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Diminished susceptibility to didanosine due to 184I/Vand thymidine analog mutations in isolates without major IAS-USA didanosine-specific and cross-resistant mutations.

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OBJECTIVES

Recent reports by Eron et al. (1) indicate that viruses with the 184I/V mutation have diminished phenotypic susceptibility to didanosine (ddI).

According to the 2007 IAS-USA list (2) the 184I/V mutation is not considered to indicate resistance to ddI on its own. Therefore we investigated whether the above relationship can be explained by the presence of thymidine analogue mutations (TAMs).

METHODS

We extracted genotype-phenotype pairs from the Stanford HIV-DB from patients with a measured IC50 fold change (FC) value for ddI obtained with Monograms PhenoSense assay.

Pairs containing genotypes harbouring the following mutations from the 2007 IAS-USA list (2):

62V, 65R, 69-insertion,

74V, 75I, 77L, 116Y or 151M

in the reverse-transcriptase gene were omitted as these mutations are known to reduce ddI-susceptibility and we wanted to asses the effect of 184I/V and TAMs in absence of these potentially confounding factors.

Data was split into groups based on the presence or absence of the 184I/V mutation and the number of TAMs; defined as the following mutations:

41L, 67N, 70R, 210W, 215F/Y, 219E/Q.

We calculated the mean difference in IC50 FC values between viruses with/without the 184I/V mutation grouped by 0, 1, 2, 3, 4 and >5 TAMs, respectively.

Further we created linear models to asses the effect of 184I/V (model 1), 184I/V and number of TAMs (model 2) and interaction between 184I/V and the number of TAMs (model 3).

RESULTS

604 genotype-phenotype pairs were extracted, of which 209 (34.6%) had no TAMs.

Plots of the IC50 FC values are shown in **Figure 1** and the mean difference in IC50 FC values between viruses with/without the 184I/V mutation and grouped by number of TAMs are shown in **Table 1**.

Data in **Figure 1** and **Table 1** confirm that a large number of TAMs is needed to increase the ddI IC50 FC and that the IC50 FC is increased, on average, by a further 0.43 if 184I/V is detected.

The increase in IC50 FC was significantly associated with an increasing number of TAMs (p<0.0001) and presence of 184I/V (p<0.0001) and both were found to be independent predictors of increasing IC50 FC (see **Table 2**).

As shown in **Table 2,** we found no evidence for statistical interaction between 184I/V and number of TAMs (p=0.68) indicating that there is no evidence that the increase in IC50 associated with detection of 184I/V varies according to the number of TAMs detected.

Figure 1

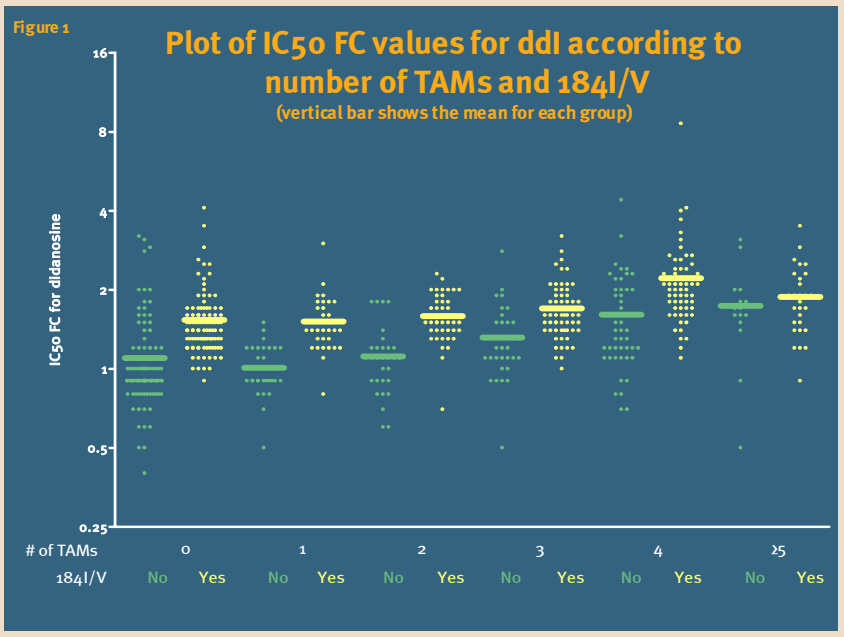

Table 1

Mean difference between groups according to # of TAMs and presence of 184I/V

# of TAMs	0		1		2		3		4		>5	
184I/V	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Mean IC50 FC	1.10	1.54	1.01	1.52	1.12	1.60	1.32	1.70	1.61	2.22	1.74	1.88
N (number of pairs)	111	98	29	34	30	44	35	67	51	62	15	28
Mean difference (t-test)	0.44 (p<0.0001)		0.50 (p<0.0001)		0.47 (p<0.0001)		0.38 (p<0.0001)		0.61 (p=0.0004)		0.14 (p=0.47)	

Table 2

Linear models to asses effect of 184I/V, # of TAMs and interaction between 184I/V and # of TAMs

- shown are the estimated coefficients for the variables and their significance

	Variables included in the model		
	Presence of 184I/V (0/1)	# of TAMs	184I/V * # of TAMs
Estimated coefficients from model 1	0.47 (p<0.0001)	-	-
Estimated coefficients from model 2	0.43 (p<0.0001)	0.12 (p<0.0001)	-
Estimated coefficients from model 3	0.45 (p<0.0001)	0.12 (p<0.0001)	-0.01 (p=0.68)

CONCLUSIONS

Viruses harbouring 184I/V were found to have a higher mean IC50 FC value than those without; this effect could not be explained by a possible confounding effect of TAMs; 184I/V should be taken into account in patients starting a ddI-containing regimen irrespective of TAMs that may be present.

Further investigations of the effect of 184I/V on virological response to ddI-containing regimens in clinical practice are warranted.

REFERENCES:

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2 Johnson VA, Brun-Vezinet F, Clotet B, Gunthard HF, Kuritzkes DR, Pillay D, et al. Update of the Drug Resistance Mutations in HIV-1: 2007 7. Top HIV Med 2007 Aug;15(4):119-25.

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