Mutations Associated with Reduced Susceptibility to PIs

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Disclosures

- Gilead Sciences (2022): Advisory board and speaking honorarium.
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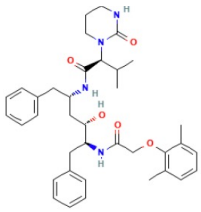
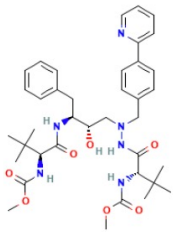
These are my disclosures.

HIV-1 Protease Inhibitors

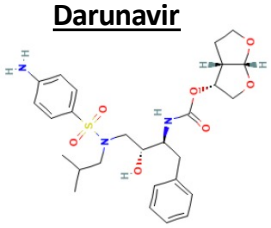
Lopinavir

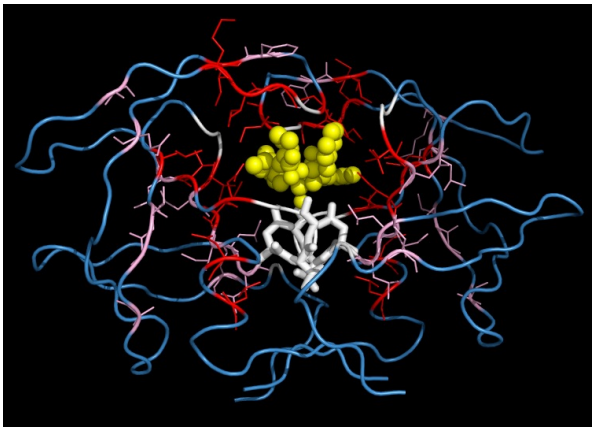


Atazanavir



Darunavir

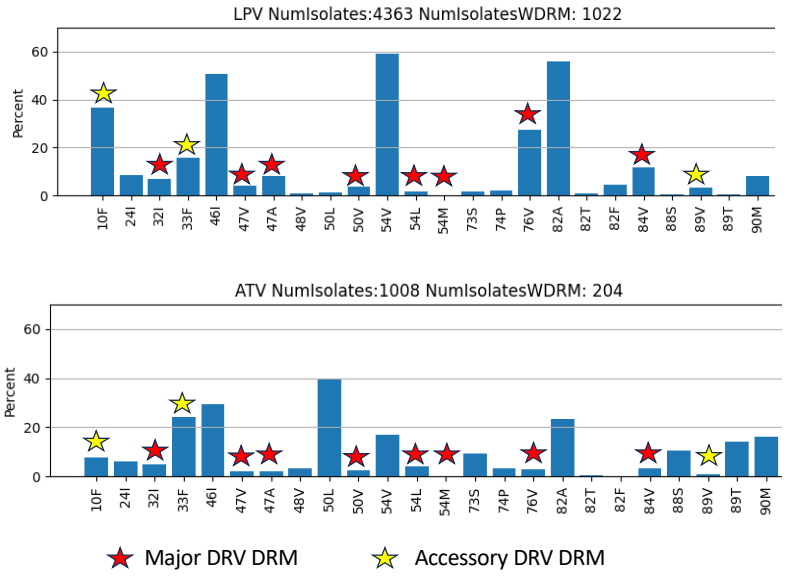




Active site Inhibitor DRMs

1. There are three main PIs in current use: LPV co-formulated with the PK booster RTV; ATV - which is co-formulated with the PK booster cobicistat but which can be co-administered with RTV and which is aalso pproved for use without boosting; and DRV which is co-formulated with cobicistat and which can also be co-administered with RTV.
2. Each of the PIs mimics that natural substrate of the polypeptides that are cleaved by the protease enzyme.
3. The figure on the right shows the 3-D structure of the HIV-1 protease bound to a OI in yellow which resides in the enzyme's substrate cleft.
4. Most of the major PI DRMa reside in the substrate cleft where they directly contact PIs. Some are in the flap which opens and closes to allow entry of the HIV-1 polypeptide.
5. Several additional mutations are situated further away and reduce PI susceptibility by impacting neighboring residues or by compensating for the reduced fitness associated with substrate cleft mutations.

