



# CREST

## A Randomised comparison of two resistance test platforms: genotype and VirtualPhenotype™

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### BACKGROUND

HIV infected patients with an HIV RNA viral load >2000 copies/mL, currently taking antiretroviral (ARV) therapy, who were willing to change ARV regimen were eligible to participate in this study. Patients were randomised 1:1 to receive either a genotype or a genotype and VirtualPhenotype™. Genotypes were performed at nine laboratories, using different platforms, and were all reported using a standardised algorithm. Resistance results were made available to investigators within 28 days of the randomisation visit.

### Objective 1

- To evaluate the impact/difference of genotypic and VirtualPhenotypic™ resistance testing on antiretroviral (ARV) prescribing.

### Method

Prior to randomisation the investigators were required to provide the next, planned ARV therapy for the patient based on their clinical judgement alone. This was then compared to the actual regimen prescribed following receipt of the resistance results at the baseline visit. Tests of significance were made using a chi-square test.

### Objective 2

- To compare concordance with the two different methods of resistance testing.

### Method

The assays were compared on the basis of concordance/discordance between resistance reported for each antiretroviral (ARV) therapy. Comparisons were made between 'sensitive', 'intermediate resistance' or 'resistance' reported by each resistance method. A second analysis was performed using the output of a second generation VirtualPhenotype™ assay that employs drug specific biological cut-offs to determine drug resistance.

### Statistical Methods

Differences between the genotype and VirtualPhenotype results were summarised using a numerical score. Differences were scored as follows and tested using McNemar's test:

Genotype	VirtualPhenotype	Score
AZT - sensitive	AZT-resistant	2
AZT - sensitive	AZT - intermediate resistance	1
AZT-resistant	AZT - intermediate resistance	-1

