Prevalence of Minority Resistant Variants to ETR, DRV and RAL at Baseline in the ANRS 139 TRIO Trial

POSTER #605

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BACKGROUND

- ANRS 139 TRIO trial was a 96-week phase II non-comparative trial that evaluated the raltegravir (RAL), etravirine (ETR) and darunavir/r (DRV) combination in highly-experienced patients harboring multi-resistant viruses.
- 87% of the patients of the trial also received a nucleoside reverse transcriptase inhibitors (NRTI)- and/or enfuvirtide-containing optimized background therapy.
- A high level of virological suppression was observed with 93% of patients with viral load <50 copies/mL at W48, and 88% at W96. (Yazdanpanah et al., Clin Inf Dis 2009; Fagard et al., J AIDS 2012)
- **The aim of this sub-study was to assess the prevalence of minority resistant variants (MRV) at baseline in ANRS 139 TRIO trial.**

PATIENTS AND METHODS

- Baseline bulk sequencing of reverse transcriptase (RT), protease (PR), and integrase (IN) regions was performed and sequences were interpreted according to the Agence Nationale de Recherche sur le SIDA et les hépatites virales (ANRS) procedures described at www.hivfrenchresistance.org.
- MRV were assessed using both MiSeq and 454 technologies, with an arbitrarily assigned limit of detection of 1%.

RESULTS

- Among the 103 patients enrolled in the ANRS 139 TRIO trial, baseline median viral load was 4.2 $\log_{10}$ copies/mL (IQR = 3.6-4.6).
- Baseline bulk sequencing showed a median number of major protease inhibitors, non NRTI (NNRTI) and NRTI resistance-associated mutations (RAM) of 4, 1, and 6, respectively.
- However, all patients exhibited viruses susceptible to all three drugs of the regimen: etravirine, darunavir, raltegravir.
- Deep sequencing was available in 73, 46 and 87 samples for RT, PR and IN regions, respectively.

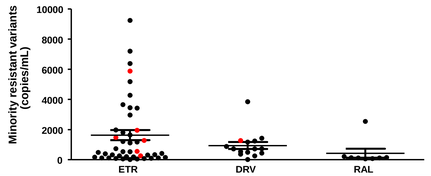
PREVALENCE OF MINORITY RESISTANT VARIANTS AT BASELINE IN THE ANRS 139 TRIO TRIAL

Minority resistant variants at baseline in the ANRS 139 TRIO trial

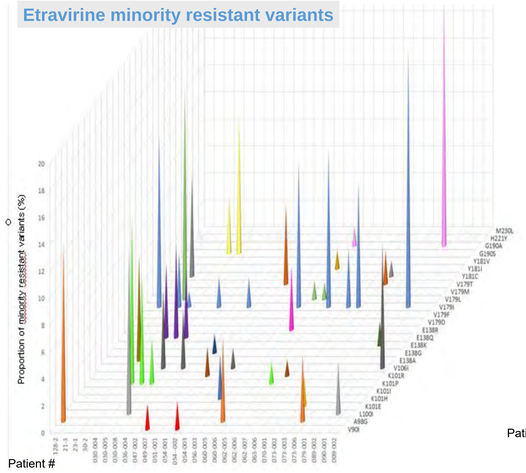
	ETR	DRV	RAL
n	73	46	87
Number of patients with MRV, n (%)	29 (40%)	13 (28%)	6 (7%)
Proportion of MRV, median (IQR)	4.4% (2.0-8.3)	9.8% (4.9-13.8)	1.7% (1.5-5.6)
Number of MRV, copies/mL, median (IQR)	531 (170-1,969)	722 (437-1,242)	127 (85-196)

Resistant viral load at baseline in the ANRS 139 TRIO trial

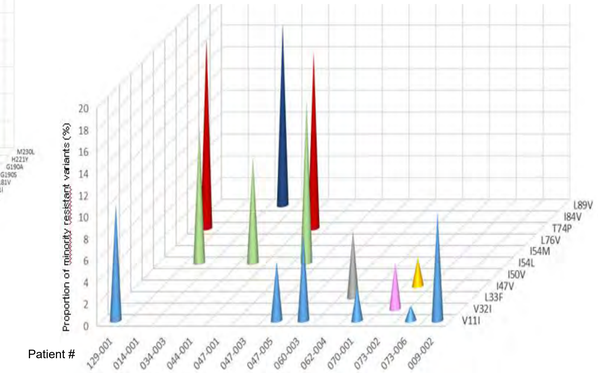
Among patients exhibiting MRV at baseline we calculated MRV copy number based on percentage of MRV by ultra-deep sequencing and the plasma viral load.



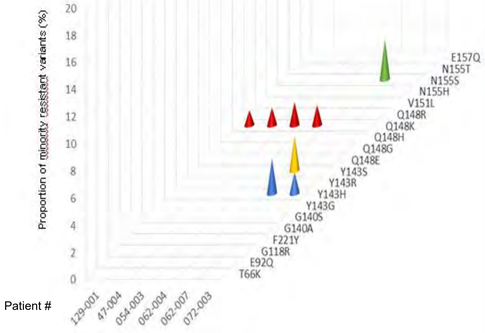
Etravirine minority resistant variants



Darunavir minority resistant variants

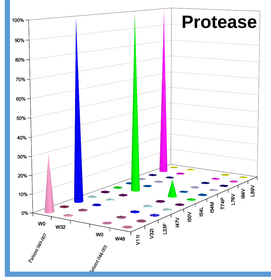


Raltegravir minority resistant variants

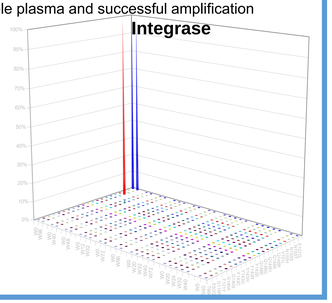


EVOLUTION OF MINORITY RESISTANT VARIANTS BETWEEN BASELINE AND VIROLOGICAL FAILURE

- During ANRS 139 TRIO trial follow-up ,until W96, 19 patients exhibited virological failure: 12 before W48, and 7 between W48 and W96.
- Median plasma viremia at time of virological failure was 97 copies/mL (IQR = 60-288).
- Ultra-deep sequencing was performed at time of virological failure in samples with available plasma and successful amplification



Reverse Transcriptase



ASSOCIATION BETWEEN MINORITY RESISTANT VARIANTS AND VIROLOGICAL RESPONSE

- Prevalence of baseline ETR/DRV/RAL MRV according to the virological outcome is depicted in the table below.

	ETR (n = 73)		DRV (n = 46)		RAL (n = 87)	
	Virological failure (n = 13)	Virological success (n = 60)	Virological failure (n = 9)	Virological success (n = 37)	Virological failure (n = 16)	Virological success (n = 71)
MRV +	6 (46%)	23 (28%)	1 (11%)	12 (32%)	0 (0%)	6 (8%)
MRV -	7 (54%)	37 (62%)	8 (89%)	25 (68%)	16 (100%)	65 (92%)

CONCLUSIONS

- **In these highly pre-treated patients, but naïve to integrase inhibitors, minority resistant variants to ETR, DRV, and RAL were detected in 40%, 28% and 7% of patients.**
- **The frequency of patients with baseline minority resistant variants was not higher in patients experiencing virological failure when compared to those in success.**
- **Further analysis of this dataset should help determine what role, if any, the level of detection of minority resistant variants can play in resistance assessments.**