PI- Selected Mutations



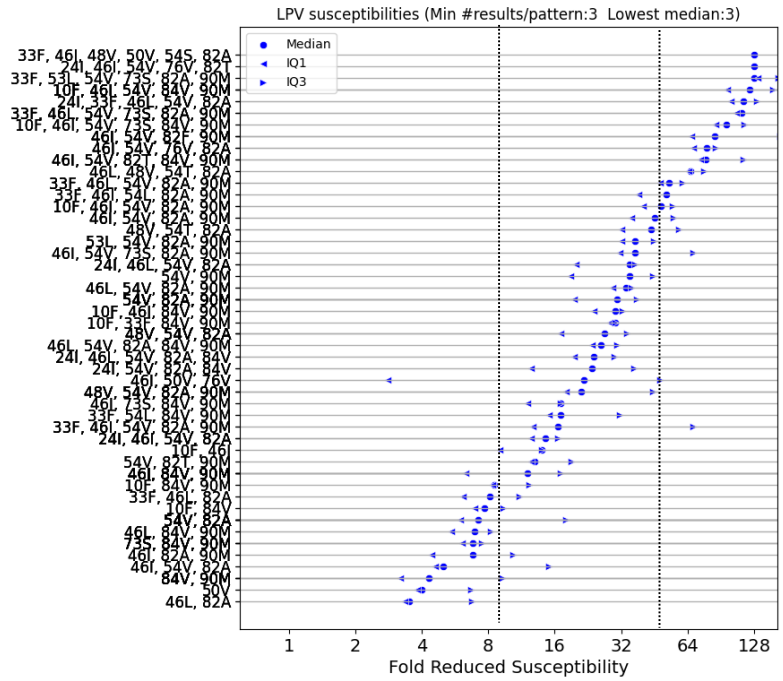
PI	#Pts
LPV	4363
ATV	1008
DRV	164

DRV resistance in PI-naïve persons receiving b-DRV is exceedingly rare.

1. The top figure show the DRMs selected in patients receiving LPV/r but no other PI.
2. The bottom figure shows the the DRMs selected in patients receiving ATV with or without PI boosting.
3. Fewer data are available for DRV, because in the early years of it use, it was often used to treat patients in whom other PIs failed.
4. As you can see from the figure headers only 20% to 25% of those with VF on an LPV or ATV containing regimen containing-regimen develop PI-associated DRMs.
5. This is a well-recognized phenomena that speaks to the high genetic barrier to resistance to these PIs which often requires about 2 years before DRMs to develop.
6. The stars indicate the major and accessory DRV-associated DRMs which is relevant because DRV is the PI used to treat patients in whom other PIs failed.
7. M46I, I54V, and V82A are the most commonly selected LPV resistance mutations. These are of interest because they do not cause cross resistance to LPV. Other common DRMs, which are associated with DRV cross-resistance include V32I, I47AV, L76V, I84V, the common accessory DRMs L10F and L33F and the uncommon substrate cleft DRM I50V.
8. ATV selects for two major signature DRMs that are not selected for by LPV - I50L

and N88S. There is also some overlap with the DRMs selected by LPV in that V32I, M46I, I54V, V82A, I84V, and L90M have also been selected by ATV. Of note I50L is associated with increased susceptibility to each of the other PIs including LPV and DRV.

9. Fewer DRMs may have been selected by ATV/r because most samples were obtained from UICs where patients were more likely to receive ATV for first-line therapy with active NRTIs and because VF was usually detected earlier before the accumulation of multiple DRMs.
10. Not only are there fewer available data for DRV but the development of PI-associated DRMs is exceedingly rare in patients receiving DRV. In fact, it is possible that the few cases that have been reported represent transmitted PI resistance or incorrect treatment histories.
11. Even in vitro it has not been possible to select for DRV-resistance mutations while it has been possible to select for LPV and ATV resistance mutations.



LPV Susceptibility

Codons 10, 20, 33, 36, 47, 48, 54, 82, and 84 were found to be most predictive in 2007.

