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Original Article

Effectiveness of etravirine-based therapy for treatment-experienced HIV-infected patients

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Abstract

Introduction: Treatment options are limited for HIV-1-infected individuals who have received extensive previous antiretroviral therapy. ETV has shown significant clinical benefits in treatment-experienced HIV-1+ patients with antiretroviral resistance. The aim of this study was to evaluate the effectiveness of ETV plus optimized background regimen in real-life conditions in a cohort of highly HIV-1 antiretroviral-experienced patients.

Methodology: Retrospective cohort of treatment-experienced HIV-1-infected adults with virological failure who started therapy with an ETV-containing regimen. The effectiveness was evaluated using HIV-1 RNA viral load and changes in CD4+ cell count after 48 weeks of treatment.

Results: Forty-two patients ≥ 16 years of age were included; 74% were men, and the median age was 45 years (IQR 41–53). All participants had prior non-nucleoside reverse transcriptase inhibitor use (55% nevirapine, 83%, efavirenz, and 28% both). Baseline median HIV-1 RNA viral load was 15,598 copies/mL (IQR 2651–84,175) and CD4+ cell count was 276 cells/μL (IQR 155–436). After 48 weeks of treatment, 90.5% (95% CI 78–96) of patients had HIV-1 RNA viral load < 200 copies/mL and 76% (95% CI 61–86) had < 50 copies/mL. CD4+ cell counts increased from baseline to 48 weeks of treatment to a median of 407 cells/μL (IQR 242–579); $p < 0.001$. Virological outcome was associated with virological failure at baseline HIV-1 RNA viral load ≥ 100,000 copies/mL (OR 7.6; 95% CI 1.2–44.80; $p = 0.025$).

Conclusions: Our study provides clinically important evidence of the effectiveness and safety of ETV in highly antiretroviral-experienced HIV-1-infected patients.

Key words: etravirine; treatment-experienced; virologic suppression; drug resistance; HIV-1 RNA; virological outcome.

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Introduction

Current antiretroviral therapy (ART) for HIV has improved treatment durability for a substantial proportion of patients; however, for some patients, therapy fails and viral rebound occurs with progression of disease and mortality [1]. Among HIV-infected patients, 21% of treatment-experienced and 11% of treatment-naive patients experience triple-class virological failure six years after starting ART [2]. Furthermore, once patients have triple-class virological failure, treatment options are extremely limited and patients are at increased risk of mortality [3]. Thus, there is a need for new antiretroviral agents with which to construct active treatment regimens for patients infected with drug-resistant HIV strains who have experienced triple-class treatment failure [4].

Etravirine (ETV) has shown significant clinical benefits in treatment-experienced HIV type-1 (HIV-1)-infected patients with antiretroviral resistance in phase III DUET-1 and DUET-2 trials. These parallel, multicenter, randomized studies evaluated the use of ETV versus placebo, each combined with a darunavir/ritonavir (DRV/r)-containing optimized background regimen (OBR), in 1,203 patients

experiencing virological failure on ART with evidence of multiclass resistance. The pooled 96-week DUET-1 and -2 data demonstrated that 57% of patients in the ETV group achieved HIV-1 RNA < 50 copies/mL compared with 36% in the placebo group ($p < 0.001$) [4,5].

Important data regarding combination therapies, especially with DRV/r, came from the subset of DUET patients who had no ETV resistance-associated mutations (RAMs); those with as many as three DRV RAMs (a subgroup with diminished response to DRV/r) had a high 24-week response rate of 78%, the same response rate observed in patients with no DRV RAMs [6].

ETV was approved for use in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to non-nucleoside reverse transcriptase inhibitor (NNRTI) and other antiretroviral agents [7]. Several clinical trials have reported a dramatic increase in the proportion of patients safely achieving virological response despite harboring multidrug-resistant HIV-1 viruses [8-10]. Among these investigations, the ANRS 139 TRIO trial reported that 86% of patients reached HIV-1 RNA < 50 copies/mL at week 48 with a salvage regimen containing raltegravir (RAL), ETV and DRV/r, and OBR with NRTIs or enfuvirtide [9].

The present observational study in antiretroviral treatment-experienced, HIV-1-infected adults explored the efficacy of ETV plus OBR.

Methodology

Design

This study was based on a retrospective cohort of treatment-experienced HIV-1-infected adults who started therapy with an ETV-containing regimen. The first analysis end-point was an HIV-1 RNA viral load < 50 copies/mL (by reverse transcription polymerase chain reaction [RT-PCR) after patients completed 48 weeks of treatment. Secondary end-points were the evaluation of HIV-1 RNA viral load < 200 copies/mL (by RT-PCR) and an increase of CD4+ cell counts at 48 weeks of treatment.

