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Introduction

- Patients with multi-drug resistant virus face limited protease inhibitor (PI) treatment options.
- Darunavir (DRV) and tipranavir (TPV) are active against highly PI-resistant strains but have not been directly compared in clinical studies.
- The more frequent side effects and drug-drug interactions associated with tipranavir can limit its use in PI-resistant patients, and the correct setting for its use is not well-defined.
- Over 20 genotypic interpretations systems (GIS) exist, but few independent datasets have been used to compare their performances for these new generation PIs.
- For drugs for which limited clinical data is available, the phenotype may provide a more reliable measure of drug activity.

Results

Frequency of Mutations by Protease Position (%)

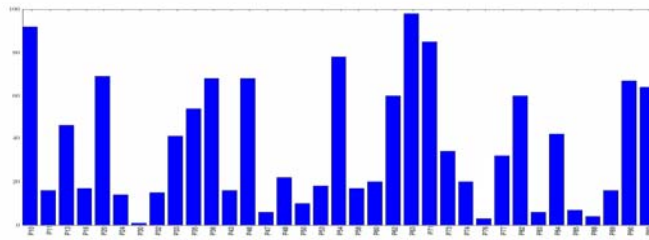


Figure 1: Susceptibility of Isolates to DRV and TPV (n=100)*

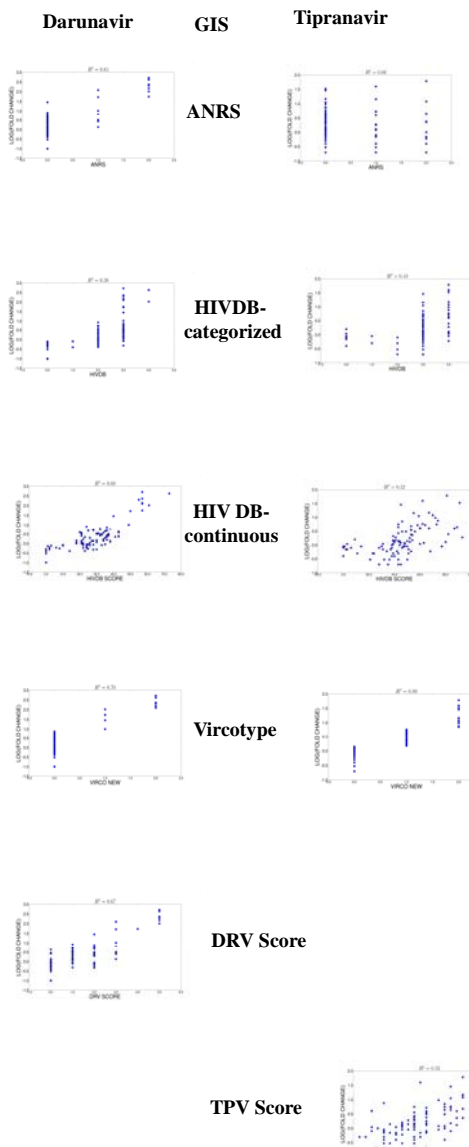
	DRV Susceptible	DRV Intermediate	DRV Resistant
TPV Susceptible	67	2	3
TPV Intermediate	16	0	4
TPV Resistant	6	0	2

*DRV CCO1=10; DRV CCO2=106.9
TPV CCO1=1.5; TPV CCO2=7

Methods & Materials

- All genotypic resistance tests in Québec are performed centrally.
- Since 2005, the interpretation of the genotype is provided by the Vircotype.
- The virtual phenotype, or Vircotype, uses available genotype-phenotype pairs within the company's database to predict the phenotype based on the patient's genotype.
- In Québec, per protocol, a phenotype was performed on isolates predicted to be resistant to all PIs other than DRV and TPV on the Vircotype.
- Isolates from 2005-2008 for which the genotype, Vircotype, and phenotype were available were included in this analysis.
- We defined the clinical cutoffs (CCO) of DRV and TPV according to recent published literature (DRV CCO1=10; DRV CCO2=106.9; TPV CCO=1.5; TPV CCO2=7).
- ANRS was categorized into 0=susceptible, 1=intermediate, and 2=resistant.
- Stanford HIV Database (HIVdb) was categorized into 0=susceptible, 1=potential low-level resistance, 2=low-level resistance, 3=intermediate resistance, and 4=high-level resistance. We also evaluated HIVdb using the numeric score produced by the website.
- Vircotype was categorized into 0=susceptible, 1=diminished response, and 2=resistant.
- The Darunavir Score used the 11 mutations originally identified in the POWER studies.
- The weighted tipranavir score used the 16 mutations identified from the RESIST studies.
- We plotted each GIS versus the log₁₀ of the phenotypic fold change (to improve the fit) and compared their predictive ability with an R-squared calculation.
- We performed forward stepwise multivariate logistic regression with AIC (Akaike Information Criterion) to predict isolates with increased susceptibility to DRV vs. TPV (and TPV vs.DRV) based on the CCO for each drug.
- Bootstrap analyses with 2,500 replications was performed to confirm our multivariate modeling. We list the mutations that appeared in at least 25% of the models.

Correlation between GIS and log₁₀ of phenotype



Mutations with Improved DRV vs. TPV Susceptibility

Mutation	Mean Odds Ratio	% of Models	Mean Rank in Models
82T	1.6	86%	2.5
84V	1.5	97%	1.9
74P	1.4	35%	4.8
60E	1.3	46%	3.4
35D	1.2	72%	3.7
10F	0.74	82%	3.3
32I	0.73	45%	4.4

Presence of 82T, 84V, and lack of 10F predicts OR=2.8 for improved DRV susceptibility.

Mutations with Improved TPV vs. DRV Susceptibility

Mutation	Mean Odds Ratio	% of Models	Mean Rank in Models
54L	2.0	99%	1.5
47V	1.7	88%	2.3
32I	1.4	94%	2.3
50V	1.2	47%	3.7
74P	0.80	49%	4.1

Presence of 54L, 47V, and 32I predicts OR=4.4 for improved TPV susceptibility.

Conclusions

- In this independent clinical dataset comprised of patients with highly resistant to PIs, resistance to DRV and TPV was rare.
- All GIS performed reasonably well in predicting darunavir susceptibility (R²=0.38-0.70).
- The Vircotype was unique in its ability to predict tipranavir susceptibility (R²=0.80 vs. 0.00, 0.18, 0.32 and 0.33 for the other scores).
- Stanford HIVdb performed substantially better when the continuous score was used rather than the categorized score.
- In our dataset, the presence of 84V, 82T, or lack of 10F favored darunavir over tipranavir in multivariate analysis.
- The presence of 54L, 32I, or 47V favored tipranavir over darunavir.
- In particular, an isolate with 54L, 47V, and 32I was substantially more likely to be susceptible to TPV (OR=4.4) and their presence, especially in combination, may identify a patient population that may benefit from TPV over DRV.