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Clinically Relevant Phenotypic Resistance and Cross Resistance to Tipranavir among Recent Routine Clinical Isolates

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Background

- Tipranavir (TPV), a non-peptidic inhibitor of HIV-1 protease, has recently been approved for use in combination therapy for highly treatment-experienced patients or those resistant to multiple protease inhibitors.
- Evaluation of the clinical impact of viral resistance in such populations is a complex and evolving process.

Methods

- Based on >6,000 clinical isolates with both drug susceptibility phenotypes (Antivirogram®) and viral genotypes, a multiple linear regression model (VirtualPhenotype-LM, VPT-LM) was developed to predict TPV fold change in IC_{50} (FC) from the viral genotype (virco®TYPE HIV-1 4.0.00).
- Using data from RESIST 1 and 2, a separate linear regression model was developed to predict 8-week change in viral load on regimens containing ritonavir-boosted TPV (TPV/r). 495 and 250 TPV/r containing regimens were used to define and validate two clinical cut-offs (CCO) corresponding to predicted TPV FC values associated with a 20% or 80% loss of the TPV/r response predicted for subjects infected with wild type strains.
- Predicted protease inhibitor FC values for >50,000 clinical isolates submitted for routine resistance analysis in 2004-5 were used to assess current resistance and cross-resistance to TPV.

Results

Figure 1. A Linear Regression Model (Virtual phenotype-LM, VPT-LM) was developed to predict TPV drugs suseceptibility from the viral genotype based on >6,000 viral genotypes with TPV phenotypes in Virco's databases

VPT-LM Selects 87 Protease Gene Mutations and Pairs of Mutations as Significant in Predicting TPV FC

10F & 47V	22V & 84V	34Q & 84V	**36L**	46L & 82T	**53L**	54V	**74S**
10F & 82A	**24I & 82A**	35D & 36I	36L & 58E	47V & 54M	54A & **55R**	54V & **70E**	**76V**
10F & 84V	**24I** & 82T	35D & 54A	36L & 83D	47V & 54V	54A & 84V	54V & 74P	**82A** & 84V
10V	**30N**	35D & 54V	**36L & 95F**	47V & 83D	**54L**	54V & 84V	**82C**
10V & 33F	**30N & 74S**	35D & 58E	**38W**	47V & 84V	**54L & 82A**	58E & 84V	82L
10V & **88D**	33F	**35D & 73T**	**41K**	**48A & 71V**	54M	**60E**	82T
13V & 69K	33F & **82A**	35G & **71V**	**41T**	**48M & 53L**	54M & **74S**	**66F**	84V
13V & **71V**	33I & 36I	**35N** & 84V	**43T**	**48V**	54M & **82A**	69K	**85V**
13V & **82S**	**33M**	36I & 47V	43T & 82T	**48V** & 54V	**54S**	**71V & 73T**	**88D**
13V & 84V	**33V**	36I & **54T**	46L & **53L**	**50L**	**54S** & 82T	**71V & 95F**	**90M**
20R	33V & 84V	36I & 84V	46L & **71V**	**50V**	54V	74P & **82A**	

Decrease in FC ← → Increase in FC

VPT-LM Provides an Accurate Assessment of TPV FC

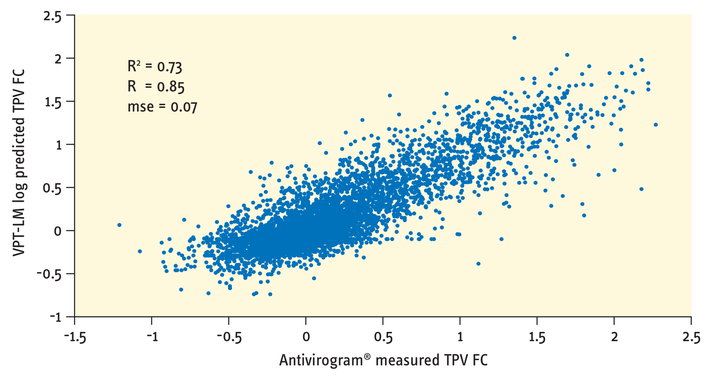


Figure 2. VPT-LM predicted FC values and clinical outcome data from the RESIST1 and RESIST2 studies were used to define and validate TPV/r clinical cut-offs (CCO) for the virco®TYPE HIV-1 assay (v4.0.00)

Defining virco®TYPE HIV-1 Clinical Cut-offs for Boosted Tipranavir

1 Gather Resistance, Treatment, and Outcome Data for Patients Using TPV/r in a Combination Regimen

709 TPV/r containing regimens from Resist 1 & 2

- 461 — Dataset for CCO Development
- 248 — Unseen Dataset for CCO Validation

The Patient Population Studied to Define TPV/r CCO Took Fewer Active Drugs in the Background Regimen than Other Drugs for which virco®TYPE CCOs have been Defined

