

Title

HIV-1 Protease and Reverse Transcriptase Mutations: Correlations with Antiretroviral Therapy in
Subtype B Isolates and Implications for Drug-Resistance Surveillance

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Table 1. Protease Inhibitor-Related Mutations According to Previous Classifications and Extent of Polymorphism in HIV-1 Isolates from PI-Naive Persons*

	Nonpolymorphic [†]					Polymorphic [†]				
	Pos	AA	Naïve	Rx	p [¶]	Pos	AA	Naïve	Rx	p [¶]
Recognized PI-related mutations	10	F	0.2	5.3	<0.001	10	I	7.9	35.4	<0.001
		R	0	0.8	<0.001		V	2.1	4.5	<0.001
	20	I ^{††}	0.1	5.8	<0.001	20	R	1.3	8.8	<0.001
		T	0.1	2.6	<0.001		M	0.5	2.2	<0.001
	24	I	0	5.4	<0.001	33	I	0.6	1.5	0.002
	30	N	0	11.6	<0.001	36	I	12.7	26.9	<0.001
	32	I	0	4.7	<0.001		V	0.5	2	<0.001
	33	F ^{††}	0.1	4.8	<0.001	63 ^{**}	P	55.2	73.9	<0.001
	46	I	0.1	20.4	<0.001	71	T	4.8	11.1	<0.001
		L ^{††}	0.2	9.7	<0.001		V	2.2	29.9	<0.001
	47	A	0	0.3	0.03 [§]	77 ^{**}	I	24.5	35.0	<0.001
		V	0.1	2.1	<0.001	93 ^{**}	L	25.4	38.9	<0.001
	48	V	0	4.3	<0.001					
	50	L	0	0.5	0.001					
		V	0	1	<0.001					
	53	L	0.1	3.9	<0.001					
	54	A	0	0.6	<0.001					
		L	0	1.8	<0.001					
		M	0	1.1	<0.001					
		T	0	1	<0.001					
		V	0	19.8	<0.001					
		S	0	0.2	0.04 [§]					
	73	A	0	0.4	0.002					
		C	0	1.1	<0.001					
		S	0	9.1	<0.001					
		T	0	2.1	<0.001					
	82	A	0	23.1	<0.001					
		F	0	1.6	<0.001					
		S	0	0.5	0.005 [§]					
		T	0	2.9	<0.001					
	84	A	0	0.3	0.03 [§]					
		C	0	0.4	0.002					
	V	0	12.7	<0.001						
88	D	0	7.4	<0.001						
	S	0	2	<0.001						
90	M	0.1	34.4	<0.001						
New mutations at recognized PI-related positions	20	V	0	0.6	<0.001					
	24	F	0	0.3	0.03 [§]					
	46	V	0	0.3	0.02 [§]					
	48	M	0	0.3	0.01 [§]					
	53	Y	0	0.4	0.002					
	71	I	0.1	2.1	<0.001					
88	T	0	0.3	0.03 [§]						
New mutations at positions not	11	I ^{††}	0.2	0.9	0.001	18	H	0.5	1.4	0.001
	22	V	0	0.4	0.002	45	R	0.5	2	<0.001

recognized as PI-related positions	23	I	0	0.9	<0.001	72	L	0.5	1.5	<0.001
	34	Q	0	0.8	<0.001	92	K	0.6	1.6	<0.001
	35	G ^{††}	0.1	0.9	<0.001					
	43	T	0.1	2.9	<0.001					
	55	R	0.2	2.9	<0.001					
	58	E	0.2	3.5	<0.001					
	66	F	0	1	<0.001					
		L	0	0.4	0.003					
		V	0	0.5	<0.001					
	67	F	0	0.7	<0.001					
	74	A ^{††}	0.2	1.1	<0.001					
		P	0	1	<0.001					
		S ^{††}	0.1	4.8	<0.001					
	76	V	0	1.8	<0.001					
	79	A	0	0.6	0.001					
	85	V	0	3.5	<0.001					
	89	I ^{††}	0	0.5	0.004					
		V	0	1.2	<0.001					
	92	R	0.2	1.2	<0.001					
	95	F	0	1.4	<0.001					

*Expert panel-recognized positions and mutations were categorized using two recently published reviews on HIV-1 drug resistance and recent updates to the IAS-USA expert panel mutation list [1, 2, 6].

