

D4T Virtual Phenotype can Predict Virologic Response to d4T Monotherapy after ZDV treatment, but Not at the Current Cutoff

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BACKGROUND

The Virtual Phenotype® (VPT, Virco) is a proprietary method for interpreting HIV genotypic data that involves comparing the protease or reverse transcriptase sequence to matching sequences in a large database of isolates for which both genotype and phenotype have been determined. The VPT is the ratio of the average of the IC50 values of the corresponding genotypic matches in the Virco database over the wild type virus. This method gives a reasonable estimate of the fold change in IC50 of a given genotype compared to wild type, however clinical outcome data supporting specific reported fold-change cutoffs for the VPT are lacking. The current VPT reports D4T as susceptible for anything less than 1.8 fold change over wildtype. This data is based on the biological cutoff data and not on clinical outcome data.

OBJECTIVES

1. To determine if VPT can predict the antiviral activity of d4T monotherapy in ZDV-experienced patients.
2. If predictive, to determine the best "clinical" cutoff for d4T virtual phenotype

METHODS

The cohort used in the analysis was a previously described cohort¹⁻³ of who had received ZDV monotherapy in ACTG 175 and subsequently were randomized to the D4T monotherapy arm of ACTG 302. Subjects had received greater than 3 years of ZDV monotherapy.

Genotyping (ABI) and was performed previously on baseline HIV isolates obtained from 31 of the 42 patients in ACTG 302 randomized to D4T monotherapy. VPTs were determined for these sequences. Phenotype (ViroLogic) results were available for 26/31 isolates including 7/8 responders. Baseline and follow-up (8 wks) plasma HIV-1 RNA levels were measured and patients who had a decrease >0.3 logs were classified as responders. The exact Wilcoxon test was used to detect differences in D4T VPT, phenotype, and number of TAMs in the responders vs. non-responders.

