Poster 964 – 45th Annual Meeting of the Infectious Diseases Society of America (IDSA), 4–7 October 2007, San Diego, CA, USA

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IMPROVED VIROLOGIC RESPONSE IN TRIPLE-CLASS-EXPERIENCED PATIENTS WITH ENFUVIRTIDE (ENF) COMBINED WITH NEW ANTIRETROVIRAL AGENTS

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Introduction

- Triple-class-experienced patients are a challenging segment of the HIV-infected population.
- In such patients, the use of at least two fully active agents is critical to achieving undetectable viremia.[1]
- Enfuvirtide (ENF) has been shown to have a potent virologic effect when combined with novel protease inhibitors (PIs).[2,3] The unique mechanism of action of the fusion inhibitor ENF avoids cross-resistance and provides activity when other classes may fail.[4]
- New agents have recently become available, including those in new classes.[5-11]
- This analysis studies the effect of ENF when combined with new agents or new classes of agent in triple-class-experienced patients.

Methods

- A review was undertaken of recent publications and presentations of phase 2 and 3 studies in triple-class-experienced patients in which a subset received a boosted PI (PI/r), a CCR5 antagonist, an integrase inhibitor, or a non-nucleoside reverse transcriptase inhibitor (NNRTI), without (–) or with (+) ENF in the optimized background regimen (OBR).
- The objective was to collate and update available efficacy data across well-controlled studies of PI/r regimens, and new classes of agents – or + ENF in triple-class-experienced patients.
- To be considered, the PI/r must have demonstrated substantial activity in triple-class-experienced patients in the setting of PI resistance. Tipranavir/r (TPV/r) and darunavir/r (DRV/r) were included.
- Results from subgroups in 11 controlled studies were selected:
  - RESIST 1 & 2: TPV/r + OBR, – or + ENF[2]
  - POWER 1 & 2: DRV/r + OBR, – or + naïve ENF[3]
  - MOTIVATE 1 & 2: maraviroc + OBR, – ENF (reused or evidence of resistance) or + naïve ENF[5,6]
  - BENCHMRK 1 & 2: raltegravir + OBR, – or + naïve ENF[7,8]
  - Study 0105: elvitegravir/r + OBR, – or + naïve ENF[9]
  - DUET 1 & 2: etravirine + OBR, – ENF (reused or not used) or + naïve ENF.[10,11]
- Baseline information included demographics and disease characteristics. Where possible, 48-week virologic responses were abstracted, or the most recent available data used. In the case of etravirine only 24-week data are currently available; for raltegravir and elvitegravir the 16-week data are used.

Results

- In all studies, ENF was used at the discretion of the investigators and so it was not possible to demonstrate comparability between ENF and non-ENF populations.
- Overall baseline characteristics for each study, where available, are shown in **Table 1**. The majority of patients were white (65–83%) men (84–94%), aged in their forties. Median/mean baseline HIV RNA levels ranged from 4.6 to 4.9 $\log_{10}$ copies/mL and median/mean CD4 counts at baseline ranged from 99 to 196 cells/mm^3, indicating different severity of disease populations in the various studies. 'ENF use' relates to those patients receiving ENF and the experimental agent.
- Key virologic response data are shown in **Table 2** and **Figures 1–6**.
- Across studies and endpoints, the addition of ENF to the OBR was associated with an increase in virologic response rates.

Table 2. Summary of Virologic Responses Without (–) and With (+) Enfuvirtide (ENF).

Study: week		Patients (%) with HIV RNA <50 copies/mL	Patients (%) with HIV RNA <400 copies/mL	Patients (%) with HIV RNA ≥1 $\log_{10}$ reduction
RESIST 1 & 2 (TPV/r): week 48[2]	– ENF	21	27	Mean change –0.98
	+ ENF	**28**	**43**	**Mean change –1.67**
POWER 1 & 2 (DRV/r): week 48[3]	– ENF	44	N/A	56
	+ naïve ENF	**58**	**N/A**	**81**
MOTIVATE 1 & 2 (maraviroc BID): week 48[6]	– ENF[a]	32	43	N/A
	+ naïve ENF[b]	**61**	**71**	**N/A**
BENCHMRK 1 & 2 (raltegravir): week 16[7,8]	– ENF[c]	60	74	N/A
	+ naïve ENF[c]	**72**	**91**	**N/A**
Study 0105 (elvitegravir/r): week 16[9]	– ENF[d]	44	N/A	N/A
	+ naïve ENF	**74**	**N/A**	**N/A**
DUET 1 (etravirine): week 24[10]	– ENF[e]	55	70	N/A
	+ naïve ENF	**59**	**84**	**N/A**
DUET 2 (etravirine): week 24[11]	– ENF[e]	58	71	N/A
	+ naïve ENF	**73**	**86**	**N/A**

[a]ENF reused or evidence of resistance.
[b]ENF/LPV/r first use in OBR.
[c]Raltegravir + OBR – DRV.
[d]Elvitegravir with ≥2 active NRTIs in the OBR.
[e]ENF reused or not used (combined).
BID, twice daily; DRV, darunavir; N/A, data not available; NRTI, nucleoside reverse transcriptase inhibitor; OBR, optimized background regimen; r, ritonavir; TPV, tipranavir.

