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CROSS-RESISTANCE PROFILES OF THE NNRTIS IN DEVELOPMENT TO PREVENT HIV-1 INFECTION

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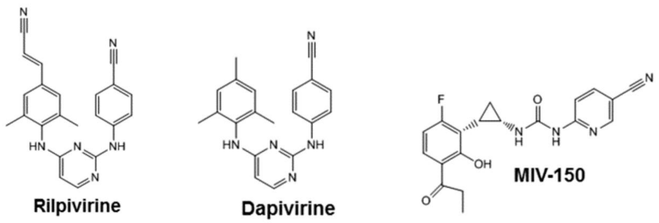
Introduction

The NNRTIs dapivirine (DPV), rilpivirine (RPV) and the phenylethylthiazolylthiourea analog MIV-150 are in development as pre-exposure prophylaxis (PrEP) modalities to prevent the acquisition of HIV-1 infection.



It is not known whether these NNRTIs will prevent infection of circulating NNRTI-resistant HIV-1 variants. In this regard, there is a paucity of information in regard to the resistance and cross-resistance profiles of DPV and MIV-150.

Here we evaluated the cross-resistance profiles for the diarylpyrimidines RPV and DPV, as well as the urea-PETT derivative MIV-150.

Results

Table 1: Susceptibility of HIV-1 containing single NNRTI resistance mutations to RPV, DPV and MIV-150.

	RPV			DPV			MIV-150		
	EC_{50} ± S.D.	Fold-R[1]	*p-value*[2]	EC_{50} ± S.D.	Fold-R[1]	*p-value*[2]	EC_{50} ± S.D.	Fold-R[1]	*p-value*[2]
WT	0.33 ± 0.13			0.64 ± 0.13			0.68 ± 0.09		
V90I	0.59 ± 0.13	1.8		1.09 ± 0.47	1.7		0.98 ± 0.14	1.4	
L100I	0.36 ± 0.13	1.1		9.36 ± 1.37	14.7	<0.01	5.03 ± 1.35	7.4	<0.01
L100V	0.27 ± 0.13	0.8		6.15 ± 1.79	9.6	<0.01	5.06 ± 2.42	7.5	0.02
K101E	1.12 ± 0.24	3.4	<0.01	2.29 ± 0.68	3.6	<0.01	3.25 ± 0.75	4.8	<0.01
K101P	13.1 ± 1.70	40.0	<0.01	≥ 62.5	≥ 100	<<0.01	≥ 62.5	≥ 100	<<0.01
K103N	0.53 ± 0.11	1.6		3.03 ± 0.47	4.8	<0.01	23.4 ± 2.81	34.6	<0.01
K103S	0.49 ± 0.11	1.5		4.61 ± 0.43	7.2	<0.01	15.30 ± 2.03	22.7	<0.01
V106I	0.48 ± 0.17	1.5		0.94 ± 0.14	1.5		0.78 ± 0.11	1.2	
V108I	0.38 ± 0.01	1.2		0.96 ± 0.20	1.5		0.89 ± 0.15	1.3	
E138A	0.80 ± 0.41	2.5	0.06	1.29 ± 0.33	2.0	0.02	1.32 ± 0.30	2.0	0.01
E138K	0.96 ± 0.18	2.9	<0.01	2.79 ± 0.70	4.4	<0.01	1.89 ± 0.17	2.8	<0.01
V179D	0.39 ± 0.15	1.2		0.81 ± 0.33	1.3		0.73 ± 0.35	1.1	
V179F	0.003 ± 0.002	0.01		0.20 ± 0.01	0.3		0.03 ± 0.01	0.1	
G190A	0.41 ± 0.03	1.3		0.77 ± 0.15	1.2		0.40 ± 0.09	0.6	
G190S	0.25 ± 0.17	0.8		0.84 ± 0.01	1.3		0.09 ± 0.01	0.1	
Y181C	0.60 ± 0.25	1.8		5.06 ± 1.50	7.9	<0.01	10.20 ± 1.60	15.1	<0.01
Y181I	7.68 ± 0.78	23.5	<0.01	≥ 62.5	≥ 100	<<0.01	≥ 62.5	≥ 100	<<0.01
Y181V	7.36 ± 1.20	22.6	<0.01	≥ 62.5	≥ 100	<<0.01	39.60 ± 4.10	58.6	<0.01
Y188C	0.08 ± 0.04	0.3		0.39 ± 0.20	0.6		0.21 ± 0.05	0.3	
Y188H	0.11 ± 0.04	0.3		0.69 ± 0.33	1.1		1.16 ± 0.48	1.7	
Y188L	1.70 ± 0.23	5.2	<0.01	55.30 ± 6.53	86.7	<0.01	≥ 62.5	≥ 100	<<0.01
H221Y	0.45 ± 0.20	1.4		0.85 ± 0.20	1.3		0.91 ± 0.19	1.3	
P225H	0.30 ± 0.17	0.9		0.69 ± 0.25	1.1		0.76 ± 0.32	1.1	
F227C	1.11 ± 0.27	3.4	0.01	4.37 ± 0.78	6.9	<0.01	10.01 ± 3.16	14.8	<0.01
F227L	0.28 ± 0.26	0.8		0.61 ± 0.19	1.0		0.88 ± 0.31	1.3	
M230L	2.58 ± 1.13	7.9	0.01	10.10 ± 0.38	15.8	<0.01	15.30 ± 2.87	22.6	<0.01
P236L	0.60 ± 0.10	1.7		1.00 ± 0.18	1.6		0.63 ± 0.07	0.9	
N348I	0.50 ± 0.13	1.5		1.07 ± 0.47	1.7		0.99 ± 0.34	1.5	

