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

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 mutations[1] 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 ETR-susceptible (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 ETR-susceptible 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 ETR-treated patients with a Tibotec susceptible ETR WGS ≤2, or an Antivirogram® FC ≤3 at baseline, respectively, achieved <50 HIV RNA copies/mL at Week 48[2]
- The objective of this analysis was to investigate the prevalence of ETR susceptibility in clinical samples referred for routine resistance testing using the Tibotec ETR WGS and the MGR ETR WGS and PhenoSense® assay

## Methods

- 14,940 samples submitted to MGR for routine resistance testing from June 2008 to June 2009 were analysed
- **Samples were defined as NNRTI-resistant genotypically if they carried at least one of the following mutations**
  - **A98G, L100I, K101E, K101P, K103N, K103S, V106A, V106I, Y181x, Y188x, G190x, P225x, F227x (where x = any amino acid substitution), M230L and P236L**
- MGR's ETR WGS consisting of 30 mutations[1] was used to define genotypic susceptibility to ETR
  - a score ≤3 denotes full genotypic susceptibility
- Tibotec's ETR WGS consisted of 17 ETR resistance-associated mutations (RAMs), where a score of ≤2 denotes full genotypic susceptibility to ETR[2]
- Phenotypic susceptibility to ETR was determined using the PhenoSense® assay
  - lower CCO 2.9, upper CCO 10
- The impact of K103N on genotypic susceptibility to ETR was investigated

## ETR WGS scoring

- The ETR WGS was calculated by cumulative addition of the following 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), E138Q (1), *V179D* (1), V179E (3), *V179F* (1), V179L (2), V179M (1), *Y181C* (4), Y181F (1), *Y181I* (4), *Y181V* (4), Y188L (2), V189I (1), G190E (1), G190Q (3), G190T (1), H221Y (1), P225H (1), *M230L* (3), K238N (3) and K238T (1)
  - **Tibotec WGS:**[2] *V90I* (1), A98G (1), *L100I* (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 scoring systems

## Frequency of all ETR mutations (MGR and Tibotec WGS)

| ETR mutation: MGR WGS | ETR mutation: Tibotec WGS | Number of samples | Proportion of samples (%) | ETR mutation: MGR WGS | ETR mutation: Tibotec WGS | Number of samples | Proportion of samples (%) |
|---|---|---|---|---|---|---|---|
| V90I | V90I | 952 | 6.4 | | V179T | 54 | 0.4 |
| | A98G | 374 | 2.5 | Y181C | Y181C | 981 | 6.6 |
| L100I | L100I | 413 | 2.8 | Y181F | | 18 | 0.1 |
| K101E | K101E | 413 | 2.8 | Y181I | Y181I | 49 | 0.3 |
| K101H | K101H | 90 | 0.6 | Y181V | Y181V | 26 | 0.2 |
| K101P | K101P | 109 | 0.7 | Y188L | | 391 | 2.6 |
| V106A | | 79 | 0.5 | Y189I | | 370 | 2.5 |
| | V106I | 600 | 4.0 | | G190A | 761 | 5.1 |
| V106M | | 68 | 0.5 | G190E | | 19 | 0.1 |
| E138A | E138A | 411 | 2.8 | G190Q | | 16 | 0.1 |
| E138G | | 118 | 0.8 | | G190S | 160 | 1.1 |
| E138K | | 85 | 0.6 | G190T | | 7 | 0.1 |
| E138Q | | 71 | 0.5 | H221Y | | 444 | 3.0 |
| V179D | V179D | 362 | 2.4 | P225H | | 574 | 3.8 |
| V179E | | 174 | 1.2 | M230L | M230L | 68 | 0.5 |
| V179F | V179F | 30 | 0.2 | K238N | | 30 | 0.2 |
| V179L | | 28 | 0.2 | K238T | | 263 | 1.8 |
| V179M | | 28 | 0.2 | | | | |

The five highest frequency ETR mutations (regardless of WGS) are shown in the rows shaded blue from a total of 35 mutations in the 14,940 samples received between June 2008 and June 2009

## MGR ETR WGS in samples with NNRTI resistance

- Among the 5,482 (36.7%) samples with resistance to EFV or NVP, 67.2% were classified as genotypically susceptible to ETR using the MGR ETR WGS[1]

| MGR ETR WGS[1] | Number of samples | Proportion of samples (%) |
|---|---|---|
| 0 | 2,142 | 39.1 |
| 1 | 787 | 14.4 |
| 2 | 510 | 9.3 |
| 3 | 243 | 4.4 |
| 4 | 735 | 13.4 |
| 5 | 502 | 9.2 |
| ≥6 | 563 | 10.3 |
| | N=5,482 | |

67.2% susceptible to ETR

Scores 0–3 denote full ETR susceptibility; scores ≥4 denote reduced ETR susceptibility

## 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 |
| 0.5–1 | 857 | 15.6 |
| 1.5–2 | 372 | 6.8 |
| 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 | |

67.5% susceptible to ETR

Scores 0–2 denote full ETR susceptibility; scores ≥2.5 denote reduced ETR susceptibility

## 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 ≥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 |
| | N=5,482 | | | | | | |

76.4% susceptible to ETR

FC <2.9 denotes full ETR susceptibility; FC ≥2.9 denotes reduced ETR susceptibility; Q = quartile

