Paper 150: Favorable Drug Resistance Profile of Doravirine and Islatravir

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Introduction: The newer generation of non-nucleoside reverse transcriptase inhibitors (NNRTIs), doravirine and rilpivirine, demonstrate high potency and can overcome resistance caused by K103N, Y181C and G190A point mutations, Phase 2 trials showed that the doravirine, combined with islatravir, the first nucleoside reverse transcriptase translocation inhibitor, maintained viral suppression through 96 weeks. Here, we performed *in vitro* drug selections to compare the drug resistance profiles of doravirine, alone & paired with lamivudine (3TC) or islatravir.

Results: Doravirine pressure resulted in the acquisition of V108I (6/7) and V106A/I/M (5/7) mutations at weeks 8, followed by F227L (4/7), Y318F (4/7), M230L (2/7) and L234I (2/7) by weeks 24. In contrast, rilpivirine favoured the appearance of E138K (5/7), L100I/P (3/7) and.M230L (1/7). Doravirine-resistant variants retained sensitivity to rilpivirine, etravirine and efavirenz, whereas rilpivirine-resistant variants showed intermediate resistance (12-152-fold) to doravirine. There was a delay and diminution in the emergence of resistance when doravirine was combined with islatravir or 3TC. At 24 weeks, the V108I mutation (9/15) prevailed with fewer or no other changes. There was a lesser delay in emergent resistance to rilpivirine when combined islatravir or lamivudine selections. The M184I/V mutation, conferring islatravir and lamivudine resistance, rarely occurred in dual (2/28) selections.

Conclusion: Doravirine showed a more robust resistance profile compared to other NNRTIs. The high potency and long intracellular half-life of islatravir, provide the opportunity for long-acting and low dosing treatment options.

Cell culture selections with Doravirine, Doravirine + Islatravir, and Doravirine + 3TC

Virus	Subtype	Doravirine		Doravirine + Islatravir	Doravirine + 3TC
		Week 8	Week 24	Week 24	Week 24
14637	B	V108I	V108I, F227F/L, **M230L**, **L234I**	V108I	V106A. **M184IM**
14969	B	V108I	V108I, A62V, V106I, **E138K**, H221Y	V108IV, H221Y	None
5326	B	V106A	V106A, A62AV, V108IV	V108I	V106A
4742	C (E138A)	(E138A) V108I	(E138A), V108I, **V106M,** Y318F	(E138A), V108IV, Y188YH	(E138A), V108I
6343	CRF01_AE	None	V108I, H221Y, **L234I**	None	V108I, H221Y, L234I
96USSN20	CRF02_AG	Y318F	V106A, F227L, Y318F	V108I, **M184IM**, Y318F	F227FV, Y318FY
pNL4.3	B	V108I	V108I, F227L, **M230L**, Y318FY	V108I	V108I

Individual clinical isolates were grown in increasing weekly concentrations of drugs from EC_{50} levels. The acquisition of resistance mutations reached for doravirine, lamivudine and islatravir are shown for weeks 8 and 24. Isolate 4742 is a subtype C strain with a baseline natural polymorphism of E138A in a treatment-naïve patient. Isolate 96USSN20 had baseline D67D/N, T69D, K70R mutations associated with resistance to thymidine analogues. Mutations (red bold) are associated with highest levels of reduced susceptibility in Stanford Resistance database. The M184IM is a resistance mutation for islatravie or 3TC

Doravirine first acquired mutations (2x decreases in viral susceptibility)	Doravirine secondary mutations (combined intermediate resistance)	Doravirine major mutations (Intermediate-high resistance)
V108I (6/7), V106A (2/7) or Y318F (3/7)	F227L, L234I, Y318F	M230L, V106M (subtype C)

Cell culture selections with Rilpivirine, Rilpivirine + Islatravir, and Rilpivirine + 3TC