[1] The concentrations of drug required to inhibit viral replication by 50% (EC_{50}) from 3 independent experiments. Data reported as a mean ± standard deviation from at least 3 independent experiments.
[2] Mean fold change in EC_{50} of mutant versus WT virus. EC_{50} values were log_{10} transformed and compared for statistically significant differences (p-value < 0.05) using the two-sample Student's paired *t* test.

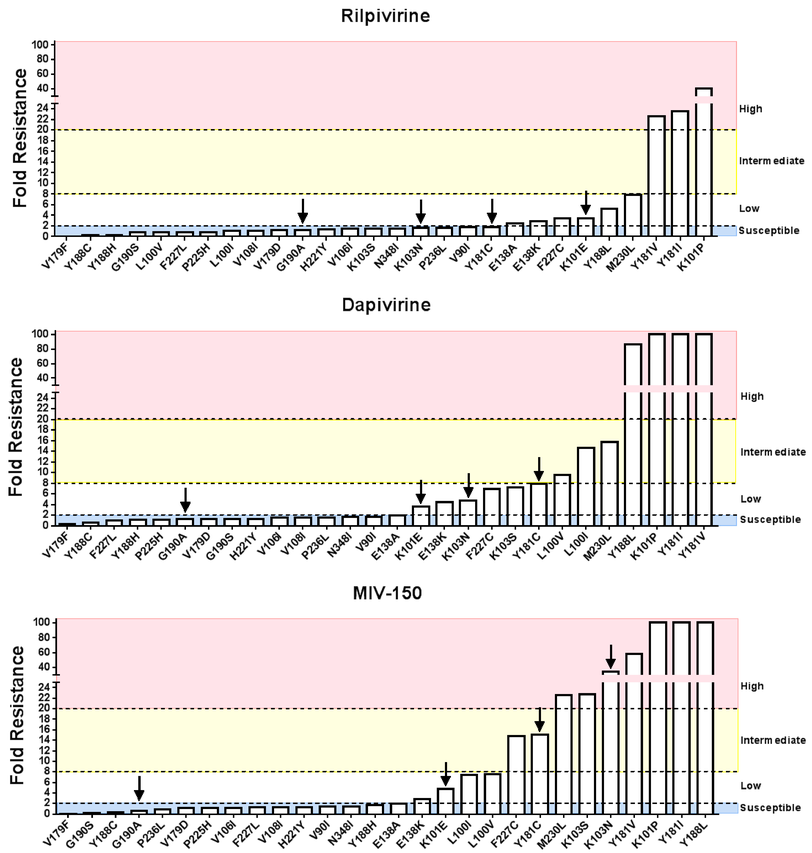


Figure 1: Cross-resistance profiles for RPV, DPV and MIV-150.

Low-, intermediate- and high-level resistance was defined as 2-8, 8-20, and >20-fold changes in drug susceptibility compared to the wild type virus.

Arrows indicate the four most commonly transmitted drug resistance mutations, G190A, K101E, Y181C, and K103N.

E138A

Recently we reported that an E138A substitution occurs more frequently in subtype C (range: 5.9-7.5%) than B (range: 0-2.3%) sequences from treatment-naïve individuals ($p<0.01$)

Because E138A in subtype C HIV-1 decreases RPV susceptibility, we proposed that this polymorphism may impact prevention (and treatment) strategies that include RPV in geographic areas where subtype C infection is prevalent.