King MS. Predictive Genotypic Algorithm for Virologic Response to LPV/r in PI-Experienced Patients. AAC 2007

Lower Clinical Cutoff: 9-fold
Upper Clinical Cutoff: 55-fold

Coakely EP. Defining Phenotypic Clinical Cutoffs for Tipranavir/r, Lopinavir/r, Saquinavir/r and Amprenavir/r in the RESIST dataset by the PhenoSense Assay. ICAAC 2006

1. The other main form of data that teaches us about HIVDR is in vitro susceptibility or phenotypic data.
2. The figure shows the fold reduction in susceptibility determined by the Monogram PhenoSense assay to LPV associated with those patterns of DRMs present in at least 3 viruses. The figure would be much larger if all patterns were included. The median and IQR are shown. In addition, only those patterns associated with a median fold-reduction ≥3-fold are shown also because of space limitations. Isolates were only included if fewer than one-third of the DRMs had a mixture.
3. What do we know about the clinical significance of LPV-associated DRMs and their accompanying fold reductions in susceptibility.
4. An analysis of the earliest studies in which LPV was used to treat patients who had developed VF after receiving other PIs, reported that mutations at 9 positions were found to be the most predictive of a reduced virological response to LPV. This analysis only looked at whether there was a mutation at a position not what the mutation was. The data was also skewed by the fact that most patients in these studies had previously received older PIs such as nelfinavir, saquinavir, amprenavir, and indinavir.
5. An analysis performed at the same time suggested that isolates with a fold-

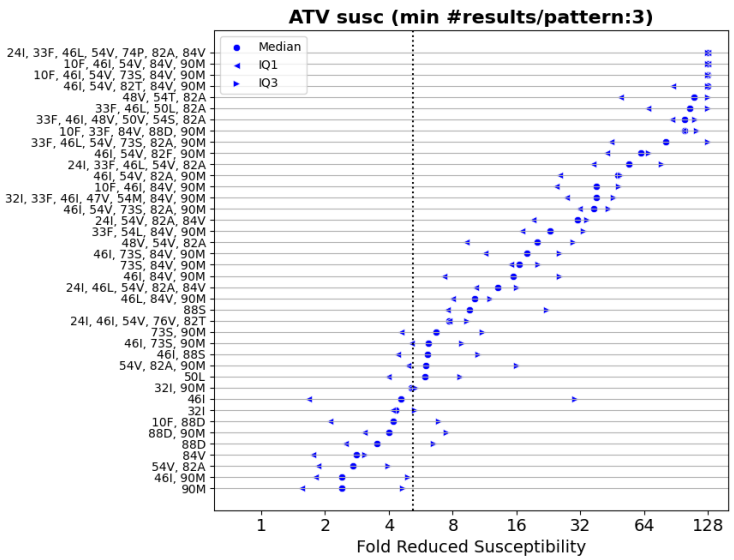
reduction of >9-fold had a reduced virological response to LPV and those with a fold-reduction >55-fold had no virological response to LPV.

ATV Susceptibility

Clinical cutoffs: In AI-424-045 (ATV/r), proportions with VL<400 for those with baseline ATV FC <5.2 and ≥5.2 were 77% and 12%, respectively.

Johnson M. ATV/r or SQV, and LPV/r in patients experiencing multiple virological failures (AI424-045). AIDS 2005

Coakley EP. Determination of phenotypic clinical cutoffs for ATV and ATV/r from AI424-043 and AI424-045. HIVDR Workshop 2005



1. This figure shows the median and interquartile range of the fold reduction in ATV susceptibility associated with patterns of PI-resistance DRMs that occurred in at least three patients. Only those patterns associated with a median fold-reduction ≥2-fold are shown because of space limitations.
2. In contrast to LPV and DRV, there has been no large study that has developed a genotype score for ATV/r. There have been several small studies but the DRMs often differed between these studies.
3. Moreover, ATV is primarily used for first line therapy and does not have an important role following the VF

of other PIs.

4. Boosted ATV/r has a lower genetic barrier than LPV and DRV as an analysis based on one clinical trial in which ATV/r was used in PI-experienced patients found that was a marked drop off in virological suppression for isolates with a >5-fold reduction in ATV susceptibility.
5. The figure shows that this reduction can be reached with certain individual DRMs such as N88S and I50L and with certain combinations of 2 or 3 DRMs.