## RESULTS

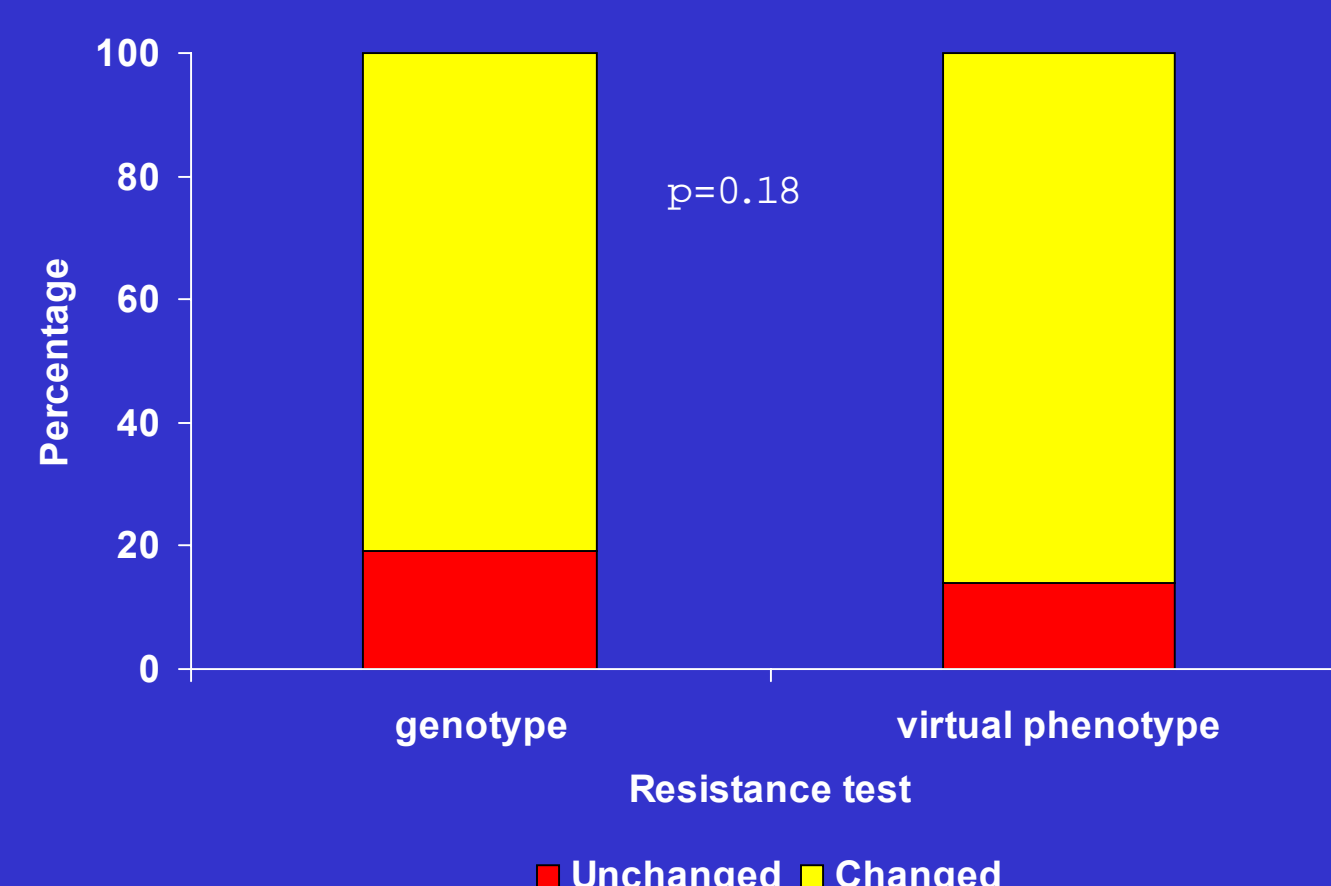
### Patient Disposition

- 338 patients were randomised in the CREST study.
- 330 patients completed their baseline visit following randomisation and were included in this analysis.
- 168 were randomised to Genotype only
- 162 were randomised to Genotype & VirtualPhenotype™

### Baseline Data

	Genotype	VirtualPhenotype™
N	168	162
% male	96	94
Risk factor MSM	89	87
Mean CD4+ cell count (cells/μL)	338	337
Mean plasma HIV RNA (copies/mL)	71,594	69,363
Prior AIDS (%)	35	33
Median prior number of ARV drugs	8	8
Median duration of ARV treatment (years)	5.8	5.5