Boosted Protease Inhibitors

RESIST 1 & 2 (TPV/r)[2]

- RESIST 1 & 2 compared TPV/r with an investigator-selected comparator PI/r, in combination with an OBR.
- In the combined analysis, the use of ENF in the OBR was associated with a greater proportion of treatment responders, defined as two consecutive viral load measurements >1 $\log_{10}$ copies/mL below baseline, than in the group that did not use ENF (**Figure 1**).
- The addition of ENF was associated with a significantly greater proportion of participants achieving HIV RNA <50 copies/mL ($P = 0.0093$), compared with participants who did not receive ENF (**Figure 1**).

POWER 1 & 2 (DRV/r)[3]

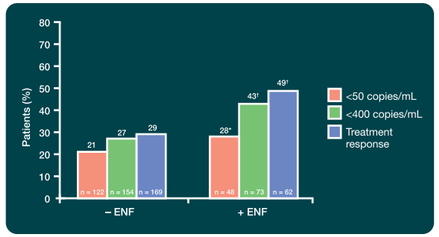
- Data from two randomized, phase 3 studies (POWER 1 & 2) using DRV/r or control PIs, plus OBR, were combined in a subgroup analysis.[3]
- Use of ENF in the OBR was stratified but not randomized.
- The naïve use of ENF was associated with a greater proportion of participants achieving HIV RNA <50 copies/mL, compared with participants who did not receive ENF (**Figure 2**).

Table 1. Overall Study Data and Enfuvirtide (ENF) Use.

	RESIST (TPV/r)[2]	POWER 1 & 2 (DRV/r)[3]	MOTIVATE 1 & 2 (maraviroc)[5,6]	BENCHMRK 1 & 2 (raltegravir)[7]	Study 0105 (elvitegravir/r)[9]	DUET 1 (etravirine)[10]	DUET 2 (etravirine)[11]
Patients on experimental treatment (n)	746 (TPV/r)	513 (DRV/r)	840 (maraviroc)	462 (raltegravir)	73 (elvitegravir)	304 (etravirine)	295 (etravirine)
ENF use (ENF + experimental agent) (n)	169	60	350	93 (naïve ENF)	19 (naïve ENF)	121	152
Baseline demographics							
Male (%)	84	89	88	88	N/A	87	94
Median age (years)	43	44 (mean)	46 (mean)	45	N/A	45	46
White (%)	77	81	83	65	N/A	65	77
Baseline factors							
Median HIV RNA ($\log_{10}$ copies/mL)	4.73 (mean)	4.6 (mean)	4.9 (mean)	4.8	4.7 (mean)	4.8	4.8
Median CD4 (cells/mm^3)	196 (mean)	153	193 (mean)	119	157 (mean)	99	100

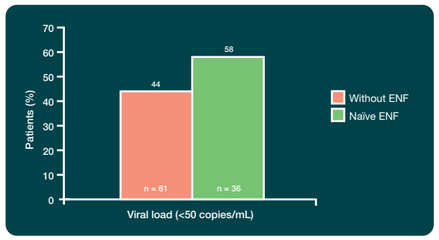
DRV, darunavir; N/A, data not available; r, ritonavir; TPV, tipranavir.

Figure 1. RESIST 1 & 2: Virologic Responses at Week 48 in Participants Receiving Boosted Tipranavir without (–) or with (+) Enfuvirtide (ENF).[2]



*$P = 0.0093$; †$P < 0.0001$ (ENF use compared with non-use).

Figure 2. POWER 1 & 2: Virologic Response at Week 48 in Participants Receiving Boosted Darunavir without or with Naïve Enfuvirtide (ENF).[3]



CCR5 Antagonist

MOTIVATE 1 & 2 (Maraviroc)[5,6]

- Randomized, double-blind, placebo-controlled, phase 3 studies of the CCR5 antagonist maraviroc with OBR in antiretroviral (ARV)-experienced patients.
- The use of ENF was included as a stratification factor before randomization.
- Data were pooled to determine efficacy of maraviroc-based therapy when ≥1 active agent, including ENF, was used in the OBR.
- A higher proportion of participants receiving ENF achieved undetectable levels of HIV-1 RNA when naïve to ENF or without evidence of resistance to ENF (**Figure 3**).

Integrase Inhibitors

BENCHMRK 1 & 2 (Raltegravir)[7,8]

- BENCHMRK 1 & 2 were randomized, double-blind studies comparing the integrase inhibitor raltegravir 400 mg twice daily vs placebo in triple-class-experienced patients.
- When ENF and DRV/r were not in the OBR, 74% of participants had HIV RNA <400 copies/mL at Week 16.
- When ENF was included in the OBR, 72% of participants who were naïve to ENF use had HIV RNA <50 copies/mL at Week 16 (**Figure 4**).

