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Prevalence of genotypic and phenotypic susceptibility to etravirine in US samples received for routine resistance testing

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MOPDB105

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Abstract

Background

In the Phase III DUET trials of the NNRTI etravirine (ETR; TMC125), 77.0% and 74.1% of ETR-treated patients with a Tibotec susceptible ETR weighted genotypic score (WGS) ≤2 or an Antivirogram[®] fold-change (FC) ≤3 at baseline, respectively, achieved <50 HIV RNA copies/mL at Week 48. The prevalence of ETR susceptibility was investigated in clinical samples referred for routine resistance testing using Monogram Biosciences (MGR) ETR WGS and PhenoSense® assay.

Methods

Fourteen thousand, nine hundred and forty samples submitted to MGR for routine resistance testing from June 2008 to June 2009 were analysed. Samples were defined as NNRTI-resistant if they carried at least one of the following mutations: A98G, L100I, K101E, K101P, K103N, K103S, V106A, V106I, Y181x, Y188x, G190x, P225x, F227x, M230L and P236L, where x represents any amino acid substitution. MGR's ETR WGS consisting of 30 mutations¹ was used to define viral susceptibility to ETR, with a genotypic score ≤3 denoting full susceptibility. Phenotypic susceptibility to ETR was determined using 2.9 and 10 as low and high clinical cut-offs (CCOs), respectively. The impact of K103N on genotypic susceptibility to ETR was also investigated.

Results

Among 5,482 (36.7%) NNRTI-resistant samples, 67.2% were classified as genotypically susceptible and 76.4% as phenotypically susceptible (median FC 0.9) to ETR, with 10.7% having FC ≥10. Using Tibotec's WGS, 67.5% of NNRTI-resistant samples were ETRsusceptible (WGS ≤2). Among NNRTI-susceptible samples (n=9,458), 99.5% had ETR FC <2.9 (median 0.8) and 0.5% had FC ≥2.9 and <10 (median 3.5). In a subset of NNRTI-resistant samples (n=4,514), with (n=3,598) or without (n=1,884) the K103N mutation, the proportion of ETR genotypically-susceptible samples (average median FC 1) was 76.9% and 48.6%, respectively.

Conclusions

Using different interpretation systems, most samples received for routine resistance testing with or without evidence of NNRTI resistance were susceptible to ETR. Among NNRTI-resistant samples, more were ETRsusceptible phenotypically than genotypically, and more were ETR-susceptible among those with K103N.

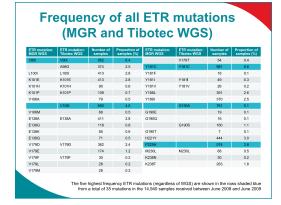
Background and objectives

- ETR is a second-generation NNRTI with activity against efavirenz (EFV)- and nevirapine (NVP)-resistant clinical isolates
- In the Phase III DUET trials, 77.0% and 74.1% of ETRtreated patients with a Tibotec susceptible ETR WGS ≤2, or an Antivirogram[®] FC ≤3 at baseline, respectively, achieved <50 HIV RNA copies/mL at Week 482

ETR WGS scoring

- The ETR WGS was calculated by cumulative addition of the follow mutations when present in the viral isolate, using the individual weightings in parentheses
- MGR WGS:1 V90I (1), L100I (4), K101E (2), K101H (1) K101P (4), V106A (2), V106M (1), E138A (3), E138G (3), E138K (2), E138G (1), V179D (1), V179E (3), V179F (1), V179L (2), V179M (1), V187C (4), Y181F (1), V181 (4), V181V (4), V188L (2), V189I (1), G190E (1), G190Q (3). G190T (1), H221Y (1), P225H (1), M230L (3), K238N (3) and K238T (1)
- Tibotec WGS⁻² V90/(1) A98G (1) / 100/(2.5) K101E (1) K101H (1), K101P (2.5), V106I (1.5), E138A (1.5), V179D (1 V179F (1.5), V179T (1), Y181C (2.5), Y181I (3), Y181V (3), G190A (1), G190S (1.5) and M230L (2.5)

Italics indicate mutations used in both scor



MGR ETR WGS in samples	
with NNRTI resistance	

Among the 5,482 (36.7%) samples with resistance to EFV or NVP ied as genotypically susceptible to ETR using the MGR ETR WGS¹