†Nonpolymorphic mutations occurred in <0.5% of sequences from untreated persons

¶The method of Benjamini and Hochberg with a false discovery rate <0.01 was used to identify results that were statistically significant in the presence of multiple comparisons [7].

§These 8 rare mutations at nonpolymorphic known PI-related positions were associated with PI treatment only before correction for multiple comparisons

**These 3 mutations were <2 times more prevalent in viruses from treated compared with untreated persons. An exception was made for these mutations because they were the only recognized treatment-related mutations that did not meet this criterion, which was applied to all other mutations as outlined in the methods.

††K20I is the consensus amino acid in subtypes G and CRF02_AG. V11I, L33F, E35G, M46L, P74A/S, V89I were polymorphic in one or more non-B subtypes (range: 1% - 4%).

Table 2. Nucleoside RT Inhibitor-Related Mutations According to Previous Classifications and Extent of Polymorphism in HIV-1 Isolates from Untreated Persons*

	Nonpolymorphic [†]					Polymorphic [†]				
	Pos	AA	Naïve	Rx	p [¶]	Pos	AA	Naïve	Rx	p [¶]
Recognized NRTI-related mutations	41	L	0.5	34.1	<0.001	118	I	2.4	11.8	<0.001
	44	D ^{††}	0.3	5.8	<0.001					
	62	V	0.1	2.3	<0.001					
	65	R	0.1	1.2	<0.001					
	67	N	0	25.2	<0.001					
	69	D	0.1	5.4	<0.001					
		ins	0	0.6	0.001					
	70	R	0.2	22.7	<0.001					
	74	V	0	3	<0.001					
	75	I	0	1.8	<0.001					
	77	L	0.1	2	<0.001					
	115	F	0	1	<0.001					
	116	Y	0	2.1	<0.001					
	151	M	0	2.8	<0.001					
	184	I	0.1	0.7	0.001					
		V	0.2	52.3	<0.001					
	210	W	0	19.6	<0.001					
	215	F	0.1	6.8	<0.001					
		Y	0.1	34.2	<0.001					
	219	E	0.1	2.1	<0.001					
	Q	0.2	12.8	<0.001						
New mutations at recognized NRTI-related positions	44	A	0	0.7	<0.001	69	N	0.5	5.3	<0.001
	67	G	0	1	<0.001		S	0.5	1.5	0.001
		E	0	0.5	0.006 [§]					
	70	G	0	0.3	0.04 [§]					
	74	I	0.1	0.7	0.002					
	75	M	0	1	<0.001					
		T	0	0.8	<0.001					
	215	I	0	0.5	0.003 [§]					
		V	0.1	0.7	0.002					
	219	R	0.3	1	0.005 [§]					
New mutations at positions not recognized as NRTI-related positions	43	E ^{††}	0.1	3.8	<0.001	39	A	2.3	6.8	<0.001
		Q	0.1	2.7	<0.001	90	I	1.2	2.9	<0.001
		N	0.1	1.1	<0.001	102	R	0.6	1.7	0.002
	98	G ^{††}	0.2	1.8	<0.001	104	N	0.5	2	<0.001
	139	M ^{††}	0	0.6	0.002	135	L	0.9	2.4	<0.001
	203	K	0	2.5	<0.001	203	D	0.7	2.1	<0.001
	208	Y	0.1	4.3	<0.001					
	218	E	0	3.3	<0.001					
	223	Q	0	1	<0.001					
	228	H	0.1	3.4	<0.001					
		R	0	1.6	<0.001					

*Expert panel-recognized positions and mutations were categorized using two recently published reviews on HIV-1 drug resistance and recent updates to the IAS-USA expert panel mutation list [1, 2, 6].

[†]Nonpolymorphic mutations occurred in <0.5% of sequences from untreated persons

[¶]The method of Benjamini and Hochberg with a false discovery rate <0.01 was used to identify results that were statistically significant in the presence of multiple comparisons [7].

[§]These 4 rare mutations at nonpolymorphic known NRTI-related positions were associated with NRTI treatment only before correction for multiple comparisons.

