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SAFETY OF ENFUVIRTIDE (ENF) THROUGH 48 WEEKS OF THERAPY IN THE TORO TRIALS

Eron J[1], Delfraissy J-F[2], Kuritzkes D[3], Lange J[4], Stellbrink H-J[5], Cohen C[6], DeMasi R[7], Drobnes C[7], Chung J[8], Salgo M[8] for the TORO Study Team

[1]UNC, Chapel Hill, NC, USA; [2]Hôpital Bicêtre, Paris, France; [3]Brigham & Women's Hospital, Cambridge, MA, USA; [4]IATEC, Amsterdam, Netherlands; [5]University Hospital Eppendorf, Hamburg, Germany; [6]CRI, Boston, MA, USA; [7]Trimeris, Durham, NC, USA; [8]Roche, Nutley, NJ, USA

Joseph Eron MD
University of North Carolina at Chapel Hill
211A West Cameron Ave
CB 7215
Chapel Hill
NC 27599-7215
USA
Ph: +1 919 843 2722
Fax: +1 919 966 8918
E-mail: joseph_eron@unc.edu

Background

- Enfuvirtide (ENF) is the first of a novel class of antiretrovirals known as the HIV fusion inhibitors. In the Phase II program, the safety and tolerability of ENF in adults was demonstrated over 96 weeks.[1]
- 24-week analyses of the two Phase III TORO trials showed that ENF has a favorable safety profile and provides a highly significant reduction in HIV RNA and increase in CD4+ cell count in treatment-experienced, HIV-infected individuals.[2,3] Patients were randomized to either ENF (90 mg SC *BID*) plus an optimized background (OB) regimen based on treatment history and resistance testing, or to OB alone. They could switch from OB to ENF plus a new OB regimen if they experienced protocol-defined virological failure after week 8.
- Initial results from the 48-week TORO pooled database demonstrated the longer term efficacy and tolerability of ENF + OB compared to OB alone.[4] Here we present additional evaluations of pooled 48-week data (TORO 1 and TORO 2 combined) that provide further insight to the safety of enfuvirtide. Pooled 48-week efficacy analyses are reported elsewhere.[5]

Methods

- A total of 997 triple class-experienced patients were randomized, treated and had at least one follow-up safety measurement. See **Table 1** for baseline demographics.
- Safety assessments included clinical and laboratory evaluations; the clinical evaluations included an evaluation of injection site reactions (ISRs) separate from adverse events.
- Due to differential exposure to ENF + OB and OB, rates of adverse events (AEs) are reported here as number of patients with events per 100 patient-years of exposure.

Table 1. Baseline demographics

	ENF + OB (N=663)	OB (N=334)
Male (%)	89.7	89.8
Age (median, years)	41	42
Baseline HIV-1 RNA (median, $\log_{10}$ copies/mL)	5.2	5.1
Baseline CD4+ cell count (median, cells/mm^3)	89	97
Number of prior ARVs (median)	12	12
Years since initiating ARVs (mean)	7	7
Prior NRTI (median duration, years)	6.3	6.3
Prior NNRTI (median duration, years)	1.5	1.5
Prior PI (median duration, years)	3.8	4.0

Results

Patient disposition

- A total of 222 (66%) patients randomized to OB alone switched to ENF + OB (Switch) during the 48-week follow-up period.
- The discontinuation rates were similar for ENF + OB and Switch patients and higher for the OB patients **(Table 2).**

Table 2. Patient disposition and reasons for discontinuation at week 48

	ENF + OB (N=663)	OB (N=334)	
		Remain on original randomized treatment (N=112)	Switch to ENF plus revised OB (N=222)
Completed, n (%)	487 (73.5)	71 (63.4)	167 (75.2)
Discontinued, n (%)	176 (26.5)	41 (36.6)	55 (24.8)
Adverse events	59 (8.9)	12 (10.7)	14 (6.3)
ISR	29 (4.4)	0 (0)	10 (4.5)
Lab abnormalities	2 (0.3)	0 (0)	0 (0)
Deaths	3 (0.5)	1 (0.9)	1 (0.5)
Treatment failure	38 (5.7)	13 (11.6)	22 (9.9)
Other (non-safety)	45 (6.8)	15 (13.4)	8 (3.6)

ISR, injection site reaction

- Exposure to ENF + OB, Switch, Combined ENF [(ENF + OB) + Switch] and OB was 557.04, 119.59, 676.63 and 162.13 patient-years, respectively **(Table 3A)**.