Virus	Subtype	Riplivirine		Rilpivirine + Islatravir	Rilpivirine + 3TC
		Week 8	Week 24	Week 24	Week 24
14637	B	None	K101E	**E138EK**	**K101P**
14969	B	None	L100I, **E138K**	**E138K**	**E138K**
5326	B	**E138K**	L100I, V179I, **E138K**	None	V108IV, **E138K**
4742	C (E138A)	(E138A)	(E138A), V75I, V108I, V179I	(E138A), V189IV	(E138A), V75I
6343	CRF01_AE	None	V106A, **E138K**	**Y181C**	K101E
96USSN20	CRF02_AG	**E138K**	V108I, **E138K**, M230L	**E138K, V106A**, V179L	**E138K,** V106A, F227L
pNL4.3	B	**E138K**	A98G, L100I, **E138K**	**E138K**	K101E

Individual clinical isolates were grown in progressively increasing concentrations of drugs from EC_{50} levels. The genotype of acquired resistance mutations and drug concentrations [a] reached for rilpivirine (µM), lamivudine (µM) and islatravir (nM) are shown for weeks 8 and 24. Isolate 4742 is a subtype C strain with a baseline natural polymorphism of E138A in a treatment-naïve patient. Isolate 96USSN20 had baseline D67D/N, T69D, K70R mutations associated with resistance to thymidine analogues. Mutations in red are major resistance mutations for rilpivirine. The M184IM is a resistance mutation for islatravir or 3TC

Rilpivirine first resistance mutations	RilpivDoravirine secondary mutations	Doravirine major mutations
E138K	K101E	E138K

Phenotypic drug susceptibilities of viruses acquiring resistance to doravirine (DOR) or rilpivirine (RPV) in cell culture

Virus (Drug week selected)	Acquired resistance mutations	Fold resistance relative to matching WT		
		Doravirine	Rilpivirine	Efavirenz
5326 (DOR wk 8)	V106A	13x	S	25x
5326 (DOR wk 13)	V106A. **Y318F**	854x	S	26x
5326 (DOR wk 30)	V106A**, Y318F** V108IV, F227L, A62AV	>10000x	S	1669x
4742 (DOR wk 13)	(E138A), V108I	8x	S	S
4742 (DOR wk 17)	(E138A), V108I, **Y318F**	226x	-	38x
96USSN20 (DOR wk 13)	V106AV, V108IV, **Y318F**	68x	S	6.6x
96USSN20 (DOR wk 30)	V106AV, V108IV, **Y318F**	4167x	S	25x
14637 (DOR wk 24)	V108I, F227FL, **M230L**, L234I	482x	S	6x
14969 (DOR wk 24)	A62V, V106I, V108I, **E138K,** H221Y	1563x	137x	461x
14969 (RIL wk 24)	L100I, **E138K**	152x	160x	85x
5326 (RIL wk 24)	L100I, **E138K,** V179I	12x	8000x	2139x
96USSN20 (RIL wk 24)	V108I, **E138K, M230L**	20x	>10,000x	4258x
pNL4.3 (RIL wk 24)	A98G, L100I, **E138K**	90x	**4563x**	**12x**

Viruses, harvested at select passages, were genotyped and assessed for susceptibility to doravirine, rilpivirine, and efavirenz. Phenotypic cell-based assays ascertained the fold resistance relative to the matching WT strain.

Conclusions

- Viruses acquired first resistance to doravirine through the acquisition of V108I (6/7), V106A (2/7), or Y318F (3/7), conferring low-level resistance, followed by the accumulation of three or more secondary mutations conferring intermediate-high resistance

- The acquisition of resistance to doravirine did not affect sensitivity to rilpivirine

- The emergence of resistance to rilpivirine through the acquisition of E138K (6/7) resulted in cross-resistance to doravirine and efavirenz

- Dual selections of doravirine with Islatravir or lamivudine (3TC) attenuated the development of resistance at 24 weeks, conferring low-level resistance to doravirine (< 2 to 3 fold) and sensitivity to rilpivirine.

- Dual selections of rilpivirine with islatravir or lamivudine led to resistance through the acquisition of E138K leading to rilpivirine resistance.

- Doravirine has a favorable drug resistance profile