DRV Susceptibility

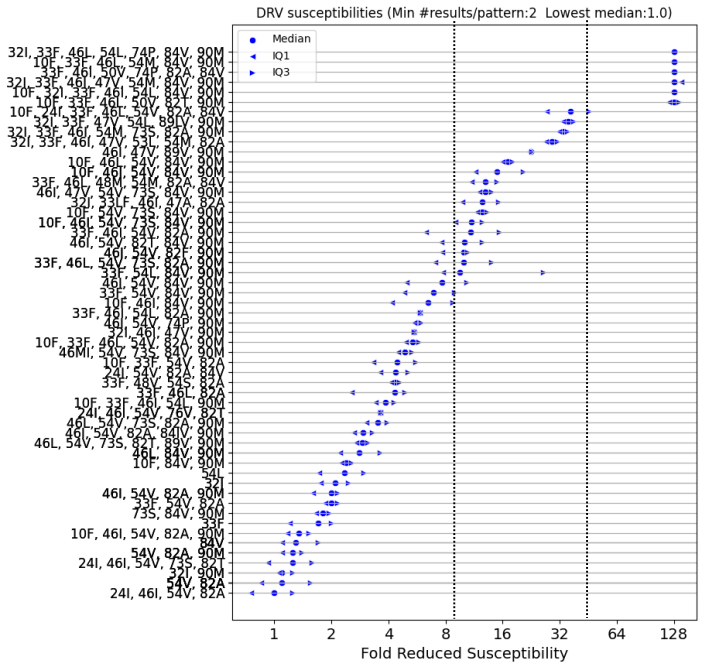
Major DRMs
- **V32I**
- **I47V**/A
- **I50V**
- **I54L/M**
- **L76V**
- V82F
- **I84V**

Accessory DRM
- L10F
- **V11I**/L
- **L33F**
- **G73S**
- **T74P**
- L**89V**

De Meyer S. Resistance profile of darunavir: combined 24-week results from the POWER trials. ARRH 2008

Phenotypic thresholds
- >10-fold: low-level resistance
- >90-fold: high-level resistance

Petropoulos C. Upper and lower phenotypic clinical cut-offs: defining darunavir/r activity within the POWER 1, 2, and 3 trials as exemplary datasets by the PhenoSense assay. 5th European HIVDRW. 2007.



1. The figure shows the fold reduction in susceptibility to DRV associated with those patterns of DRMs present in at least 2 viruses. The median and IQR are shown.
2. A very robust genotypic resistance score was developed in 2008 based on data from the POWER trials.
3. This score predicted the fold reduction in DRV susceptibility and the likelihood of responding to a DRV-containing salvage therapy regimen.
4. The highest levels of DRV resistance occur in isolates containing about 5 DRMs: 2 or 3 of the major DRMs plus 2 or3 of the accessory DRMs.
5. The DRMs in bold were in the original score. But we found that a few additional DRMs also contributed to reduced DRV susceptibility.
6. An analysis by Monogram Biosciences found that a 10-fold reduction in susceptibility was required to have a reduced virological response to DRV salvage therapy and that a 90-fold reduction was required to completely abrogate the effects of DRV salvage therapy.

Predicted Cross-Resistance Associated With LPV-Selected DRMs

No. Mut	Mutation List†	Num Pts	LPV§	ATV§	DRV§
1	L10F	1	5	0	0
	L33F	1	5	5	5
	M46L	1	10	10	0
	I47A¶	1	**60**	**70**¶	10
	I54V	1	10	15	0
	L76V	1	**30**	0	20
	V82A	1	25	15	0
	I84V	1	15	**45**	10
	L90M	1	10	20	0
2	I54V, V82A	6	**35**	**35**	0
	L10F, V82A	4	**30**	15	0
	M46I, L76V	2	**50**	7.5	20
	I54V, I84V	1	**25**	**55**	10
	M46I, V82A	1	**35**	**30**	0
	M46I, I50V	1	**30**	10	20
	V32I, I47A	1	**>60**	20	**30**
3	M46I, I54V, V82A	3	**55**	**50**	0
	I54V, L76V, V82A	2	**>60**	**45.5**	20
	L24I, V32I, I47A	1	**>60**	25	**30**
	L10F, L76V, V82A	1	**60**	15	20
4	M46I, I54V, L76V, V82A	3	**>60**	**>60**	20
	M46I, I50V, I54V, V82A¶	2	**>60**	>60¶	20
	L10F, M46I, I54V, V82A	2	**>60**	**60***	20
	L10F, I54V, I84V, L89V¶	1	**35**	**>60**¶	15
	L10F, L33F, I54V, V82A	1	**55**	**45**	5
	L10F, L24I, I54V, V82A	1	**>60**	**45**	0
5	L10F, M46I, I54V, L76V, V82A	4	**>60**	**55**	20
	L10F, M46L, I54V, L76V, V82A	1	**>60**	**55**	20
	L10F, M46I, I54V, V82A, I84V	1	**50**	**>60**	10
	L10F, M46I, I54V, L76V, I84V	1	**>60**	**60**	**30**
	L10F, L24I, L33F, I54V, V82A	1	**>60**	**55**	5
	L10F, L33F, I54V, L76V, V82A	1	**>60**	**40**	25
6	L10F, L24I, L33F, M46I, I54V, V82A	1	**>60**	**>60**	5
	L10F, L24I, L33F, M46L, I54V, V82A	1	**>60**	**>60**	5
	L10F, L33F, M46I, I54V, V82A, L90M	1	**>60**	**>60**	5
	L10F, L33F, M46I, I50V, I54V, V82A	1	**>60**	**>60**	25
7	L10F, L24I, L33F, M46I, I54V, L76V, V82A	1	**>60**	**>60**	25