Adverse events (excluding injection site reactions)

- The most commonly reported events were diarrhea (37.1 per 100 patient-years on Combined ENF vs. 73.4 on OB), nausea (26.2 vs. 50.0) and fatigue (25 vs. 37.6), all higher on OB **(Table 3A, Figure 1).**
- Other common constitutional signs/symptoms also reported at a lower frequency on Combined ENF than on OB were headache (15.8 per 100 patient-years on Combined ENF vs. 24.1 on OB), insomnia (16.6 vs. 19.7) and vomiting (15.8 vs. 26.5).
- Among the events reported more commonly on the Combined ENF arms were peripheral neuropathy (16.3 per 100 patient-years on Combined ENF vs. 13.6 on OB), weight decrease (12.1 vs. 10.5), sinusitis (9.3 vs. 6.2), appetite decrease (8.3 vs. 4.9), lymphadenopathy (7.1 vs. 1.2) and pneumonia (collapsed term, 6.7 vs. 0.6) **(Table 3A and 3B).**

Table 3A. Exposure-adjusted adverse events rates at 48 weeks, AEs ≥ 10 per 100 patient-years of exposure on ENF + OB or Switch (events higher on Combined ENF highlighted)

	ENF + OB (N=663)	Switch (N=222)	Combined ENF§ (N=885)	OB (N=334)	Risk ratio (95% CI)#
Total exposure to treatment regimen (patient-years)	557.04	119.59	676.63	162.13	
Total patients with at least one adverse event (per 100 patient-years)	644 (115.6)	199 (166.4)	843 (124.6)	303 (186.9)	0.67 (0.58, 0.76)
Adverse event	**Rates per 100 patient-years of exposure (≥10 per 100 patient-years on ENF + OB or Switch)**				
Diarrhea	210 (37.7)	41 (34.3)	251 (37.1)	119 (73.4)	0.51 (0.40, 0.63)
Nausea	151 (27.1)	26 (21.7)	177 (26.2)	81 (50.0)	0.52 (0.40, 0.69)
Fatigue	134 (24.1)	35 (29.3)	169 (25.0)	61 (37.6)	0.66 (0.49, 0.90)
Insomnia	88 (15.8)	24 (20.1)	112 (16.6)	32 (19.7)	0.84 (0.56, 1.28)
Peripheral neuropathy	**86 (15.4)**	**24 (20.1)**	**110 (16.3)**	**22 (13.6)**	**1.20 (0.75, 1.99)**
Vomiting	84 (15.1)	23 (19.2)	107 (15.8)	43 (26.5)	0.60 (0.41, 0.87)
Pyrexia	83 (14.9)	22 (18.4)	105 (15.5)	39 (24.1)	0.65 (0.44, 0.96)
Upper respiratory tract infection	80 (14.4)	17 (14.2)	97 (14.3)	31 (19.1)	0.75 (0.50, 1.16)
Depression	80 (14.4)	16 (13.4)	96 (14.2)	27 (16.7)	0.85 (0.55, 1.36)
Weight decreased	**62 (11.1)**	**20 (16.7)**	**82 (12.1)**	**17 (10.5)**	**1.16 (0.68, 2.08)**
Dermatitis	68 (12.2)	12 (10.0)	80 (11.8)	38 (23.4)	0.50 (0.34, 0.76)
Cough	64 (11.5)	13 (10.9)	77 (11.4)	23 (14.2)	0.80 (0.50, 1.34)
Oral candidiasis	52 (9.3)	17 (14.2)	69 (10.2)	22 (13.6)	0.75 (0.46, 1.28)
Nasopharyngitis	56 (10.1)	11 (9.2)	67 (9.9)	19 (11.7)	0.84 (0.50, 1.49)

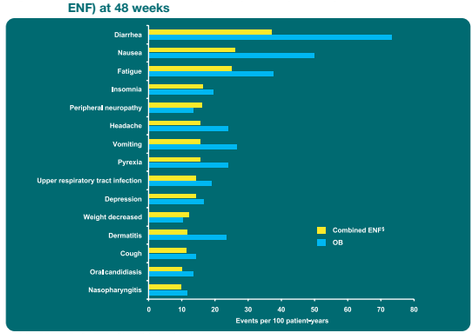
§ Combined ENF = (ENF + OB) + Switch
# Combined ENF vs. OB

Table 3B. Exposure-adjusted adverse events rate at 48 weeks, AEs 5–10 per 100 patient-years of exposure on ENF + OB or Switch, higher on Combined ENF (those higher on OB omitted)

