HIV-GRADE Drug Resistance Interpretation Web-Tool Update for Capsid- and Post-Attachment-Inhibitors

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BACKGROUND

With the approval of new drug classes with different modes of action and new drug resistance mutations in targets that are currently not covered by the existing analysis tools an update for these region was necessary and implemented. Mutations for capsid inhibitors can be found in the gene region of gag coding for the capsid protein, while mutations against post-attachment inhibitors can be found in the env gene gp120 region.

METHODS

The existing framework of the HIV-GRADE (**G**enotypic **R**esistance-**A**lgorithm **DE**utschland.tool, a web-web based tool to identify and interpret viral drug resistancehttps://www.hiv-grade.de/cms/grade/) was extended to recognize and correctly number highlight the amino acid positions of the capsid region and the gp120 region. Subtype specific consensus sequences were gathered from Los Alamos National Laboratories (LANL) HIV Sequence database. These sequences were then realigned and patterns for recognition of the gene regions extracted (92 each for capsid and gp120capsid and gp120: 92 each). Test sequences were also extracted retrieved from LANL HIV sequence database (459 each). Interpretation rules were generated by the HIV-GRADE expert team based on published data and translated into ASI-XML files.

HIV-GRADE

HIV-GRADE group

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RESULTS

a)

EIGP120	GRADE 09/2024			ANRS 35_04/2024			HIVDB 9.6		
	Mutation List	Rating	SIR	Mutation List	Rating	SIR	Mutation List	Rating	SIR
FTR	M475I, S375H	Resistance	R	M475I, S375H	Resistance	R			
IBA		Susceptible	S						
Scored mutations for Drugclass EIGP120: S375H, M475I									
EIGP120 Comments (4)									

b)

EIGP120	GRADE 09/2024			ANRS 35_04/2024			HIVDB 9.6		
	Mutation List	Rating	SIR	Mutation List	Rating	SIR	Mutation List	Rating	SIR
FTR		Susceptible	S		Susceptible	S			
IBA	N460Q	Intermediate	I						
Scored mutations for Drugclass EIGP120: N460Q									
EIGP120 Comments (2)									

Figure 1: Output env sequences with M475I/S375H (a) or N460Q (b) mutations

a)

Gene	Differences from Consensus B / Drug Resistance Mutations
p24	V27I, Q63P, A65AV, **Q67L**, **N74DN**, E76R, A77C, A78C, E79R, E79R_S, P90S, T148V, E180D

CAPI	GRADE 09/2024			ANRS 35_04/2024			HIVDB 9.6		
	Mutation List	Rating	SIR	Mutation List	Rating	SIR	Mutation List	Rating	SIR
LEN	N74DN	Resistance	R	N74DN	Resistance	R	N74DN	High-Level Resistance (Score: 60)	R
Scored mutations for Drugclass CAPI: N74DN									
CAPI Comments (1)									

b)

Gene	Differences from Consensus B / Drug Resistance Mutations
p24	L6A, Q13T, A14P, S33N, T48L, Q50L, L52V, T58A, A64G, M68V, **K70R**, T72V, L83M, M96L, M118A, N120A, E128D, K131R, I134V, K140R, I141V, R143K, S146C, T148V, R154K, R162K, L172M, N183T, E187D, T200Q, A208G, T210S, G225A

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CAPI	GRADE 09/2024			ANRS 35_04/2024			HIVDB 9.6		
	Mutation List	Rating	SIR	Mutation List	Rating	SIR	Mutation List	Rating	SIR
LEN	K70R	Resistance	R	K70R	Resistance	R	K70R	Low-Level Resistance (Score: 20)	I
Scored mutations for Drugclass CAPI: K70R									

Figure 2: Output gag sequences with N74D (a) or K70R (b) mutation

RESULTS

All of the 459 test sequences for each gene region could be correctly identified and interpreted. Known drug resistance mutations were identified and drug resistance was predicted interpreted based on the ruleset defined by the HIV-GRADE team. This includes subtype specific mutations that can lead to pre-existing drug resistance.

CONCLUSIONS

With the upgrade of the HIV-GRADE tool v.07/24 drug resistance interpretation of new drug classes can now be substantially simplified. This allows for more accessible drug resistance interpretation in patients individuals with limited treatment options.