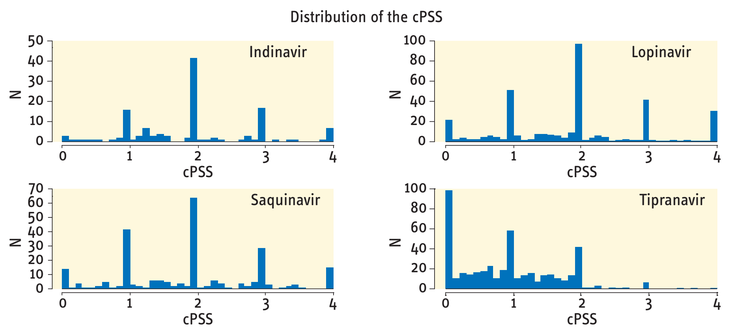


Figure 3. The linear regression model developed to predict 8 week viral load response considered 4 baseline characteristics

2 Develop a Linear Regression Model Predicting Viral Load Response as a Function of Baseline Characteristics

- Outcome modeled: 8 week change from baseline viral load
  - 15% of patients were BQL at week 8
- Baseline characteristics:

		Median	IQR
Log baseline viral load		4.79	4.32 - 5.26
cPSS of background regimen	0	45%	
	1	42%	
	2	11%	
	>2	2%	
TPV FC	<CCO1	46%	
	between CCOs	49%	
	>CCO2	6%	
Use of T20		22%	

Illustrations of Response Model Predictions for Patients with Specific Baseline Characteristics

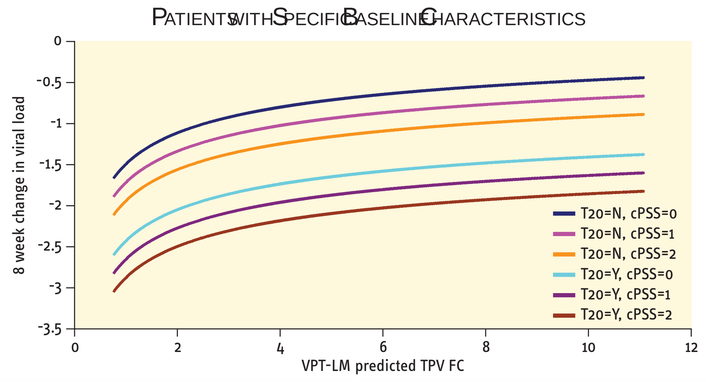
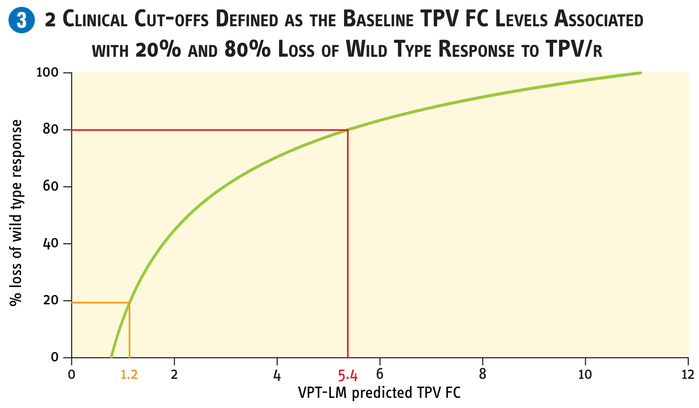
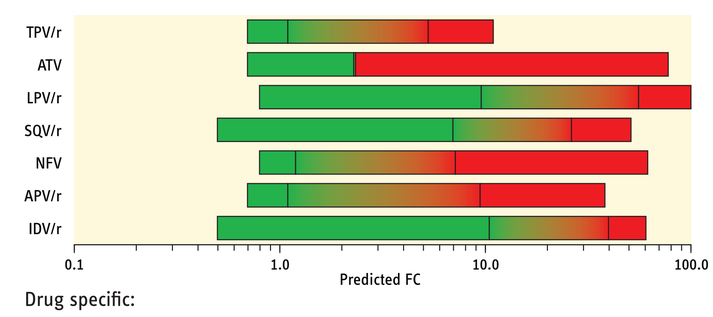


Figure 4. Two CCO were defined as the baseline TPV FC associated with 20% and 80% loss of wild type response to TPV/r