	ENF + OB (N=663)	Switch (N=222)	Combined ENF§ (N=885)	OB (N=334)	Risk ratio (95% CI)#
Adverse event	**Rates per 100 patient-years of exposure (5 - 10 per 100 patient-years on ENF + OB or Switch)**				
Sinusitis	53 (9.5)	10 (8.4)	63 (9.3)	10 (6.2)	1.51 (0.77, 3.30)
Appetite decreased	48 (8.6)	8 (6.7)	56 (8.3)	8 (4.9)	1.68 (0.80, 4.07)
Anxiety	42 (7.5)	11 (9.2)	53 (7.8)	11 (6.8)	1.15 (0.60, 2.45)
Influenza	36 (6.5)	13 (10.9)	49 (7.2)	10 (6.2)	1.17 (0.59, 2.60)
Lymphadenopathy	33 (5.9)	15 (12.5)	48 (7.1)	2 (1.2)	5.75 (1.51, 48.85)
Skin papilloma	37 (6.6)	9 (7.5)	46 (6.8)	5 (3.1)	2.20 (0.88, 7.11)
Myalgia	39 (7.0)	6 (5.0)	45 (6.7)	9 (5.6)	1.20 (0.58, 2.79)
*Pneumonia	37 (6.6)	8 (6.7)	45 (6.7)	1 (0.6)	10.78 (1.84, 435.2)
Constipation	30 (5.4)	9 (7.5)	39 (5.8)	9 (5.6)	1.04 (0.49, 2.44)
Dry skin	28 (5.0)	3 (2.5)	31 (4.6)	7 (4.3)	1.06 (0.46, 2.86)

§ Combined ENF = (ENF + OB) + Switch
# Combined ENF vs. OB
* Collapsed term including all pneumonias

Figure 1. Exposure-adjusted AEs (≥ 10 per 100 patient-years on Combined ENF) at 48 weeks



§ Combined ENF = (ENF + OB) + Switch

Incidence of pneumonia

- Pneumonia, primarily bacterial, was observed in 45 subjects (6.7 per 100 patient-years of exposure) on Combined ENF and in 1 subject (0.6 per 100 patient-years of exposure) on OB **(Table 4)**.
- The incidence observed in Combined ENF patients was within expected ranges reported in the literature for this patient population. The incidence of pneumonia seen in the OB alone arm was lower than rates reported in the pre-HAART HIV literature (5–9 per 100 patient-years).[6–9] Data from the Adult Spectrum of Disease Study, Seattle show a lowering of the rate of pneumonia with the advent of HAART use, however, rates of bacterial pneumonia of 6–12 per 100 patient-years were reported.[10]
- It is unclear if the increased incidence of pneumonia is related to ENF use. However, because of this finding, patients with HIV infection should be carefully monitored for signs and symptoms of pneumonia, especially if they have underlying conditions that may predispose them to pneumonia. Risk factors for pneumonia included low baseline CD4+ cell count, high baseline viral load, intravenous drug use, smoking, and a prior history of lung disease.
- Of the 45 patients with pneumonia on Combined ENF, organisms were identified and reported in 13 cases, and chest X ray results available in 17 cases.
- 76% of patients reported with pneumonia had CD4+ counts < 100 cells/mm^3 at baseline; 64% had counts < 50 cells/mm^3 at baseline. At the time of their pneumonia, 62% had CD4+ counts < 200, 42% < 100, and 27% < 50 cells/mm^3.
- Besides low CD4+ count, most had 1 to 4 other risk factors including prior (33%) or current (36%) tobacco use, prior lung disease (47%) or intravenous drug abuse (13%).
- Approximately 76% of patients were on some type of prophylactic antibiotics at the time of their pneumonia and 7 days before.

Table 4. Types of pneumonia reported at 48 weeks

New collapsed term	MedDRA preferred terms	Combined ENF§	OB	Risk ratio (95% CI)#
		Rates per 100 patient-years of exposure		
Pneumonia	Pneumonia bacterial nos	6 (0.9)	-	NA
	Pneumonia Bordetella	1 (0.1)	-	NA
	Pneumonia nos	26 (3.8)	1 (0.6)	6.23 (1.02, 255.41)*
	Pneumonia Pseudomonal	2 (0.3)	-	NA
	Pneumonia Staphylococcal	1 (0.1)	-	NA
	Pneumonia Streptococcal	3 (0.4)	-	NA
	Pneumonitis nos	1 (0.1)	-	NA
	Bronchopneumonia nos	3 (0.4)	-	NA
	Pneumonia pneumococcal	2 (0.3)	-	NA
		45 (6.7)	1 (0.6)	10.78 (1.84, 435.2)*

§Combined ENF = (ENF + OB) + Switch
#Combined ENF vs. OB

Other adverse events of interest

Hypersensitivity

- Five cases of systemic hypersensitivity reaction were considered related to ENF (< 1%), and in some cases have recurred upon re-challenge.
- Reactions that may be manifestations of hypersensitivity to enfuvirtide have included individually and in combination: rash, fever, nausea and vomiting, chills, rigors, hypotension and elevated serum liver transaminases as well as one case of glomerulonephritis and one of Guillain-Barre syndrome.[11]
- Risk factors that may predict the occurrence or severity of hypersensitivity to ENF have not been identified.