RESULTS

Δ log HIV RNA D4T VPT Phenotype RT mutations - TAMS in black

-0.95	0.9	1	V60I, K70R, R83K, V90I, S162A, T200A, E204D, R211Q, A272P, I293V
-0.86	0.9	1	K70R, D123E, I135V, T200IV, R211KR, K277KR
-0.79	0.9	1	E6D, V60I, K70R, R83K, V90IV, I135V, S162A, T200A, Q207E, V245E
-0.78	0.9	1.1	K70R, A272P
-0.63	1.1	1	R83K, I132IT, I135T, T215NSTY, K223KN
-0.62	0.9	1	K49KR, T69ST, K70R, R83K, D123E, I135T, S162CY, E169AE, I202V, L228LR, K277R
-0.52	0.9	1	V60IV, T69S, K70R, R83K, D123E, D177E, I178L, V179I, T200AT, R211K
-0.5	0.9	na	E28G, K49KR, K70R, V90IV, K104RK, K122E, T286A
-0.3	1.1	1.6	T39A, M41L, V60IV, K122E, D123S, I135M, S162Y, V179I, T215Y, R284K, T286A, I293V, T296ST, E297R
-0.26	0.9	1	K20R, K49R, I135T, S162C, V245T, K277R, Q278HQ, I293V
-0.25	0.9	0.9	V35T, E36A, T39E, E40D, D123E, K173A, D177E, T200A, Q207E, V245Q, P247PT, D250DE, A272P, K277R, T;
-0.25	1.4	1.6	V35I, D67N, K70R, D123E, I135T, I142V, D177E, R211EK, T215Y, K219Q, H235HR, V245M
-0.19	1.1	1.8	M41L, K43KN, Q207E, R211KR, T215Y, A272P, K277R
-0.17	0.9	na	V35I, T69S, K70R, R83K, A158S, R211K, V245M, E248D, T286A, T296S, E297K, A299AG
-0.15	1.1	1.9	M41L, I135T, S162C, T215Y, V245K, S251I, A272P
-0.13	1.1	1.9	K20R, V60I, D67N, T69N, K70R, K104N, T200A, I202V, Q207AE, R211KR, T215Y, K219Q, T286A, I293V
-0.12	1.1	1.7	K20R, K64R, I135T, S162H, E204DE, Q207D, R211K, T215Y, M230MV, K277R, T286A, E297K, A299AG
-0.11	0.9	1.1	K64KR, T69ST, K70R, K82KR, A98S, K104R, Q174H, R211K, F214FL, V245EKMV, S251I, A272Q
-0.1	0.9	na	K32KR, K122E, T200A, A272P
0.01	1.1	na	K20RK, V60I, D67N, K70R, K104N, K122E, K166KR, E194D, T200A, I202V, E203D, K219Q, A272P, I293V
0.01	1.1	1.6	K70R, S162C, T215Y, A272P, V292I, A299AG
0.07	1	1.3	E36D, T69N, K70R, D121Y, K122E, I135L, S162C, D177DE, I178IMV, V245MT, K277R
0.15	2.5	4.1	K20R, V35M, M41L, K43DEKN, E44DE, V60I, D67N, T69D, K104N, K122E, L210W, R211K, T215Y, V245Q
0.16	1.1	1.7	T39AT, S48T, D67N, K70R, K103R, K122E, D123N, I135T, T165I, Q197E, T200I, R211KR, F214L, K219G, L22E
0.21	1.2	1.2	N57HN, K70R, F77FL, A98AS, I142V, Q197PQ, T200A, Q207HQ, T215NY, K219KM
0.21	0.9	1	A98S, K122E, G196E, T200A, A272S, K281R, I293V
0.23	0.9	1.1	K20KR, E248DN
0.27	1.1	1.7	T39A, D67N, T69D, K70R, K103R, T200K, I202V, Q207E, R211K, F214L, K219Q, A272P
0.32	1.1	1.6	T69AT, K70KR, R83K, K122P, A158S, D177E, T200A, Q207E, T215NSTY, A272S, T286A, E297A
0.88	1.1	na	I31V, S68G, S162C, P176S, T200A, R211K, T215Y
1.33	1.1	1.9	D67N, T69S, K70R, V90IV, I135M, S162C, Q174H, G196E, Q207R, K219Q, V245K, A272P, K261KR, T286A

Of the 26 subjects with both phenotypes, 25/26 (96%) had a lower D4T virtual phenotype than D4T actual phenotype (p<0.001). Recall that the VPT is derived from phenotypes of a different method (Antivirogram, Virco) than the actual phenotypic data (PhenoSense, Virologic).

	Responders			Non-Responders			P-value
	N	Median	Range	N	Median	Range	
D4T virtual phenotype	8	0.9	0.9-1.1	23	1.1	0.9-2.5	0.014
D4T actual phenotype	7	1.0	0.9-1.1	19	1.6	0.9-4.1	0.008
Number TAMs	8	1	1-1	23	2	0-4	0.11

D4T VPT CUTOFF DETERMINATION

We attempted to look at different D4T VPT fold change cutoffs. Sensitivity = responders less than the cutoff, specificity = non-responders greater than the cutoff. The VPT for wildtype HIV is 0.7 FC.

FC Cutoff	Sensitivity	Specificity
1.0	7/8 (88%)	16/23 (70%)
1.1	7/8 (88%)	15/23 (65%)
1.2	8/8 (100%)	3/23 (13%)
1.8 (current)	8/8 (100%)	1/23 (4%)

The single best cutoff for this cohort was a D4T VPT FC predicted fold change of less than 1.0.

CONCLUSIONS

The virtual phenotype was predictive of a short term response to D4T monotherapy in ZDV experienced patients.

The data is limited by the homogeneity in the genotypic pattern seen in the responders.

The current D4T cutoff of 1.8 used in the VPT interpretation report is too high.

The best cutoff in this cohort was a predicted fold change of <1.0.

VPT was not as predictive as actual phenotype for predicting a response to D4T monotherapy, but was superior to counting the number of TAMs.

REFERENCES

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