Patients

Patients were recruited for HIV treatment from seven referral centres in four Mexican states. Patients were ≥ 16 years of age with confirmed HIV-1 infection by enzyme-linked immunosorbent assay and western blot and had virological failure and mutations detected from three classes of antiviral drugs. Patients had previous treatment with at least three classes of antiretroviral drugs including nucleos(t)ide reverse-transcriptase inhibitors (NRTIs), NNRTIs, and protease inhibitors (PIs), with mutation resistance documented for each class known by genotype.

The regimen included three to four ARV agents, according to HIV-1 resistance testing and previous antiretroviral drug experience.

Measurements

Clinical history regarding ARV regimens, CD4+ cell count, HIV-1 RNA viral load, and serum laboratory parameters at the beginning of the therapy with ETV at baseline, 24, and 48 weeks were recorded. Once provided with each patient's genotype, tropism-testing, and previous regimens, an expert committee evaluated each case to decide the better option for a salvage regimen using ETV plus an OBR, considering the previous use of ARV regimens.

Mutations were assessed by plasma HIV-1 *pol* sequences using the Stanford HIV database (HIVdb). Resistance was defined according to Stanford HIVdb (SS) ranges as follows: 0–9, susceptible; 10–14, potential low-level resistance; 15–29, low-level resistance; 30–59, intermediate resistance; and ≥ 60, high-level resistance.

The effects of salvage treatment susceptibility on HIV-1 RNA viral load suppression were analyzed using the genotypic susceptibility score (GSS) for the salvage regimen, calculated based on the drug resistance scores extracted from the Stanford HIVdb. Each antiretroviral drug was assigned a score according to the five-level Stanford HIVdb interpretation: 1.00, 0.75, 0.50, 0.25, and 0.00 for susceptible, potential low-level resistance, low-level resistance, intermediate resistance, and high-level resistance, respectively. GSS was defined as the sum of the genotypic sensitivities for all the drugs in a patient's treatment regimen. The GSS was defined as the total number of drugs (excluding ETV) in a participant's OBR antiretroviral regimen to which their HIV isolate had genotypic sensitivity, as evaluated by gene sequence and mutation analyses.

Once genotyping and tropism testing was done and the previous use of antiretroviral regimens was considered, an expert committee evaluated each case to decide the better option for a salvage regimen, namely ETV plus OBR.

The effectiveness of ETV treatment was evaluated with percentage of HIV-1 RNA viral load < 50 copies/mL after 48 weeks of treatment. Changes in CD4+ cell counts were also evaluated.

RAMs associated with ETV at baseline, RAMs associated with DRV, OBR, GSS, and the ETV

Stanford score were analyzed for potential risk factors of virological failure.

Other evaluations were changes in fasting lipids levels (total cholesterol, triglycerides) and creatinine from baseline to 48 weeks.

Statistical analysis

Baseline characteristics were analyzed for medians and interquartile ranges (IQR) for continuous variables and proportions for categorical variables. Explorative statistical methods were used to determine the efficacy end-points and changes in safety-relevant laboratory parameters. Significant changes from baseline were tested using the Wilcoxon signed-rank test.

Baseline differences between patients who reached or did not reach viral load < 50 copies/mL at week 48 were tested in a bivariate analysis, including crude odds ratios (ORs), Fisher's exact test, and the Chi-squared test. Independent risk factors associated with virological response at week 48 were identified in a multivariate logistic regression analysis that included variables from bivariate analyses. All analyses were conducted using SPSS software version 17 (SPSS Inc, Chicago, USA).

Results

Forty-two multidrug-experienced patients who started ETV-based salvage therapy between 2009 and 2013 were identified. Forty-two patients who were followed through the 48-week analyses were included. The median age of the overall cohort at ETV initiation was 45 years (IQR 41–53), and 74% of the patients were men. Centers for Disease Control Class C AIDS was found in 50% of patients, and the median years of previous ARV treatment was six (IQR 4–7); all had prior NNRTI use (55% nevirapine, 83% efavirenz, and 28% both) (Table 1).

Median CD4+ cell counts increased from 276 cells/μL (IQR 155–436 cells/μL) at baseline to 407 cells/μL after 48 weeks of treatment (IQR 242–579 cells/μL) ($p < 0.001$). Consistently, plasma HIV-1 RNA reached < 50 copies/mL in 76% of patients (95% CI 61–86) and 90.5% (95% CI 77–96) with < 200 copies/mL.