Injection site reactions (ISRs)

- ISRs were reported on at least one visit for 98% of patients on ENF + OB and were severe, required analgesics or limited usual activities in 11% over the 48 weeks (1–3% at any given visit, **Figure 2).**
- The most frequent signs and symptoms of a local ISR were pain/discomfort (96%), erythema (91%), induration (90%), and nodules and cysts (80%) **(Table 5)**.
- 1.8% of patients experienced an injection site infection.
- The proportion of patients who discontinued due to ISRs was 4.4% on ENF + OB and 4.5% on Switch.

Figure 2. Incidence of injection site reactions (ISRs)* by study week and by grade, 48 weeks

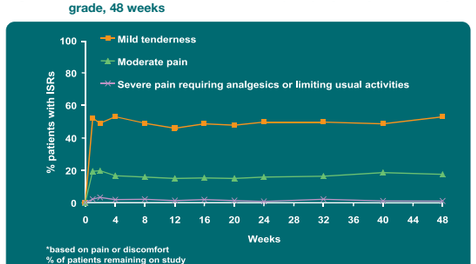


Table 5. Summary of individual signs/symptoms characterizing local ISR at 48 weeks (N=663)

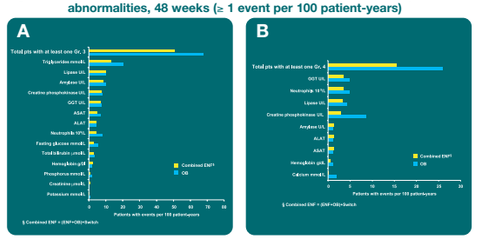
Event category	Any severity grade	% of events comprising Grade 3 reactions	% of events comprising Grade 4 reactions
Pain/Discomfort[a]	96%	11%	0%
Erythema[b]	91%	24%	11%
Induration[c]	90%	44%	19%
Nodules and Cysts[d]	80%	29%	0.2%
Pruritus[e]	65%	4%	NA
Ecchymosis[f]	52%	9%	5%

[a] Grade 3 = severe pain requiring analgesics (or narcotic analgesics for ≤ 72 hours) and/or limiting usual activities;
Grade 4 = severe pain requiring hospitalization or prolongation of hospitalization, resulting in death, or persistent or significant disability/incapacity, or life-threatening, or medically significant.
[b] Grade 3 = ≥ 25 mm but < 50mm; Grade 4 = ≥ 50 mm average diameter
[c] Grade 3 = ≥ 50 mm but < 85 mm average diameter; Grade 4 = ≥ 85 mm average diameter
[d] Grade 3 = ≥ 3 cm; Grade 4 = if draining.
[e] Grade 3 = refractory to topical treatment or requiring oral or parenteral treatment;
Grade 4= not applicable (NA).
[f] Grade 3 = > 3 cm but ≤ 5 cm; Grade 4 = > 5 cm

Laboratory abnormalities

- Aside from treatment-emergent eosinophilia (> 0.7 x 10^9 cells/L, 12.9 per 100 patient-years on Combined ENF versus 5.5 per 100 patient-years on OB), which was not associated with clinical events or hypersensitivity in either treatment group, exposure-adjusted Grade 3/Grade 4 laboratory abnormalities generally showed higher rates in the OB group **(Figure 3).**

Figure 3. Treatment emergent Grade 3 (A) and Grade 4 (B) laboratory abnormalities, 48 weeks (≥ 1 event per 100 patient-years)



Conclusions

- Results of the combined analyses of the TORO trials confirm the safety profile and tolerability of ENF over 48 weeks in this multidrug-resistant, treatment-experienced population, and show that the addition of ENF to a background regimen does not exacerbate most of the adverse events commonly associated with ARVs in the background regimen, especially gastrointestinal adverse events.
- ISRs were the most common AE associated with ENF, seen in most patients. These were generally mild to moderate, and limited treatment in < 5% of the patients.
- The rates of constitutional adverse events e.g. diarrhea, nausea, fatigue, headache, insomnia and vomiting were less on ENF.
- An increased rate of pneumonia was observed in subjects treated with ENF compared to the control arm, but the rate was within expected ranges for this patient population. Drug relationship was not established.
- Systemic hypersensitivity to ENF was reported in a small number of patients (< 1%).

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[2]Hôpital Bicétre, Paris, France;
[3]Brigham & Women's Hospital, Cambridge, MA, USA;
[4]IATEC, Amsterdam, Netherlands;
[5]University Hospital Eppendorf, Hamburg, Germany;
[6]CRI, Boston, MA, USA;
[7]Trimeris, Durham, NC;
[8]Roche, Nutley, NJ, USA