3 2 Clinical Cut-offs Defined as the Baseline TPV FC Levels Associated with 20% and 80% Loss of Wild Type Response to TPV/r



virco®TYPE HIV-1 CCO for Protease Inhibitors

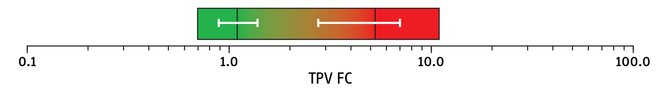


Drug specific:

- Dynamic range of resistance observed in clinical isolates
- Clinical Cut-offs

Figure 5. Validation of Clinical Cut-offs

1 Assess Variability of CCO through Bootstrap Analysis (1000 iterations)

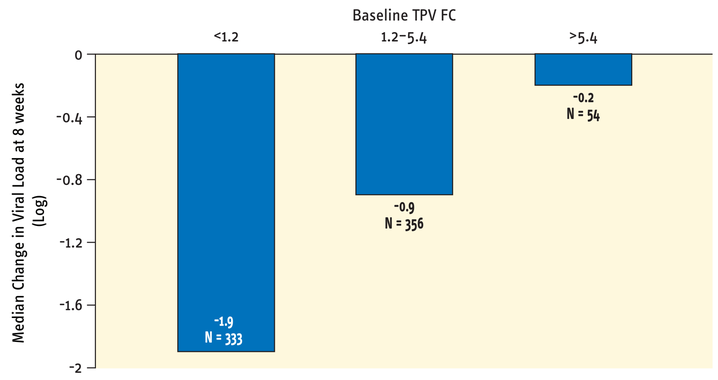


2 Test Association of Baseline TPV Susceptibility with Response

	Odds ratio for response (≥1 log viral load reduction at 8 weeks)	
	Development Dataset (N=461)	Unseen validation dataset (N= 248)
BCO (1.6)	3.4	3.5
CCO (1.2 / 5.4)	6.9	7.9

Figure 6. What do the virco®TYPE HIV-1 CCOs for TPV/r mean?

A In the RESIST Study Population



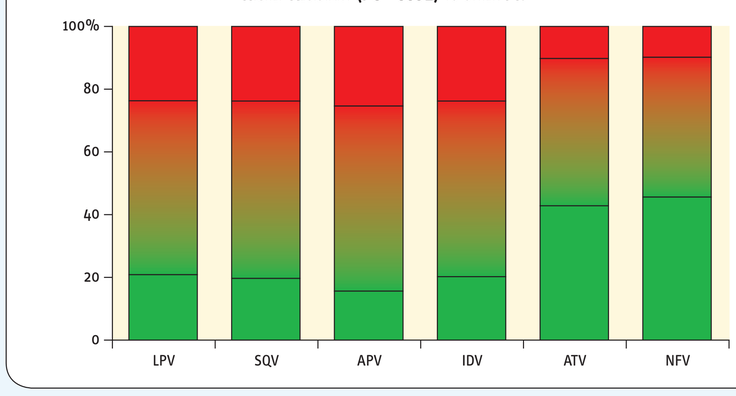
B Among Clinical Isolates in General

- Analysis of >50,000 clinical isolates submitted for routine resistance analysis in 2004-5
- FC for protease inhibitors predicted by virco®TYPE HIV-1 4.0 (VPT-LM based predictions) from the viral genotype
- PI resistance assessment based on virco®TYPE HIV-1 CCOs when available

PI Resistance and Cross Resistance Among Recent Samples Submitted for Routine Resistance Testing

Protease Inhibitor	TPV/r	LPV/r	SQV/r	APV/r	IDV/r	NFV	ATV
CCO1	1.2	9.7	7.1	1.2	10.6	1.3	–
CCO2	5.4	56	27	9.6	40	7.3	–
BCO	–	–	–	–	–	–	2.0
FC>CCO1	7.7%	8.7%	7.0%	12%	7.9%	29%	–
FC>CCO2	1.3%	4.0%	3.5%	4.3%	3.0%	13.1%	–
FC>BCO	–	–	–	–	–	–	12.7%

Cross Resistance to Tipranavir/r among Isolates Highly Resistant (FC >CCO2) to other PIs



Conclusions

- virco®TYPE HIV-1 resistance analysis based on linear regression modeling integrates complex interactions among multiple protease gene mutations to provide a quantitative prediction of TPV drug susceptibility
- virco®TYPE HIV-1 clinical cut-offs for ritonavir boosted tipranavir of 1.2 FC and 5.4 FC have been defined and validated on unseen data
  - *Since the highly treatment experienced population used to define these CCO was specifically selected, it is unknown whether these values are applicable across the entire spectrum of antiretroviral treatment experience*
- Most clinical isolates with clinically relevant resistance to older PIs retain at least partial susceptibility to TPV/r with 16% to 46% <CCO1 for TPV/r.

Acknowledgements

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