MGR ETR WGS ¹	Number of samples	Proportion of samples (%)	
0	2,142	39.1)
1	787	14.4	67.2%
2	510	9.3	susceptible to ETR
3	243	4.4	J
4	735	13.4	í.
5	502	9.2	
≥6	563	10.3	
	N=5,482		

Tibotec ETR WGS in samples with NNRTI resistance

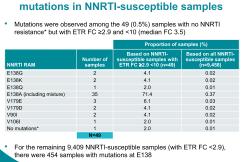
• Using Tibotec's WGS,² 67.5% of samples with resistance to EFV or NVP were classified as genotypically susceptible to ETR (WGS ≤2)

Tibotec ETR WGS ¹	Number of samples	Proportion of samples (%)	
0	2,469	45.0	67.5%
0.5–1	857	15.6	> susceptible
1.5-2	372	6.8	to ETR
2.5-3.5	1,335	24.4	-
4-4.5	216	3.9	
5-5.5	132	2.4	
≥6	101	1.8	
	N=5,482		
		ceptibility; scores ≥2.5 denote redu	

MGR ETR FC in samples with NNRTI resistance

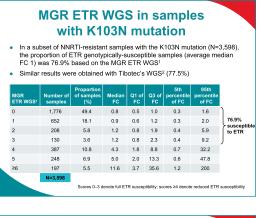
Among 5.482 samples with resistance to EFV or NVP. 76.4% were classified as phenotypically susceptible to ETR (median FC 0.9) based on the MGR ETR FC, with 10.7% having FC \geq 10

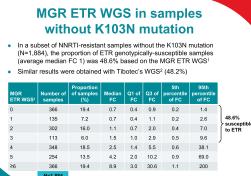
MGR ETR FC	Number of samples	Proportion of samples (%)	Median FC	Q1 of FC	Q3 of FC	5th percentile of FC	95th percentile of FC
<2.9	4,187	76.4	0.9	0.6	1.2	0.3	2.2
≥2.9, <10	709	12.9	5.0	3.7	6.9	3.0	9.2
≥10	586	10.7	24.5	14.7	54.3	10.7	200



Frequency of reverse transcriptase

ns at E138

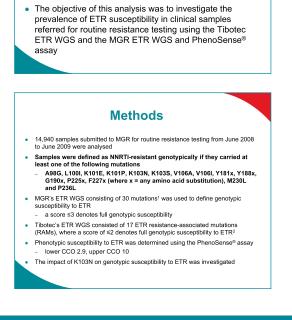




Conclusions

- Using different interpretation systems, most samples received for resistance testing, with or without evidence of NNRTI resistance, were susceptible to ETR
- The five most frequent ETR mutations in this dataset (regardless of WGS) were Y181C, V90I, G190A, V106I and P225H
- Among NNRTI-resistant samples, more were ETRsusceptible phenotypically than genotypically, and more were ETR-susceptible among those with K103N
- Among NNRTI-susceptible samples, modest increases in ETR FC above the lower CCO were associated primarily with the presence of mutations at position 138
- however, the majority of samples with an E138A mutation were phenotypically susceptible to ETR

References





MGR ETR FC in **NNRTI-susceptible samples**

Among 9,458 NNRTI-susceptible* samples, 99.5% had ETR FC <2.9 (median FC 0.8) and 0.5% had FC \geq 2.9 and <10 (median FC 3.5) based on the MGR ETR FC

MGR ETR FC	Number of samples	Proportion of samples (%)	Median FC	Q1 of FC	Q3 of FC	5th percentile of FC	95th percentile of FC	
<2.9	9,409	99.5	0.8	0.6	1.0	0.3	1.5	<pre> 99.5% suscept to ETR </pre>
≥2.9, <10	49	0.5	3.5	3.1	4.3	3.0	6.5	UEIK
≥10	0	N/A	N/A	N/A	N/A	N/A	N/A	
	N=9,458							

The frequency of reverse transo described on the following slide

FC <2.9 denotes full ETR susceptibility; FC ≥2.9 denotes reduced ETR susceptibility "Without any of the mutations defined on the Methods slide; N/A = not applicable

1. Benhamida J, et al. Antivir Ther 2008;13(Suppl. 3). A142. 2. Vingerhoets J, et al. AIDS 2010;24:503-14.

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