed as rescue treatment in clinical practice, is probably due to the availability of more active agents than were available during the initial clinical trials.

With the exception of the DUET trials, in which ETR proved to be more effective than placebo,[2,3] few studies have evaluated the efficacy and safety of ETR. ETR with raltegravir and darunavir (or other boosted PIs) has shown outstanding efficacy rates and a good safety profile in preliminary clinical trials and different expanded-access programs, achieving undetectable viral loads at 48 weeks in as many as 70% and 81% of patients after 48 weeks of treatment.[9,10,12,16] Our results are consistent with these findings, and darunavir and raltegravir were the most frequently used antiretroviral agents in the optimized baseline treatments, with high rates of treatment response and virological suppression. In addition, viral suppression has also been observed in 92% of patients in a setting with more limited therapeutic options, namely, a PI and NRTI-sparing regimen containing ETR plus maraviroc and raltegravir.[11] In our series, the number of patients taking maraviroc or other boosted PIs (not darunavir) plus ETR was too low for conclusions to be drawn about efficacy.

The pooled 48-week results from the DUET studies showed that baseline HIV-1 RNA and $CD4^+$ T cell count, adherence, number of active agents in the background regimen, and use of enfuvirtide were predictors of virological response with ETR in rescue regimens.[15] We also found a relationship between baseline $CD4^+$ T cell count <200 cells/mm^3 and treatment response at week 48, which is consistent with the fact that advanced stages of HIV infection are associated with poorer treatment response rates. The DUET trials revealed a significantly greater response in the ETR group than in the placebo group, irrespective of the number of active

Table 2. Factors Predicting Treatment Failure in HIV-1-Infected Patients Taking Rescue Regimens Containing Etravirine Plus an Optimized Antiretroviral Regimen[a]

	Treatment failure (n = *122*)			
	Yes N = *33*	*No* N = *89*	*Univariate analysis HR (95% CI)*	*Multivariate analysis HR (95% CI)*
Baseline active drugs[b]				
≤1.5 active drugs	7	11	1.86 (0.8–4.33)	1.07 (0.24–4.70)
≤2 active drugs	11	28	1.17 (0.56–2.45)	1.20 (0.29–4.96)
≤2.5 active drugs	20	58	0.83 (0.41–1.68)	0.47 (0.12–1.81)
≤3 active drugs	26	71	1.04 (0.45–2.44)	2.07 (0.45–9.48)
Viral load ≥ 100,000 copies/ml	5	14	1.05 (0.40–2.75)	1.28 (0.37–4.35)
$CD4^+$ T cell count ≤200 (cells/mm^3)	20	36	**2.14 (1.02–4.48)**	**2.45 (1.17–5.16)**
CDC stage				
A	9	15		
B	3	14		
C	19	35	1.16 (0.52–2.59)	1.10 (0.40–3.01)
Time since HIV diagnosis (years)[c]			1.0 (0.96–1.04)	0.94 (0.8–1.1)
Time on treatment (years)[c]			0.92 (0.85–0.99)	1.04 (0.84–1.29)
No. of previous antiretroviral regimens			1.0 (0.92–1.08)	0.99 (0.9–1.09)
No. of previous antiretroviral drugs			0.97 (0.87–1.07)	1.03 (0.53–1.97)
No. of previous NRTIs			0.95 (0.73–1.22)	0.83 (0.39–1.76)
No. of previous NNRTIs			1.4 (0.72–2.7)	<0.001 (<0.001–>1000)
No. of previous PIs			0.93 (0.78–1.12)	0.89 (0.43–1.86)
Interruption/failure of previous NNRTIs				
NVP	22	60	1.0 (0.46–2.18)	1.99 (0.24–1.51)
EFV	21	46	0.85 (0.39–1.85)	0.88 (0.4–1.92)
ARV at baseline				
Darunavir/ritonavir	20	78	**0.38 (0.18–0.78)**	**0.459 (0.214–0.985)**
Raltegravir	76	61	**0.45 (0.22–0.90)**	**0.47 (0.22–0.99)**

[a]ARV, antiretroviral drugs; CDC, Centers for Disease Control and Prevention; EFV, efavirenz; NRTIs, nucleoside reverse transcriptase inhibitors; NNRTIs, nonnucleoside reverse transcriptase inhibitors; NVP, nevirapine; PI, protease inhibitor; HR, hazard ratio; CI, confidence interval.
[b]Baseline genotyping result was not available in nine patients ($n = 113$).
[c]Risk per year.

background agents. However, consistent with current HIV-1 treatment guidelines, the use of an increasing number of other active antiretrovirals with ETR was associated with an increased likelihood of treatment response.[7,15,17,18]

Similarly, we also found a higher proportion of patients whose regimen had failed with ≤2.5 active drugs than with ≥3 active drugs at baseline, although we were unable to demonstrate a statistically significant difference ($p = 0.802$). The low number of patients taking ≤2.5 active drugs could have masked any existing differences, as has been observed in other salvage studies. In addition, we were unable to find a relationship between response to treatment and baseline HIV-1 RNA >100,000 copies/ml, a predictor that is universally associated with higher rates of treatment failure. In our series, the number of individuals with baseline viral load >100,000 copies/ml was very low (5/122 patients); therefore, the difference was not statistically significant. This major drawback has also been encountered in many current clinical rescue trials reporting lower median viral loads in patients whose current antiretroviral treatment has failed in recent years.[19,20] These data suggest that the number of active drugs is probably a stronger predictor of response than a higher viral load in treatment-experienced patients.

We found no relationship between prior interruption or failure with NVP or EFV and response to ETR. This is concordant with what was observed in the DUET trials.[21]

As expected, and consistent with the results of other studies,[2,3,14,15] there was a significant increase in $CD4^+$ T cell count during follow-up. The only adverse event related to the administration of ETR was rash, which occurred in 50% of patients who experienced possibly or probably drug-related side effects, although this led to discontinuation in only three patients (2.5%), while the remaining five patients presented mild and transient rash that did not require discontinuation. An association between female gender and ETR-related rash has been reported,[14] although we were not able to observe this relationship in our study, probably due to the low number of women included and the low prevalence of rash. No other unexpected side effects leading to discontinuation of ETR were observed. However, the rescue regimen was modified during follow-up, due to the side effects induced by other families of antiretrovirals: zidovudine-related anemia; peripheral neuropathy associated with zidovudine, didanosine, and abacavir; dizziness caused by emtricitabine; and gastrointestinal disorders induced by PIs.

In conclusion, in conditions of routine clinical practice, ETR-containing rescue regimens are generally well tolerated and achieve rates of virological suppression that exceed those observed in clinical trials. This is probably due to a higher number of new active drugs in the regimen. Darunavir and raltegravir are safe and very effective antiretrovirals when administered in combination with ETR. Studies that evaluate

the efficacy and safety of ETR in combination with other PIs and maraviroc are still needed.

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Author Disclosure Statement

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Address correspondence to:
José R. Santos
Fundació Lluita contra la SIDA
Hospital Universitari Germans Trias i Pujol
Ctra de Canyet, s/n
08916 Badalona, Barcelona
Spain

E-mail: jrsantos@flsida.org