Sluis-Cremer N, Jordan MR, Huber K, Wallis CL, Bertagnolio S, Mellors JW, Parkin NT, Harrigan PR. 2014. E138A in HIV-1 reverse transcriptase is more common in subtype C than B: implications for rilpivirine use in resource-limited settings. Antiviral Res. **107**:31-34.

We synthesized (GenScript, Piscataway, NJ, USA) and cloned into our HIV-1^{LAI} viral vector full length subtype C RT sequences from 2 antiretroviral-naïve individuals that did not harbor E138A, and from 6 antiretroviral-naïve individuals that contained E138A.

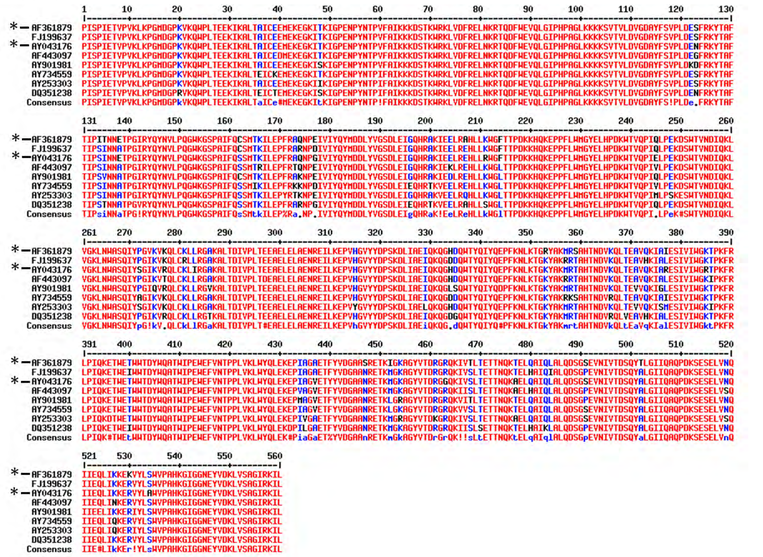


Figure 2: Sequences of patient-derived full-length subtype C RT sequences
Asterisks (*) indicates sequences without E138A

Table 2: Susceptibility of recombinant viruses containing full-length patient-derived WT subtype C RT sequences with and without E138A to RPV, DPV and MIV-150.

	RPV			DPV			MIV-150		
	EC_{50} ± S.D.	Fold-R[1]	*p-value*[2]	EC_{50} ± S.D.	Fold-R[1]	*p-value*[2]	EC_{50} ± S.D.	Fold-R[1]	*p-value*[2]
***AF361879**	0.30 ± 0.03			0.68 ± 0.10			0.56 ± 0.10		
***AY043176**	0.24 ± 0.04			0.49 ± 0.02			0.36 ± 0.05		
***Average**	0.27 ± 0.04			0.58 ± 0.13			0.46 ± 0.13		
DQ351238	0.40 ± 0.12	1.5		1.20 ± 0.33	2.1	<0.01	1.40 ± 0.59	3.1	<0.01
AY901981	0.64 ± 0.14	2.4	<0.01	1.80 ± 0.51	3.0	<0.01	1.50 ± 0.23	3.2	<0.01
AF443097	0.41 ± 0.12	1.5		1.30 ± 0.50	2.3	<0.01	0.86 ± 0.16	1.9	<0.01
AY253303	0.23 ± 0.04	0.9		0.83± 0.13	1.4		0.60 ± 0.05	1.3	
AY734559	0.36 ± 0.14	1.3		0.77 ± 0.26	1.3		0.63 ± 0.15	1.4	
FJ199637	0.54 ± 0.07	2.0	<0.01	2.70 ± 0.19	4.7	<0.01	1.60 ± 0.31	3.4	<0.01

[1] The concentrations of drug required to inhibit viral replication by 50% (EC_{50}) are reported as a mean ± standard deviation from at least 3 independent experiments.
[2] Mean fold change in EC_{50} of WT-E138A vs WT virus. EC_{50} values from 3 independent experiments were log_{10} transformed and compared for statistically significant differences (p-value < 0.05) using the two-sample Student's paired *t* test.

Conclusions

DAP and MIV-150 activity is compromised by many HIV-1 variants containing a single NNRTI resistance mutation. Both NNRTIs exhibit decreased susceptibility toward the K101E, K103N and Y181C mutations which are major NNRTI transmitted drug resistance mutations in all geographic regions and HIV-1 subtypes.

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