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Assessing Phenotypic Effect of Integrase Strand Transfer Inhibitor (INSTI)-Based Resistance Substitutions Linked to Failures on Cabotegravir

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CAB resistance profiles established based on clinical trials*

Main mutation	Mutations pattern	Mutations
Q148R	Q148R +/- 1 mutation	Q148R
		Q148R + N155H
		Q148R + L74I
	Q148K/R + E138A/K +/- G140A/S +/- other mutations	Q148R + E138A/K
		Q148K + E138K+ M50I
		Q148R + E138K + G140S + E157Q + L74I + Q146R
		Q148R + E138K + G140A + M50I
	Q148R + N155H + R263K +/- other mutations	Q148R + N155H + R263K + Q146L
N155H	N155H +/- other mutations	N155H + S230R
		N155H
		N155H + R263K
R263K	R263K +/- other mutations	R263K
		R263K + M50I
Other mutations		G140R
		V151I
		T97A
		L74I
		M50I
		G118R

*HPTN 083,[1] HPTN 084,[2] ATLAS,[3] ATLAS-2M,[4–6] FLAIR,[7,8] SOLAR[9]
CAB, cabotegravir.

1. Eshleman SH, et al. J Infect Dis 2022;225:1741-1749; 2. Marzinke MA, et al. Antimicrob Agents Chemother 2023;67:e0005323; 3. Swindells S, et al. N Engl J Med 2020;382:1112-1123; 4. Overton T, et al. Lancet 2020;396:1994-2005; 5. Jaeger H, et al. CROI 2021, Oral 401; 6. Overton T, et al. CROI 2022, Oral 479; 7. Orkin C, et al. N Engl J Med 2020;382:1124-1135; 8. Orkin C, et al. IAS 2021, Oral OAB0302; 9. Ramgopal MN, et al. CROI 2023, Oral 191.

IC_{50} fold changes for clinical isolates with RAM patterns associated with CAB failure

Mutations		1 RAM (n = 9)									Mean IC_{50} fold change
		N155H	N155H	N155H	N155H	N155H	N155H	Q148R	Q148R	Q148R	
IC_{50} fold change	CAB	1.57	1.35	1.61	1.77	1.98	1.85	5.32	7.35	7.30	**3.3**
	BIC	1.11	0.93	1.70	1.31	1.68	1.13	1.38	1.72	1.66	**1.4**
	EVG	28.00	22.00	30.00	23.00	34.00	19.00	> 123	> 190	> 119	**> 65.3**

Sensitive
Partially sensitive
Resistant

Mutations		2 RAMs (n = 27)																									Mean IC_{50} fold change
		E138K, Q148R	E138K, Q148R	E138K, Q148R	G140A, Q148R	G140A, Q148R	G140A, Q148R	G140S, Q148H	G140S, Q148H	G140S, Q148H	G140S, Q148H	G140S, Q148H	G140S, Q148H	G140S, Q148H	G140S, Q148H	G140S, Q148H	G140S, Q148H	G140S, Q148H	G140S, Q148H	G140S, Q148H	G140S, Q148H	G140S, Q148H	G140S, Q148R	G140S, Q148R	G140S, Q148R	G140S, Q148R	G140S, Q148R	
IC_{50} fold change	CAB	7.96	10.00	8.07	5.51	6.19	6.48	5.41	8.49	7.41	8.71	12.00	6.81	12.00	9.47	8.19	13.00	6.79	9.27	8.44	9.86	14.00	12.00	7.09	17.00	8.88	18.00	9.48	**9.5**
	BIC	1.60	1.95	1.87	1.55	2.25	1.87	1.93	2.02	1.91	1.88	2.11	2.23	2.51	3.00	2.51	2.46	2.17	2.48	2.92	2.70	2.57	2.43	2.08	4.60	3.37	4.58	3.16	**2.5**
	EVG	> 123	> 190	> 119	> 123	> 190	> 119	> 123	> 123	> 123	> 123	> 123	> 190	> 190	> 190	> 190	> 190	> 119	> 119	> 119	> 119	> 119	> 123	> 123	> 190	> 190	> 119	> 119	**> 144**

Mutations		3 RAMs (n = 16)															Mean IC_{50} fold change
		E138K, G140A, Q148K	E138K, G140A, Q148K	E138K, G140A, Q148K	E138K, G140C, Q148R	E138K, G140C, Q148R	E138K, G140C, Q148R	E138K, G140S, Q148H	E138K, G140S, Q148H	E138K, G140S, Q148H	E138K, G140S, Q148H	E138K, G140S, Q148H	E138K, G140S, Q148H	E138K, G140S, Q148H	G140S, Q148H, E138A	G140S, Q148H, E138A	
IC_{50} fold change	CAB	61.00	103.00	84.00	58.00	86.00	87.00	23.00	9.86	20.00	24.00	9.78	34.00	26.00	9.87	48.00	69.00	**47.0**
	BIC	13.00	26.00	34.00	4.18	5.67	4.68	2.08	1.96	3.06	2.67	2.97	3.24	3.17	2.58	5.34	6.84	**7.59**
	EVG	> 123	> 190	> 119	> 123	> 190	> 119	> 123	> 123	> 95	> 190	> 190	> 167	> 119	> 119	> 123	> 190	**> 144**

BIC, bictegravir; CAB, cabotegravir; EVG, elvitegravir; IC_{50}, concentration at which a substance exerts half of its maximal inhibitory effect; RAM, resistance-associated mutation.