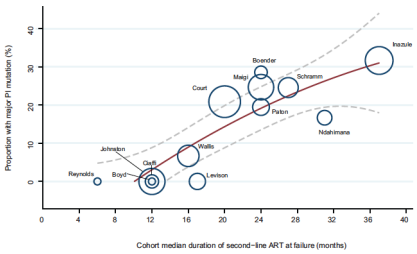
Van Zyl G. Trends in Genotypic HIV-1 ARV Resistance between 2006 and 2012 in South African Patients Receiving First- and 2nd-Line ART Regimens. PLOS One 2013

1. This slides shows the patterns of PI DRMs in 55 patients who developed VF on a 2nd-line LPV/r containing regimen in South Africa and who were found to have at least one PI-associated DRM.
2. The 3 columns show the scores associated with each of the patterns determined by the HIVDB interpretation program. 19 patients had a score of 20 or 25 associated with low-levels DRV resistance and 3 had a score of 30 associated intermediate DRV resistance. This suggests that DRV will usually be active in patients with VF on an LPV/r containing regimen, although in many patients the genetic barrier to DRV resistance will be decreased.
3. Although patients with VF on ATV/r are less likely to have DRV cross resistance, there has been no published comparably sized cohort of patients in an LMIC who received ATV/r for 2nd-line therapy.

LPV/r, b-ATV, and b-DRV have High Genetic Barriers to Drug Resistance

- Most patients with VF on a boosted PI do not initially have PI-resistance DRMs.
- Resistance to 2nd-line LPV/r usually takes about 2 years to develop.
- PI DRMs develop in a narrow window of suboptimal drug concentration that both exert selective pressure and allow virus replication.

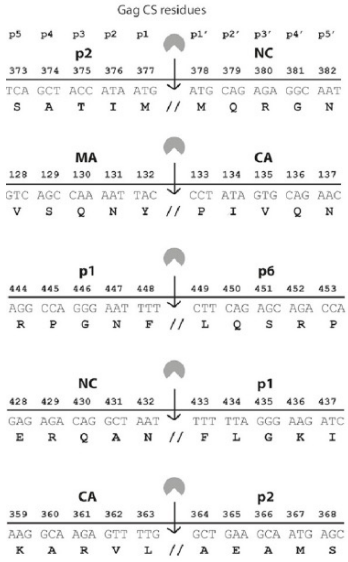
Rosenbloom D. Antiretroviral dynamics determines HIV evolution and predicts therapy outcome. Nat Med 2012



Stockdale A, et al. Effectiveness of PI/NRTI-based 2nd-line ART for the treatment of HIV-1 in sub-Saharan Africa: Systematic review and meta-analysis. Clin Infect Dis 2018

1. The PIs have a high genetic barrier to resistance.
2. Most patients with VF on a boosted PI do not initially have PI-resistance DRMs.
3. The most recent experience with PI resistance comes from 2nd-line therapy in LMICs where patients receive LPV/r in combination with NRTIs that are often compromised as a result of resistance that developed during their first-line regimen.
4. In this setting PI resistance to LPV/r usually requires about 2 years as shown in the figure and as reported in a recent systematic review.
5. Fewer data are available for b-ATV in this same scenario. And as noted earlier the risk of emergent PI resistance in PI-naïve persons receiving b-DRV is exceedingly low.
6. It has been hypothesized that PI DRMs develop in a narrow window of suboptimal drug concentration that both exert selective pressure and allow virus replication.