At baseline, the median HIV-1 RNA viral load was 4.19 $\log_{10}$ (IQR 3.8–4.9 $\log_{10}$). At week 24 of treatment, 88% of the patients (n = 37) had HIV-1 RNA < 200 copies/mL and 78% (n = 33) had < 50 copies/mL. After 48 weeks of treatment, 90% of patients (n = 38) had

Table 1. Baseline characteristics and optimized background regimen (n = 42).

Characteristics	Values[a]
Age, years	45 (41–53)
Male, n (%)	31 (74%)
Number of previous regimens	6 (4–7)
Years of experienced treatment	13 (10–17)
Baseline HIV-1 plasma viral load, $\log_{10}$ copies/mL	4.19 (3.42–4.92)
Baseline HIV-1 RNA >100,000 copies/mL, n (%)	10 (23.8%)
Baseline CD4+ cell count (cells/μL)	276 (155–436)
Baseline CD4+ cell count < 200 cells/μL, n (%)	14 (33.3%)
Patients with primary RAMS for ETV (%)	8 (19%)
Number of DRV RAMs	1 (0–2)
Patients with NNTRI RAMs, non-ETV RAMs	22 (52.4%)
GSS DRV	0.75 (0.5–1.0)
GSS OBR	1.5 (1.2–2.0)
TDF in regimen, n (%)	17 (40.5%)
MVC in regimen, n (%)	3 (7.1%)
ENF in regimen, n (%)	4 (9.5%)
DRV in regimen, n (%)	38 (90.5%)
RAL in regimen, n (%)	32 (76.2%)
*Stanford score for TDF	51 (30–65)
*Stanford score for DRV	15 (0–25)
*Stanford score for ETV	7.5 (0–22.5)
Creatinine (mg/dL)	0.80 (0.70–1.0)
ALT (IU/I)	28 (24–48)
Total cholesterol (mg/dL)	187 (137–206)
Triglycerides (mg/dL)	171 (136–262)

DRV: darunavir; RAL: raltegravir; TDF: tenofovir; ETV: etravirine; MVC: maraviroc; ENF: enfuvirtide; RAMs: resistance-associated mutations; GSS: genotypic susceptibility score; OBR: optimized background regimen; NNTRI: non-nucleoside reverse transcriptase inhibitor; ALT: alanine aminotransferase; *Genotypic score according to the Stanford HIVdb; [a]Values are medians (interquartile range), unless indicated otherwise.

HIV-1 RNA viral load < 200 copies/mL, and 76% (n = 32) had < 50 copies/mL (Table 2).

The most common regimens associated with ETV were DRV/r–RAL (47.6%), DRV/r–TDF (12%), and DRV/r–RAL– tenofovir disoproxil fumarate (TDF) (9.5%), with the rest at 5% or less. Thirteen (31%) of the patients who had two or more RAMs for DRV/r had < 50 copies/mL at week 48, ten had no ETV RAMS, and the other three had one ETV RAM (two with Y181C and one with L100I).

Changes in lipid laboratory parameters occurred after 24 weeks of treatment. Median total cholesterol showed no significant increase (p = 0.99) from baseline to 24 and 48 weeks. Median triglycerides showed no significant increase (p = 0.31) from baseline 171 mg/dL (136–262 mg/dL) to 180 mg/dL (140–263 mg/dL) at week 24, but the increase was significant at 48 weeks (227 mg/dL [198–293 mg/dL]; p = 0.042) (Table 2).

When the factors associated with virological outcome were evaluated, baseline HIV-1 RNA > 100,000 copies/mL was found to increase the risk of virological failure > 50 copies/mL (OR 10.5; CI 2.03–54.2; p = 0.005) and for > 200 copies/mL (OR 1.66; CI 1.00–2.7; p = 0.002).

In the logistic regression model, HIV-1 RNA 100,000 at baseline remained significant for virological failure with < 50 copies/mL and < 200 copies/mL (OR

Table 2. End-points after 24 and 48 weeks of treatment.

