Supplemental Figure 1. Amino acid sequence of protease region of 11 HIV_{MDR}s

	10	20	30	40	50	60	70	80	90	99
$\text{HIV}_{\text{NL4-3}}$	PQITLWQRPL	VTIKIGGQLK	EALLDTGADD	TVLEEMNLPG	RWKPKMIGGI	GGFIKVRQYD	QILIEICGHK	AIGTVLVGPT	PVNIIGRNLL	TQIGCTLNF
HIV_{A}	I	....V.....	....	....D.E...	....R.....	...V......	..P.......	V.........	.T.......M	..L.F....
HIV_{B}	I	....	....	..I..I....	.....I....	..L.R.....	.VP.......	V.S.......	.A.......M	..L......
HIV_{C}	I	....V....R	...I......	.....I....	.....L....	...V......	.VP......Q	....	.A......M.	....
HIV_{G}	I	IE..V...I.	....	....	K....L....	....	..P.......	T.........	.A.......M	....
HIV_{TM}	I	...R......	....	....	K....L....	...V......	..P.......	V.........	.A.......M	..L......
HIV_{MM}	I	.......R..	....	....	..T..L....	...V......	..P.......	V.........	.A.......M	..K......
HIV_{SS}	.........R	....	....	.....D....	.....T....	....	.VP.......	V.S...I...	.T.......M	..L......
HIV_{JSL}	I	....	...I......	..F.DIS...	.....L..E.	...V..K...	.VP.......	V.S.......	.A.......M	....
HIV_{EV}	V	.E...A..IR	....	..F.DI....	.....I...V	..LVR.K..E	.VP.......	V.........	.A......M.	....
HIV_{ES}	I	....	....	....	.....L....	....R.....	.VP.......	.LC...I...	....V....M	....
$\text{HIV}_{\text{13-52}}$	....	....	....	.....D....	.....I....	....	.VP.......	V.....I...	.A.......M	..L......

The amino acid sequences of protease deduced from nucleotide sequences of the protease-encoding region of each of the eleven HIV_{MDR}s are shown. The consensus sequence of $\text{HIV}_{\text{4-3}}$ is illustrated at the top as a reference. Identity with sequence at individual amino acid positions is indicated by dots.

Table S1. X-ray diffraction data processing details for $_{\mathrm{WT}}\mathrm{PR}^{\mathrm{D25N}}$ in complex with GRL-0476, -015, -085, and -097.

	$_{\mathrm{WT}}\mathrm{PR}^{\mathrm{D25N}}$ + GRL-0476	$_{\mathrm{WT}}\mathrm{PR}^{\mathrm{D25N}}$ + GRL-015	$_{\mathrm{WT}}\mathrm{PR}^{\mathrm{D25N}}$ + GRL-085	$_{\mathrm{WT}}\mathrm{PR}^{\mathrm{D25N}}$ + GRL-097
PDB entry	5COK	5CON	5COO	5COP
Resolution range (Å)	50.00 - 1.8	50.00 - 1.75	50.00 - 1.68	50.00 - 2.0
Unit cell - a (Å)	62.734	62.786	62.786	62.663
b (Å)	62.734	62.786	62.786	62.663
c (Å)	81.952	81.907	81.880	81.955
α (°)	90	90	90	90
β (°)	90	90	90	90
γ (°)	120	120	120	120
Space group	$P6_1$	$P6_1$	$P6_1$	$P6_1$
Solvent content (%)	43.16	43.22	43.20	43.06
No. of observed reflections	195,583	211,911	235,184	54,416
No. of unique reflection	16,990	18,426	11,367	12,252
Mean $(I/\sigma(I))$	59.78 [a](8.95)	54.46 (5.9)	58.14 (3.471)	23.03 (2.89)
[b]R_{merge}	0.079 (0.342)	0.074 (0.477)	0.084 (1.0)	0.099 (0.526)
Data redundancy	11.5 (11.3)	11.5 (11.6)	20.7 (20.2)	4.4 (3.9)
Completeness (%)	100 (100)	99.4 (98.7)	99.2 (84.2)	98.7 (99.8)

[a](Values in parentheses are for the highest resolution shell);

[b]$R_{\mathrm{merge}} = \Sigma |I - \langle I \rangle| / \Sigma I$

Table S2. Refinement statistics for structure solutions of ${}_{WT}PR^{D25N}$ in complex with GRL-0476, -015, -085, and -097.

	${}_{WT}PR^{D25N}$ + GRL-0476	${}_{WT}PR^{D25N}$ + GRL-015	${}_{WT}PR^{D25N}$ + GRL-085	${}_{WT}PR^{D25N}$ + GRL-097
PDB entry	5COK	5CON	5COO	5COP
Resolution range (Å)	45.28 - 1.8	31.393 - 1.8	31.393 - 1.8	31.332 - 2.0
No. of reflections used	16,934	16,922	16,962	12,230
${}^{a}R_{cryst}$	0.21	0.22	0.23	0.20
R_{free}	0.25	0.26	0.28	0.26
No. of protein atoms	1514	1514	1514	1514
No. of ligand atoms	40	41	43	42
No. of water molecules	164	144	132	116
Mean temperature factors - protein (Å^2)	24.567	26.834	26.312	29.582
Main chains (Å^2)	22.273	24.400	24.050	27.210
Side chains (Å^2)	27.078	29.502	28.800	32.177
Ligand (Å^2)	21.907	22.958	21.798	24.195
Waters (Å^2)	32.035	33.524	31.896	34.336
RMSD bond lengths (Å)	0.009	0.008	0.009	0.009
RMSD bond angles (Å)	1.32	1.26	1.195	1.190
Ramachandran plot - Most favored (%)	98.45	97.42	96.39	98.97
Additional allowed (%)	1.55	2.06	3.09	1.03
Generously allowed (%)	0	0.52	0.52	0
Disallowed (%)	0	0	0	0

${}^{a}R_{cryst} = \Sigma \, ||F_{obs}| - |F_{calc}|| \, / \, \Sigma|F_{obs}|$