Study 0105 (Elvitegravir)[9]

- Study 0105 was a randomized, partially blinded, active-controlled, phase 2b study comparing boosted elvitegravir with boosted comparator PIs (CPI/r) in treatment-experienced patients. Both agents were combined with ≥1 active agent in an OBR (NRTIs – or + ENF).
- The primary endpoint was the time-weighted average change in HIV RNA (DAVG) at week 24.
- The best virologic response was observed in participants using ENF for the first time in combination with elvitegravir/r.

Figure 3. MOTIVATE 1 & 2: Virologic Response at Week 48 in Participants Receiving Maraviroc Twice Daily without or with Naïve Enfuvirtide (ENF).[6]

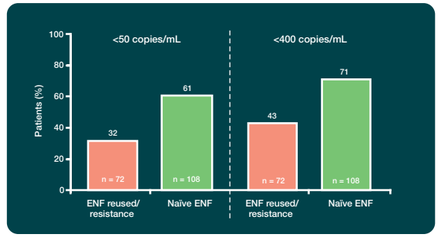
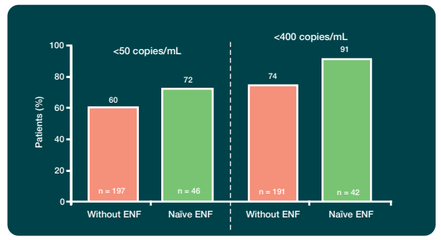
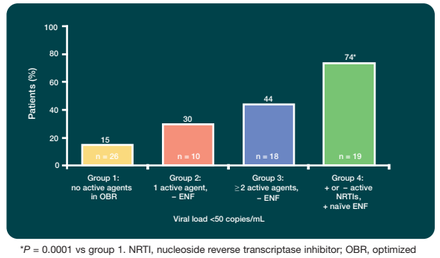


Figure 4. BENCHMRK 1 & 2: Virologic Response at Week 16 in Participants Receiving Raltegravir without or with Naïve Enfuvirtide (ENF) in a Regimen without Darunavir.[7]



- Mean overall DAVG for participants receiving elvitegravir/r with first-time use of ENF (n = 19) was –2.6 $\log_{10}$ copies/mL compared with –1.6 $\log_{10}$ copies/mL for CPI/r subjects (n = 11) with new ENF ($P = 0.03$).
- At week 16, a viral load <50 copies/mL was achieved in 74% of participants with naïve use of ENF, + or – active NRTIs, compared with 44% of those receiving ≥2 active NRTIs without naïve use of ENF (**Figure 5**).

Figure 5. Study 0105: Virologic Response at Week 16 in Participants Receiving Boosted Elvitegravir, without (–) or with (+) Naïve Enfuvirtide (ENF).[9]



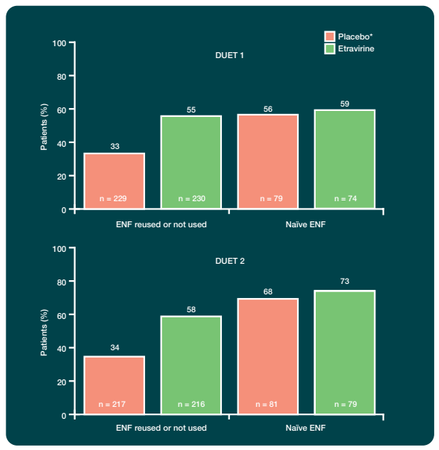
*$P = 0.0001$ vs group 1. NRTI, nucleoside reverse transcriptase inhibitor; OBR, optimized background regimen.

New NNRTI

DUET 1 & 2 (Etravirine)[10,11]

- DUET 1 & 2 were randomized, placebo-controlled, double-blind phase 3 trials using etravirine (TMC125) in combination with an OBR of DRV/r and optimized NRTIs, with optional ENF.
- In both the etravirine and placebo groups in DUET 1 & 2, the naïve use of ENF was associated with a greater proportion of participants achieving HIV RNA <50 copies/mL, compared with participants who reused or did not use ENF (**Figure 6**).

Figure 6. DUET 1 & 2: Virologic Response (<50 copies/mL) at Week 24 in Participants Receiving Etravirine with Enfuvirtide (ENF) Reused or not Used, or with Naïve Use of ENF.[10,11]



*Investigator-selected background therapy, plus DRV/r.

Discussion

- In all studies, ENF was used at the investigators' discretion and was stratified rather than randomized. As a result of the lack of detailed baseline characteristics it is not possible to determine comparability of ENF and non-ENF groups. Bias may have affected patient selection in the trials.
- The viral load suppression with both boosted PIs was consistently improved when ENF, particularly when used naïvely, was added to an active boosted PI.
- A higher proportion of triple-class-experienced patients consistently achieved a virologic response with naïve use of ENF in combination with one or two newer active ARVs, such as maraviroc, raltegravir, elvitegravir, or etravirine, than in patients not receiving or reusing ENF.

Conclusion

- In triple-class-experienced patients, the likelihood of achieving undetectable HIV RNA levels (<50 copies/mL) is increased when patients include ENF in their regimen in addition to another active agent, irrespective of class.

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