Comparison of planned and actual regimens



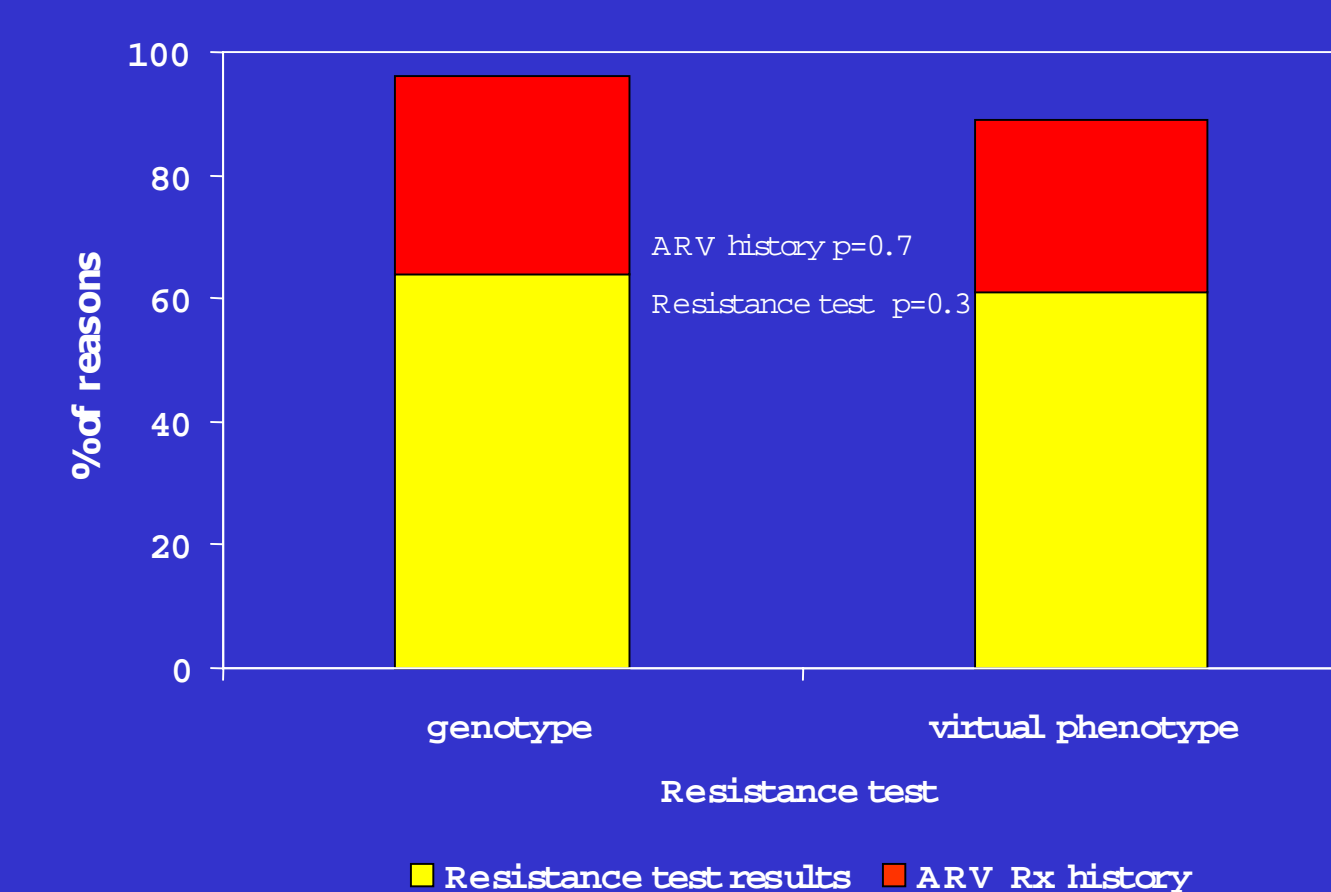
Overall comparison of genotype and VirtualPhenotype™

		P
Median (range) number of drugs resistant on virtual phenotype but not resistant on genotype	0 (0-4)	
Median (range) number of drugs resistant on genotype but not resistant on virtual phenotype	1 (0-7)	
Median total (range) score difference between genotype and virtual phenotype reports	-4 (-14-5)	<0.001

Overall comparison of genotype and second generation VirtualPhenotype™

		P
Median (range) number of drugs resistant on virtual phenotype but not resistant on genotype	1 (0-7)	
Median (range) number of drugs resistant on genotype but not resistant on virtual phenotype	0 (0-5)	
Median total (range) score difference between genotype and virtual phenotype reports	-1 (-10-12)	0.0012

Comparison of the reasons cited by Investigators as most important for selecting ARV regimen