Gag Cleavage Site Mutations



- Gag cleavage site mutations are also often required to compensate for PI DRMs in protease.

Fun A. Human Immunodeficiency Virus gag and protease: partners in resistance. Retrovirology 2012

1. One of the explanations for the high genetic barrier to PI resistance is that in additions to the frequent requirement for multiple mutations in the protease, drug resistance often requires additional mutations in Gag usually at the sites that are recognized and cleaved by the protease enzyme.

PI Notes and Handout

The table lists the most common clinically significant PI-resistance mutations. Those in bold red are associated with the highest levels of phenotypic resistance and/or with the strongest clinical evidence for interfering with successful PI therapy. Those mutations that are underlined are potential contraindications to the use of the relevant PI.

HIV-1 develops resistance to PIs as a result of protease mutations that reduce PI binding affinity and compensate for the reduced fitness associated with PI binding-site mutations. The genetic barrier to PI resistance is high because most binding-site mutations appear to require one or more additional mutations to compensate for their reduced fitness. PI-resistance mutations appear to develop only in viruses exposed to a narrow window of suboptimal drug concentrations that both exert selective pressure on the virus and allow virus replication (1). In addition, protease mutations often require one or more compensatory gag cleavage-site mutations (2).

Of the three PIs currently in use, LPV and DRV are administered in conjunction with pharmacokinetic boosting: ritonavir for lopinavir and ritonavir (r) or cobicistat for DRV. ATV can administered with or without pharmacokinetic boosting, although it is most commonly used with ritonavir or cobicistat. Throughout this page we refer to each of the three PIs as ATV, DRV, and LPV. We refer to other earlier PIs when they represent the most common PIs responsible for selecting a DRM. We provide susceptibility data only for ATV, DRV, and LPV. However, in contrast to the Notes pages for the NRTIs, NNRTIs, and INSTIs, we rarely provide estimates of fold reductions in susceptibility because the effect of individual mutations is more dependent on their mutational context as compared with mutations that confer resistance to ARVs belonging to other drug classes.

PI resistance emerges uncommonly and slowly in persons with VF in PI-naïve persons receiving a regimen with boosted ATV, DRV, and LPV. Nonetheless, resistance to LPV, the most commonly used PI globally, does emerge after two years of therapy in persons with VF on a second-line LPV/r-containing salvage therapy regimen (3). Fewer data are available on the rate of development of ATV resistance in PI-naive persons receiving ATV/r (4,5,6). The frequency with which DRV resistance emerges in PI-naive persons receiving DRV/r is extremely rare to the point of being reportable (7,8).

Although mutations outside of protease compensate for the reduced fitness associated with PI-resistance mutations in protease, alone such mutations have not been shown to significantly reduce the response to PI therapy. Indeed persons with VF without PI-resistance mutations in protease usually respond to re-treatment with the same PI (9)(9,10).

L10F/I/V/R/Y

- L10F/I/V/R/Y
- V11I/L
- K20R/I/M/T/V
- L23I
- L24I/F/M
- D30N
- V32I
- L33F
- M36I
- K43T
- M46I/L/V
- I47V/A
- G48V/M/A/S/T/Q
- I50V/L
- F53L/Y
- I54V/A/S/T/L/M
- Q58E
- A71V/T/I/L
- G73S/T/C/A/D/V
- T74P/S
- L76V
- V82A/T/S/F/L/M/C
- N83D/S
- I84V/A/C
- I85V
- N88D/S/T/G
- L89V/T
- L90M

https://hivdb.stanford.edu/dr-summary/resistance-notes/PI/

Major Protease Inhibitor (PI) Resistance Mutations

	32	46	47	48	50	54	76	82	84	88	90
Cons	**V**	**M**	**I**	**G**	**I**	**I**	**L**	**V**	**I**	**N**	**L**
ATV/r	**I**	IL	V	**VM**	**L**	VTALM		ATFS	**V**	**S**	**M**
DRV/r	**I**		VA		**V**	**LM**	**V**	F	**V**		
LPV/r	**I**	IL	V**A**	VM	**V**	**VTALM**	**V**	**AFTS**	**V**		M

Bold underline: High-level reduced susceptibility or virological response. **Bold**: Reduced suceptibility or virological response. Plain text: Reduced susceptibility in combination with other PI-resistance mutations.