Outcomes	Median (IQR)			P value
	Baseline	Week 24	Week 48	24/48 weeks
CD4+ cell count, cells/μL	**276 (155–436)**	**297 (231–447)**	**407 (242–579)**	**0.016/< 0.001**
HIV-1 RNA viral load, Log_{10}	**4.19 (3.4–4.92)**	**< 1.69 (< 1.69–< 1.69)**	**< 1.69 (< 1.69–1.73)**	**< 0.0001***
Cholesterol, mg/dL	187 (137–206)	169 (152–214)	181 (154–209)	0.99/0.33
Triglycerides, mg/dL	171 (136–262)	180 (140–263)	227 (198–293)	0.51/0.042
Creatinine, mg/dL	0.8 (0.7–1.0)	0.9 (0.8–1.0)	0.92 (0.8–1.0)	0.008/0.004

*At both 24 and 48 weeks. Blood values are statistically significant.

Table 3. Bivariate and multivariate analysis of risk factors associated with virological failure (HIV-1 RNA < 200 copies/mL) at week 48 of antiretroviral treatment.

	Bivariate			Multivariate		
	OR unadjusted	95% CI	P value	OR adjusted	95% CI	P value
Risk factor						
Male	0.93	0.1–8.1	0.95			
Age > 40 years	0.80	0.07–8.7	0.85			
Duration of ART > 15 years	1.84	0.21–16.2	0.57			
Number of previous regimens ≥ 5	2.5	0.4–15.7	0.33			
Baseline HIV-1 RNA > 100,000 copies/mL	**1.66**	**1.0–2.7**	**0.002**	**11.29**	**1.5–84.2**	**0.018**
Baseline CD4+ cell count < 200 cells/μL	2.16	0.2–17.2	0.46			
ETV RAMs	5.16	0.6–44.1	0.13			
Previous use of NVP	1.23	0.15–9.7	0.84			
Previous use of EFV	0.56	0.05–6.3	0.64			
Previous use of EFV and NVP	1.2	0.13–10.4	0.86			
TDF in regimen	5.14	0.48–54.3	0.17			
MVC in regimen	0.89	0.87–0.99	0.735			
ENF in regimen	0.89	0.80–0.99	0.65			
DRV in regimen	0,25	0.02–3.3	0.29			
RAL in regimen	0.26	0.03–2.2	0.21			
GSS in OBR < 2 vs. ≥ 2	2.72	0.30–24.1	0.36			

ART: antiretroviral therapy; RAMs: resistance-associated mutations; NVP: nevirapine; EFV: efavirenz; TDF: tenofovir; DRV: darunavir; RAL: raltegravir; ETV: etravirine; MVC: maraviroc; ENF: enfuvirtide; GSS: genotypic susceptibility score; OBR: optimized background regimen; Blood values are statistically significant.

7.6; 95% CI 1.29–44.80; p = 0.025 and OR 11.29; 95% CI 1.50–84.2; p = 0.018, respectively) (Table 3).

The number of baseline ETV RAMs showed by genotype and the baseline ETV GSS were not associated with virological failure. None of the NNRTI RAMs present at baseline affected the virological response to ETV (Table 4).

The most frequent RAMs to ETV were L100I (5%), K101P (7.1%), and Y181C (7.1%). No relationship was found between the number of ETV mutations and virological failure (Table 5).

Table 5. Etravirine (ETV) resistance mutations (n = 42).

Mutation	n (%)
Y181CIV	3 (7.1%)
K101P	3 (7.1%)
L100I	2 (4.8%)
G190SA	4 (9.5%)
NNTRIs no-ETV RAMs	
K103NS	14 (33.3%)
Y188LCH	8 (19%)

NNTRIs: non-nucleoside reverse-transcriptase inhibitors; RAMs: resistance-associated mutations

Discussion

Our study provides evidence for the effectiveness and safety of ETV among ARV-experienced patients in a clinical setting. Therapy with ETV regimens was associated with high levels of HIV-1 RNA viral load suppression over 48 weeks, with 90.4% in highly treatment-experienced patients with viral load < 200 copies/mL and 76% in those with < 50 copies/mL, which appears to be independent of SS of OBR. The outcome of 76% of patients with viral load < 50 copies/mL at week 48 is superior to the outcomes of some randomized clinical trials (60%) [5] but similar to an observational study of antiretroviral treatment-experienced patients by a different PI in the OBR in which week-48 responses were 75% [10].

What was striking in this analysis was that among the subset of DUET patients who had no ETV RAMs, those with as many as three DRV RAMs, a subgroup with less response to DRV, had a high week-48 response rate of 60%, similar to the rate observed in DUET 48-week analysis [5]. These data show the potency of ETV and its high genetic barrier to resistance since it was able to produce a high response rate even in patients in whom DRV/r was not a fully active agent. However, we must take into account that it is difficult to determine which of the OBR components has a greater impact when a salvage therapy is used in highly experienced patients.