## 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 ≥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 |
| ≥2.9, <10 | 49 | **0.5** | 3.5 | 3.1 | 4.3 | 3.0 | 6.5 |
| ≥10 | 0 | N/A | N/A | N/A | N/A | N/A | N/A |
| | N=9,458 | | | | | | |

99.5% susceptible to ETR

- The frequency of reverse transcriptase mutations in these subgroups is 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

## Frequency of reverse transcriptase mutations in NNRTI-susceptible samples

- Mutations were observed among the 49 (0.5%) samples with no NNRTI resistance* but with ETR FC ≥2.9 and <10 (median FC 3.5)

| NNRTI RAM | Number of samples | Proportion of samples (%): Based on NNRTI-susceptible samples with ETR FC ≥2.9 <10 (n=49) | Proportion of samples (%): Based on all NNRTI-susceptible samples (n=9,458) |
|---|---|---|---|
| E138G | 2 | 4.1 | 0.02 |
| E138K | 2 | 4.1 | 0.02 |
| E138Q | 1 | 2.0 | 0.01 |
| E138A (including mixture) | 35 | 71.4 | 0.37 |
| V179E | 3 | 6.1 | 0.03 |
| V179D | 2 | 4.1 | 0.02 |
| V90I | 2 | 4.1 | 0.02 |
| V106I | 1 | 2.0 | 0.01 |
| No mutations* | 1 | 2.0 | 0.01 |
| | N=49 | | |

- For the remaining 9,409 NNRTI-susceptible samples (with ETR FC <2.9), there were 454 samples with mutations at E138

*Without any of the mutations defined on the Methods slide

## MGR ETR WGS in samples with K103N mutation

- In a subset of NNRTI-resistant samples with the K103N mutation (N=3,598), the proportion of ETR genotypically-susceptible samples (average median FC 1) was 76.9% based on the MGR ETR WGS[1]
- Similar results were obtained with Tibotec's WGS[2] (77.5%)

| MGR ETR WGS[1] | Number of samples | Proportion of samples (%) | Median FC | Q1 of FC | Q3 of FC | 5th percentile of FC | 95th percentile of FC |
|---|---|---|---|---|---|---|---|
| 0 | 1,776 | 49.4 | 0.8 | 0.5 | 1.0 | 0.3 | 1.6 |
| 1 | 652 | 18.1 | 0.9 | 0.6 | 1.2 | 0.3 | 2.0 |
| 2 | 208 | 5.8 | 1.2 | 0.8 | 1.9 | 0.4 | 5.9 |
| 3 | 130 | 3.6 | 1.2 | 0.8 | 2.3 | 0.4 | 9.2 |
| 4 | 387 | 10.8 | 4.3 | 1.8 | 8.8 | 0.7 | 32.2 |
| 5 | 248 | 6.9 | 5.0 | 2.0 | 13.3 | 0.6 | 47.8 |
| ≥6 | 197 | 5.5 | 11.6 | 3.7 | 35.6 | 1.2 | 200 |
| | N=3,598 | | | | | | |

76.9% susceptible to ETR

Scores 0–3 denote full ETR susceptibility; scores ≥4 denote reduced ETR susceptibility

## MGR ETR WGS in samples without K103N mutation

- In a subset of NNRTI-resistant samples without the K103N mutation (N=1,884), the proportion of ETR genotypically-susceptible samples (average median FC 1) was 48.6% based on the MGR ETR WGS[1]
- Similar results were obtained with Tibotec's WGS[2] (48.2%)

| MGR ETR WGS[1] | Number of samples | Proportion of samples (%) | Median FC | Q1 of FC | Q3 of FC | 5th percentile of FC | 95th percentile of FC |
|---|---|---|---|---|---|---|---|
| 0 | 366 | 19.4 | 0.7 | 0.4 | 0.9 | 0.2 | 1.4 |
| 1 | 135 | 7.2 | 0.7 | 0.4 | 1.1 | 0.2 | 2.6 |
| 2 | 302 | 16.0 | 1.1 | 0.7 | 2.0 | 0.4 | 7.0 |
| 3 | 113 | 6.0 | 1.5 | 1.0 | 2.9 | 0.5 | 9.6 |
| 4 | 348 | 18.5 | 2.5 | 1.4 | 5.5 | 0.6 | 38.1 |
| 5 | 254 | 13.5 | 4.2 | 2.0 | 10.2 | 0.9 | 69.0 |
| ≥6 | 366 | 19.4 | 8.9 | 3.0 | 30.6 | 1.1 | 200 |
| | N=1,884 | | | | | | |

48.6% susceptible to ETR

Scores 0–3 denote full ETR susceptibility; scores ≥4 denote reduced ETR susceptibility

## 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 ETR-susceptible 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

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

## Acknowledgements and disclosures

- The authors would like to express their gratitude to
  – the patients and their families
  – the investigators
  – the study centre staff
  – Virco
  – Tibotec clinical trial staff
  – Tibotec clinical virology, Biometrics
  – Monogram Biosciences
- GP and JW are full-time employees of Tibotec Inc; JV and LT are full-time employees of Tibotec BVBA; EC and MH are full-time employees of Monogram Biosciences
- Editorial support was provided by Gardiner-Caldwell Communications; this support was funded by Tibotec

Presented at the XVIII International AIDS Conference, Vienna, Austria, 18–23 July 2010.

This poster is available on-line at www.tibotec.com