Abbreviations: atazanavir (ATV), darunavir (DRV), lopinavir (LPV), 'r' (ritonavir).

Additional mutations: L10F, V11I, K20TV, L23I, L33F, K43T, F53L, Q58E, A71IL, G73STCA, T74P, N83D, and L89V/T are common nonpolymorphic accessory resistance mutations. L10F, V11IL, L33F, T74P, and L89V are accessory resistance mutations associated with reduced DRV/r susceptibility. D30N and N88D are nonpolymorphic resistance mutations selected by NFV. L10RY, V11L, L24F, M46V, G48ASTLQ, F53Y, I54S, V82CM, I84AC, N88TG are rare nonpolymorphic variants.

Hypersusceptibility: I50L (each PI except ATV); L76V (ATV).

https://cms.hivdb.org/prod/downloads/resistance-mutation-handout/resistance-mutation-handout.pdf

1. The data that I reviewed in this presentation are summarized to a large extent in the Notes section of the HIV GRT interpretation program and in a very brief format in a PDF handout.
2. No major changes were made to the Notes and PDF handout since October 2022.

Individual DRM Scores

Rule	ATV/r	DRV/r	LPV/r
K20T	5	0	0
L24F	5	0	5
L24I	10	0	10
L24M	5	0	5
V32I	15	15	15
L33F	5	5	5
M46I	10	0	10
M46L	10	0	10
M46V	10	0	5
I47V	10	10	15
G48A	10	0	10
G48L	10	0	10
G48M	30	0	10
G48Q	10	0	10
G48S	10	0	10
G48T	10	0	10
G48V	30	0	10
I50L	60	-10	-10
F53L	10	0	0
I54A	15	0	15
I54L	15	20	20
I54M	15	20	20
I54S	15	0	15
I54T	15	0	15
I54V	15	0	15
G73A	10	0	5
G73C	10	0	5

Rule	ATV/r	DRV/r	LPV/r
G73D	5	0	5
G73S	10	0	5
G73T	10	0	5
G73V	5	0	5
T74P	10	5	5
V82A	15	0	30
V82C	15	0	15
V82F	15	15	30
V82L	10	0	10
V82M	10	0	25
V82S	30	0	30
V82T	30	0	30
N83D	10	0	0
I84A	60	30	60
I84C	60	15	30
I84V	60	15	30
N88D	10	0	0
N88G	15	0	0
N88S	60	-5	0
N88T	15	0	0
L90M	25	0	15
L10F	0	5	5
I47A	0	10	60
I50V	0	20	30
L76V	0	20	30
L89V	0	5	0

Combination DRM Scores

Combination Rule	ATV/r	DRV/r	LPV/r
V32I + I47AV	5	5	5
V32I + I54LM	5	5	5
M46IL + I84V + L90M	5	0	5
M46ILV + V82ACFLMST	10	0	10
M46ILV + L90M	10	0	0
I47AV + I54LM	5	5	5
F53L + L90M	10	0	0
I54ALMSTV + V82ACFLMST	10	0	10
I54ALMSTV + L90M	10	0	5
G73ACSTV + L90M	10	0	0
V82ACFLMST + L90M	10	0	5
V11IL + V32I	0	5	5
V11IL + I54LM	0	5	5
V32I + L76V	0	5	5
V32I + I84V	0	5	5
V32I + L89V	0	5	5
I47AV + I84V	0	5	5
I54LM + I84V	0	5	5
I54LM + L89V	0	5	5
M46ILV + L76V	0	0	10

https://hivdb.stanford.edu/dr-summary/mut-scores/PI/

1. The HIVDB website also contains a list of all scores, which were last updated March 2024
2. There are individual mutation penalty scores for nearly all DRMs and several penalties that go into effect only when certain DRM combinations are present.
3. The total mutation penalty score for a drug is based on adding all of the individual and combination penalty scores.