Although the response rate decreased in patients who had four or more ETV or DRV RAMs, in this study, we did not find statistical significance. Existing

Table 4. Bivariate and multivariate analyses of risk factors associated with virological failure (HIV-1 RNA < 50 copies/mL) at week 48 of antiretroviral treatment.

	Bivariate			Multivariate		
	OR unadjusted	**95% CI**	**P value**	**OR adjusted**	**95% CI**	**P value**
Risk Factor						
Male	0.70	0.17–2.8	0.61			
Age > 40 years	0.91	0.23–3.5	0.90			
Duration of ART > 15 years	1.43	0.43–4.7	0.75			
Number of previous regimens ≥ 5	1.66	0.57–4.8	0.43			
Baseline HIV-1 RNA > 100,000 copies/mL	**10.5**	**2.03–54.2**	**0.005**	**7.60**	**1.3–44.8**	**0.025**
Baseline CD4+ cell count < 200 cells/μL	**4.5**	**1.00–20.1**	**0.049**	2.16	0.37–12.3	0.384
ETV RAMs	1.04	0.17–6.2	0.96			
Previous use of NVP	1.28	0.31–5.3	0.72			
Previous use of EFV	2.07	0.21–19.6	0.52			
Previous use of EFV and NVP	2.00	0.44–8.9	0.36			
GSS in OBR < 2 vs. ≥ 2	1.13	0.2–4.6	0.86			
TDF in regimen	0.97	0.22–4.1	0.97			
ENF in regimen	0.73	0.60–0.8	0.557			
DRV in regimen	0.93	0.08–10.0	0.95			
RAL in regimen	0.65	0.13–3.2	0.600			

ART: antiretroviral therapy; RAMs: resistance-associated mutations; NVP: nevirapine; EFV: efavirenz; TDF: tenofovir; DRV: darunavir; RAL: raltegravir; ETV: etravirine; MVC: maraviroc; ENF: enfuvirtide; GSS: genotypic susceptibility score; OBR: optimized background regimen; Blood values are statistically significant.

data suggest that with several baseline DRV RAMs or an intermediate resistance (10- to 40-fold change) for DRV, it is imperative that the activity of ETV not be compromised so that the regimen does not fail [9].

If both drugs had reasonable activity, even with one or two resistance mutations, the responses would be adequate. For certain patients, the combination of ETV and DRV/r plus NRTIs may be sufficient to achieve an undetectable HIV-1 RNA viral load.

Towner *et al*. provided data about the tolerability of ETV in a real-world setting [8].

With respect to metabolic situation, we found, in our study, an increase in total triglycerides after the new regimen was started, but not in total cholesterol. Regimens in highly experienced patients often include different combinations of ARV and the variety of combinations associated with ETV could complicate the interpretation of metabolic data. However, ETV is associated with a low rate of serious adverse events (11.6%) and a very low rate of discontinuation (1.9%) as a result of adverse events [4-6]. These results confirm that an ETV-containing regimen is well tolerated in this difficult-to-treat population.

The response rates were high across the different regimen backgrounds; however, we must be cautious in attributing the response to ETV efficacy alone because of the absence of data on baseline resistance in patients with genotyping test without NNRTI pressure.

We found a direct association between baseline HIV-1 RNA ≥ 100,000 copies/mL and risk of failure in this small sample size, which emphasizes the importance of early ARV change.

This is the first multicenter cohort in Mexico to evaluate the effectiveness of ETV in highly experienced patients. However, this study has some limitations, such as its small sample size and the use of a retrospective method to enrol patients; in addition, we could not assess adherence to antiretroviral drugs in our population.

Conclusions

In summary, this study suggests that the use of ETV-based regimens for salvage therapy is an effective strategy in the clinical care setting of a developing country.

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Authors' contributions

GHG was responsible for the design of the work, drafting the work, and final approval of the version to be published. JAMM was responsible for the conception and design of the work, drafting the work, and final approval of the version to be published. JCDH was responsible for writing, data collection, review of project, and final approval of the version to be published. MCG was responsible for data collection, review of the project, and final approval of the version to be published. MIBL was responsible for writing, data collection, review of the project, and final approval of the version to be published. NNR, JECH, JLSR, and AVR were responsible for data collection, review of the project, and final approval of the version to be published. BMT was responsible for review of the project, and final approval of the version to be published. JGM was responsible for final approval of the version to be published.

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Conflict of interests: The content is solely the responsibility of the authors and does not necessarily represent the official views of the Mexican Institute of Social Security.
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