^{††}K43E is the consensus amino acid for subtype CRF01_AE. E44D, A98G, and T139M were polymorphic in one or more non-B subtypes (range: 1% - 3%).

Table 3. Non-Nucleoside RT Inhibitor-Related Mutations According to Previous Classifications and Extent of Polymorphism in HIV-1 Isolates from Untreated Persons*

	Nonpolymorphic [†]						Polymorphic [†]					
	Pos	A A	Naï ve	NRTI alone	NRTI+ NNRTI	p [¶]	Pos	A A	Naïve	NRTI alone	NRTI+ NNRTI	p [¶]
Recognized NNRTI-related mutations	100	I	0	0	5.2	<0.001	108	I	0.3	0.5	6.4	<0.001
	103	N	0.3	0.4	48.8	<0.001						
	106	A	0	0	2.5	<0.001						
		M	0	0	0.6	0.001						
	181	C	0	0.2	25.2	<0.001						
		I	0	0	1.3	<0.001						
	188	C	0	0	0.3	0.04 [§]						
		H	0	0	0.6	0.001						
		L	0	0.1	4.9	<0.001						
	190	A	0	0.2	13.4	<0.001						
		S	0	0.1	3.2	<0.001						
	225	H	0	0	2.9	<0.001						
	230	L	0	0	1.3	<0.001						
236	L	0.1	0.2	0.9	0.006							
New mutations at recognized NNRTI-related positions	103	S	0	0	1	<0.001						
	181	V	0	0	0.3	0.02 [§]						
	190	Q	0	0	0.4	0.007 [§]						
		E	0	0	0.9	<0.001						
New mutations at positions not recognized as NNRTI-related positions	101	H	0	0.1	0.8	<0.001	65	R	0.1	1.2	3.9	0.001
		N	0	0	0.6	<0.001	74	I	0.1	0.7	5.3	<0.001
		P	0	0	1.4	<0.001		V	0	3	12.5	<0.001
	111	I	0.1	0.4	1.4	0.001	75	M	0	1	3.6	0.001
	138	Q	0	0	0.6	0.001	98	G	0.2	1.8	4.6	<0.001
	179	E ^{††}	0.3	0.1	0.9	0.001	101	E	0.2	0.6	5.2	<0.001
	221	Y	0	0.3	6.1	<0.001		Q	0.4	0.8	3.8	<0.001
	227	L ^{††}	0	0.1	1.9	<0.001	179	D	1.3	0.6	2.5	<0.001
	238	T	0.1	0.1	2.1	<0.001		I	2.4	2.8	7.5	<0.001
							162	D	0.3	0.7	2.5	<0.001
							189	I	0.5	0.5	1.9	<0.001
							215	C	0.3	0.5	1.5	<0.001
							219	N	0.1	0.9	4.1	<0.001
								R	0.3	1	3.1	<0.001
							223	E	0	0.6	1.9	<0.001
						228	H	0.1	3.4	10.1	<0.001	
							R	0	1.6	4.9	<0.001	
						237	E	0.4	0.5	1.2	0.001	

*Expert panel-recognized positions and mutations were categorized using two recently published reviews on HIV-1 drug resistance and recent updates to the IAS-USA expert panel mutation list [1, 2, 6].

[†]Nonpolymorphic mutations occurred in <0.5% of sequences from untreated persons or persons receiving NRTIs but not NNRTIs.

[¶]To identify NNRTI-associated mutations, the prevalence of mutations in persons treated with both NRTIs and NNRTIs was compared to their prevalence in persons treated with NRTIs alone. For mutations associated with both NRTIs and NNRTIs the relative contributions of NRTI and NNRTI treatment was assessed using a generalized linear model that accounted for three different levels of NRTI treatment (1-2 NRTIs, 3-4 NRTIs, >4 NRTIs). The method of Benjamini and Hochberg with a false discovery rate <0.01 was used to identify results that were statistically significant in the presence of multiple comparisons [7].

[§]These 3 rare mutations at nonpolymorphic known NNRTI-related positions were associated with NNRTI treatment only before correction for multiple comparisons.

^{††}V179E occurred at a prevalence of 7% in subtype G; F227L occurred at a prevalence of 2% in subtype F.

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