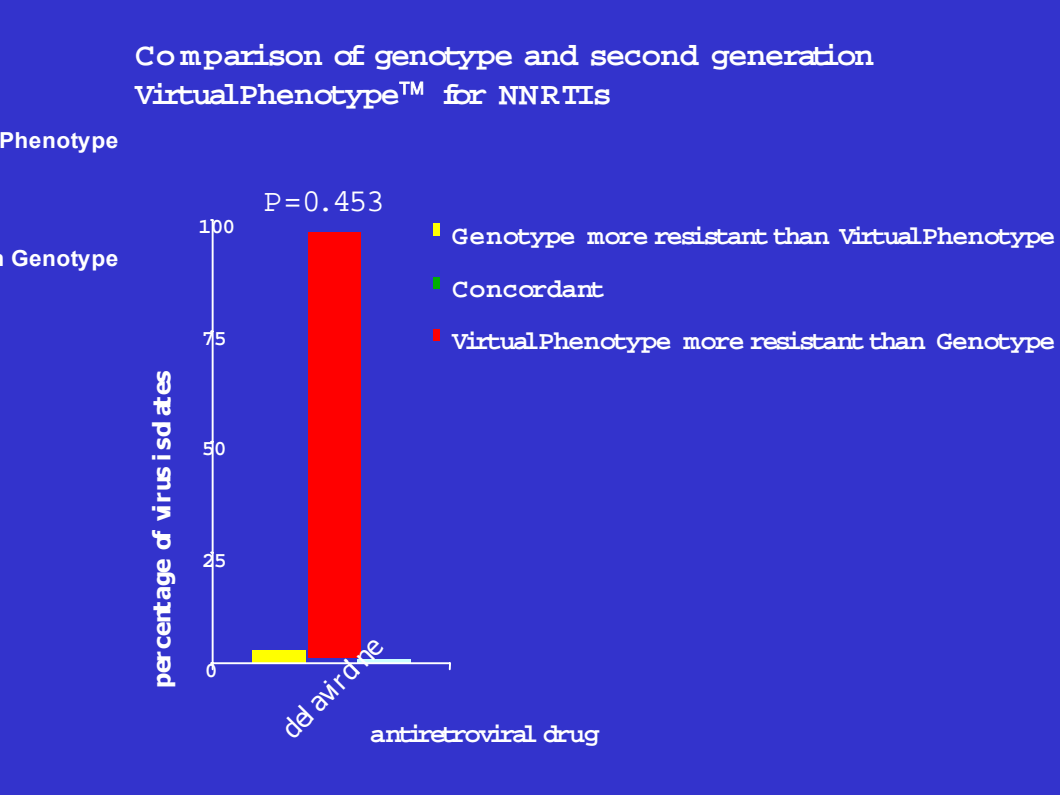
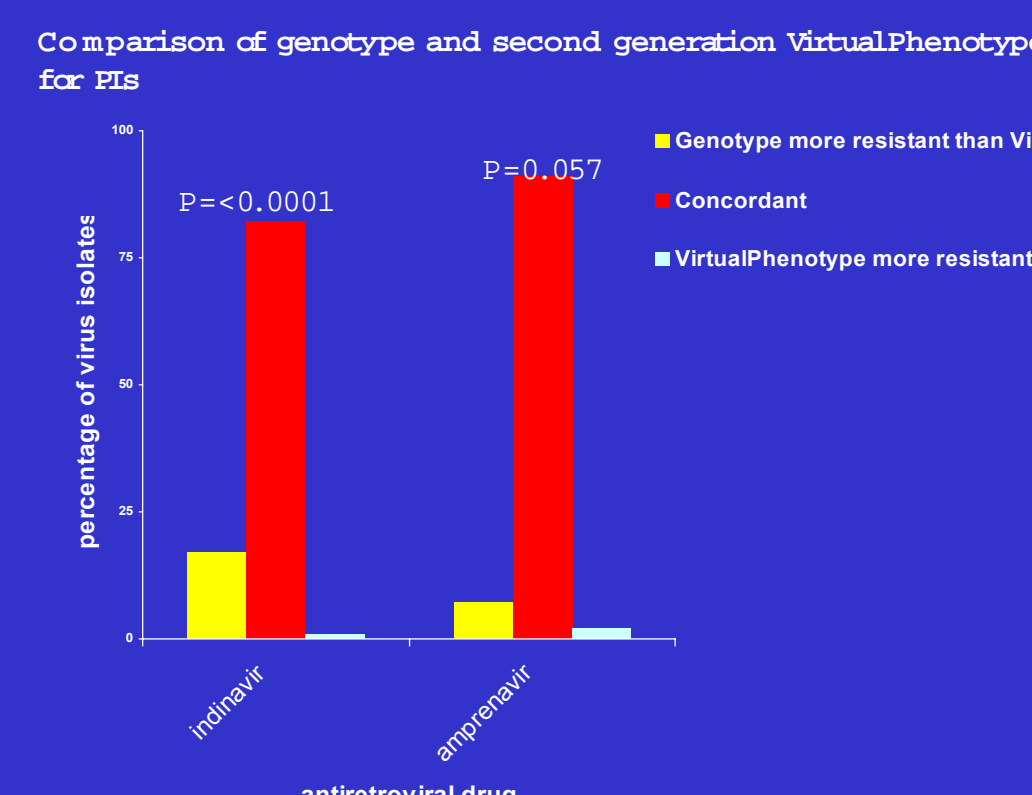
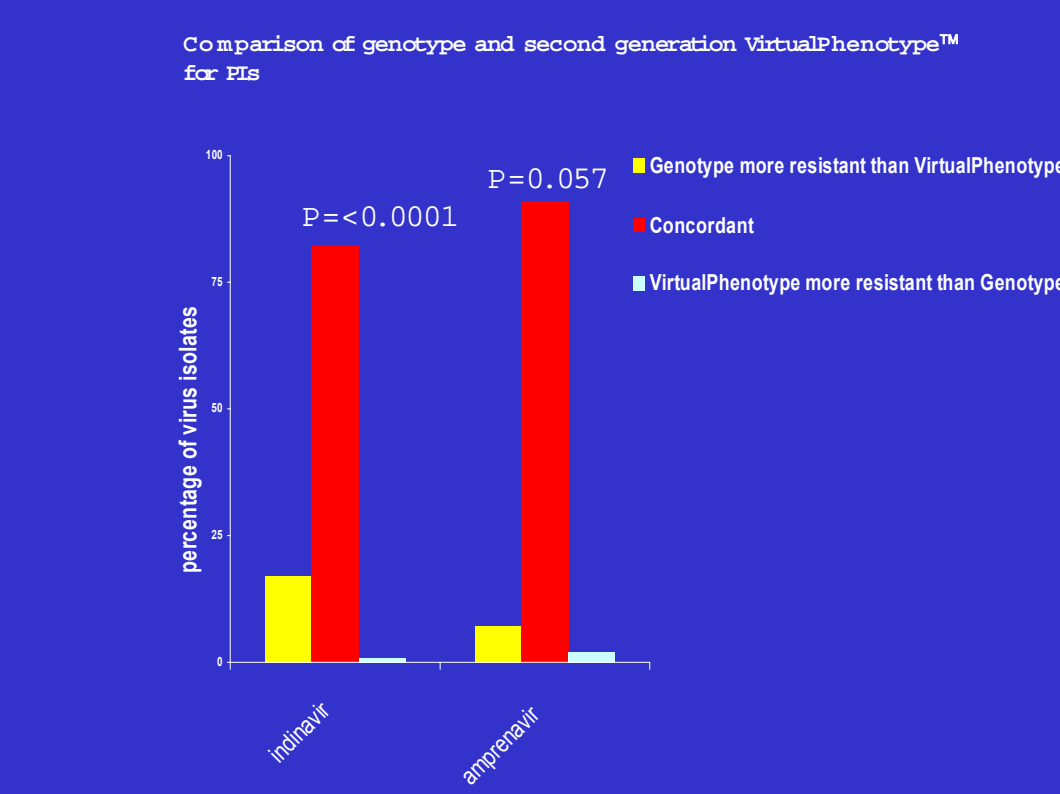
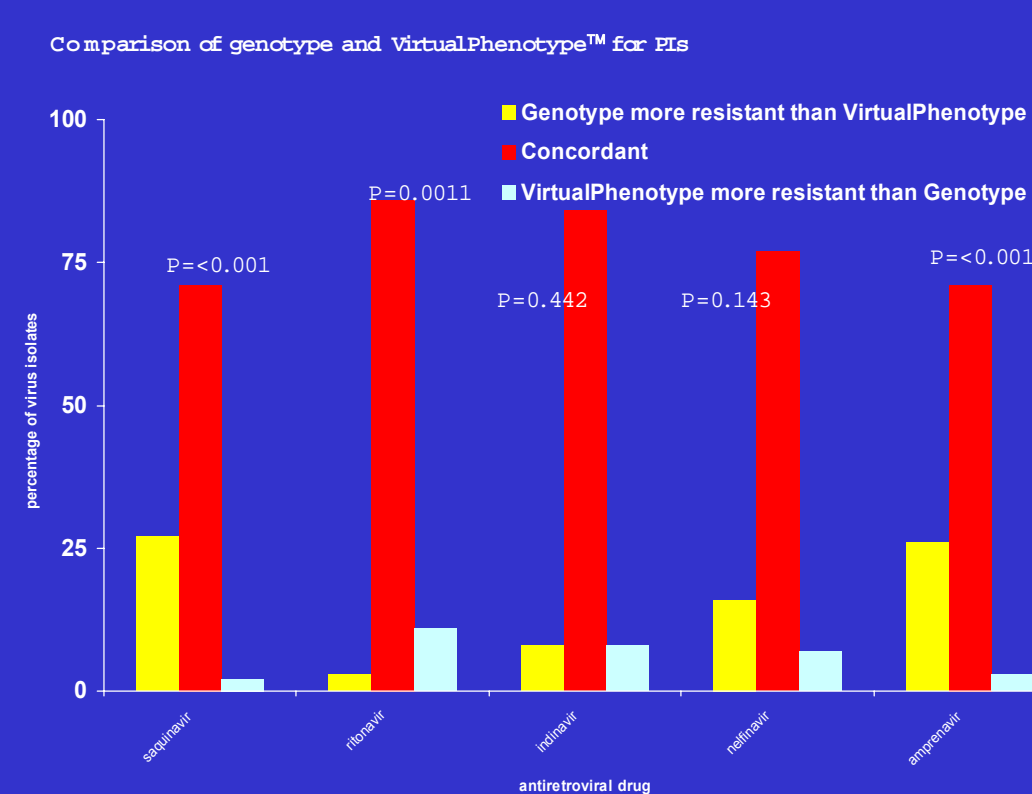
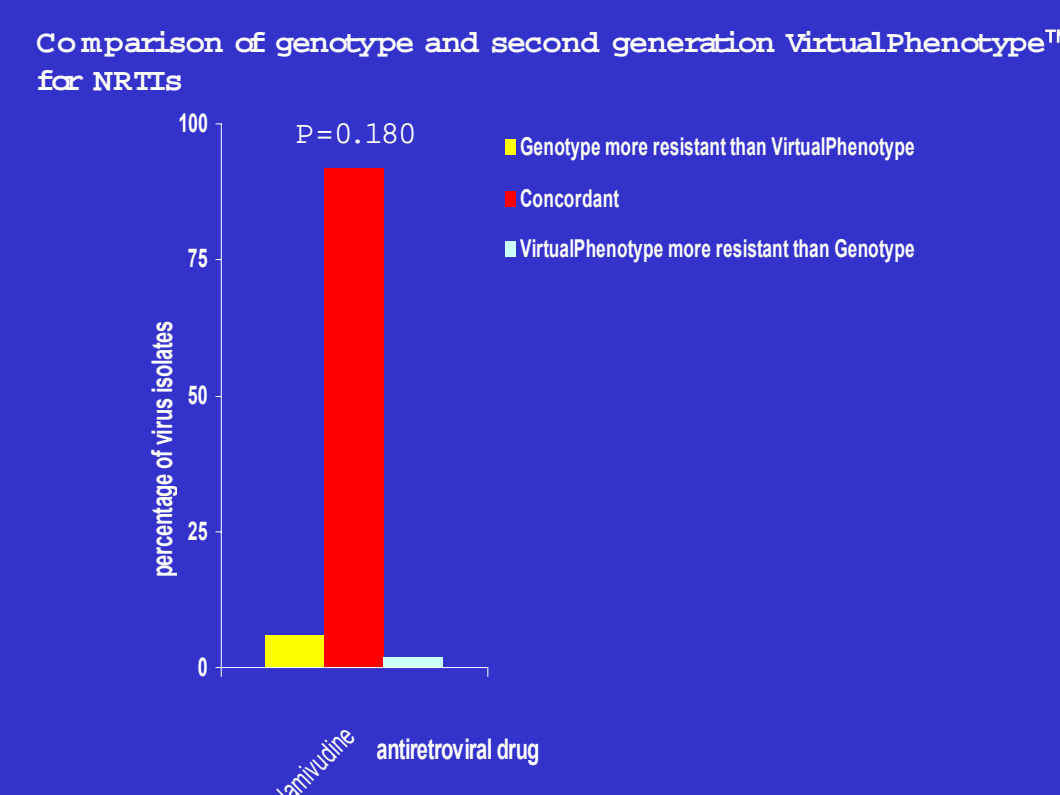
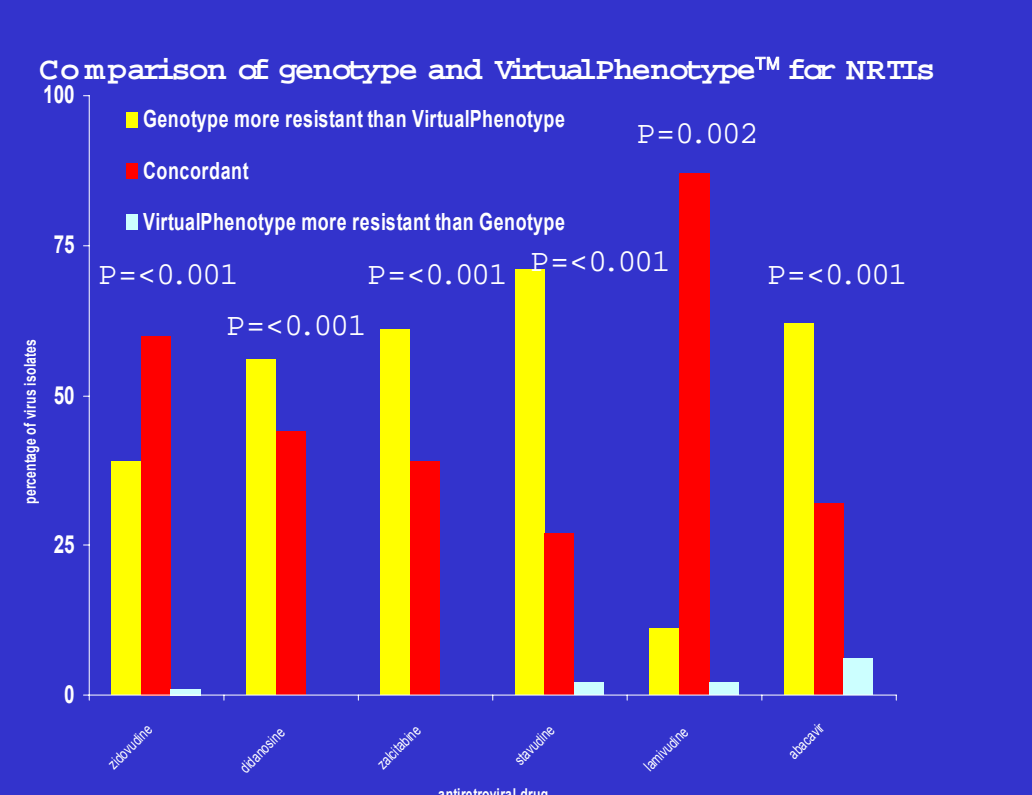


Summary of resistance results

	Genotype	Virtual Phenotype
N	165	159
Mean number of drugs to which a patient is resistant	6	6
Mean number of drugs to which a patient has intermediate resistance	3	3
Mean number of drugs to which a patient is susceptible	6	6
Proportion of patients resistant to all drugs at the time of testing (%)	2%	0%

Mean number of ARV drugs used

	Genotype	Virtual Phenotype	P
Planned regimen	3.4	3.6	
Actual regimen	3.2	3.3	0.31



## CONCLUSIONS

### Objective 1

- Resistance testing resulted in substantial modification of planned ARV regimens in this cohort, there was no significant difference between resistance test methods in this regard.
- HIV drug resistance testing did not affect the number of drugs used in new regimens.
- HIV drug resistance testing was identified most frequently as the single most significant factor in selection of a new regimen.

### Objective 2

- Significant differences in the outcome of genotype and VirtualPhenotype™ results were observed.
- The VirtualPhenotype™ reported less resistance than the genotype assay.
- Differences were consistent for all drugs (except lamivudine, indinavir, amprenavir and delavirdine) when analysed using two different VirtualPhenotype™ platforms.
- The clinical significance of these differences is not known and will be addressed by further follow-up of the randomised cohort.

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### Investigators

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