PI Comments

Condition	Comment/ Mutation Type	Comment
DRV/r=5		There is evidence for high-level DRV resistance. If DRV is administered it should be used twice daily.
DRV/r=4		There is evidence for intermediate DRV resistance. If DRV is administered it should be used twice daily.
DRV/r=3		There is evidence for low-level DRV resistance. If DRV is administered it should be used twice daily.
10F	Accessory	L10F is a common non-polymorphic, PI-selected accessory mutation associated with reduced in vitro susceptibility to LPV and DRV.
48V	Major	G48V is a nonpolymorphic mutation selected by SQV and less often by IDV and LPV. It confers intermediate resistance to ATV but has little if any effect on LPV susceptibility.
50L	Major	I50L is a non-polymorphic mutation selected by ATV. It causes high-level resistance to ATV and increases susceptibility to LPV and DRV.
50V	Major	I50V is a nonpolymorphic mutation selected by FPV, LPV and DRV. It reduces susceptibility to LPV and DRV.
53LY	Accessory	F53L is a nonpolymorphic accessory mutation selected primarily by SQV, IDV, ATV and LPV. In combination with other mutations, It is associated with reduced susceptibility to ATV and possibly LPV. F53Y is an uncommon nonpolymorphic accessory PI-selected mutation that has not been well studied.
54ATS	Major	I54A/T/S are non-polymorphic PI-selected mutations that occur almost exclusively in viruses with multiple PI-resistance mutations. I54A/T/S are associated with reduced susceptibility to each of the PIs except DRV.
54LM	Major	I54M/L are non-polymorphic mutations selected primarily by FPV and DRV. I54M/L reduce susceptibility to LPV, ATV, and DRV.
54V	Major	I54V is a non-polymorphic PI-selected mutation that contributes reduced susceptibility to each of the PIs except DRV.
58E	Accessory	Q58E is a minimally polymorphic accessory mutation selected by each of the PIs except DRV. In combination with other PI-resistance mutations, it may contribute to low-level ATV resistance.
76V	Major	L76V is a non-polymorphic mutation selected by IDV, LPV and DRV and reduces susceptibility to LPV and DRV.
82A	Major	V82A is a non-polymorphic mutation selected primarily by IDV and LPV. It is associated with reduced susceptibility to LPV and to a lesser extent ATV. It increases DRV susceptibility.
82C	Major	V82C is an uncommon nonpolymorphic 2-base-pair PI-selected mutation that occurs in viruses with multiple PI-resistance mutations. Its effect on PI susceptibility has not been well studied.
82F	Major	V82F is a nonpolymorphic mutation selected primarily by IDV and LPV. It reduces LPV and DRV susceptibility.
82I	Other	V82I is a highly polymorphic mutation that is not selected by PIs. It is the consensus amino acid in subtype G viruses.
82L	Major	V82L is a rare nonpolymorphic mutation selected primarily by TPV. Its effect on other PIs is not well characterized.

https://hivdb.stanford.edu/dr-summary/comments/PI/

1. All DRMs that receive a mutation penalty score and some that don't are accompanied by a comment.
2. The complete list of comments for each drug class can be viewed on the website
3. The comments have last been updated March 2024

Pre-Computed Scores for All DRM Patterns

Pattern	# Sequences	ATV/r	DRV/r	LPV/r
L90M	2366	25	0	15
V11I	1363	0	0	0
D30N + N88D	1104	10	0	0
Q58E	953	0	0	0
M46I	932	10	0	10
L33F	932	5	5	5
M46L	878	10	0	10
L10F	574	0	5	5
D30N	561	0	0	0
I54V + V82A	559	40	0	55
G73S + V82A + L90M	58	70	0	55
L24I	58	10	0	10
I54V + I84V + L90M	56	110	15	65
I54V + V82F	55	40	15	55
F53L + I54V + V82A + L90M	55	105	0	80
L24I + M46L + V82A	55	45	0	60
G48V + V82A	54	45	0	40

https://hivdb.stanford.edu/dr-summary/pattern-scores/PI/

1. There is also a table that lists precomputed scores for all combinations of DRMs present in the database.
2. The table can be sorted by the # sequences so that the most common DRM patterns are shown at the top or by those DRMs associated with the highest scores for a PI.
3. It is very useful for us to check this table to make sure that updates to the mutation penalty scores lead to the results intended for actual virus isolates
4. This figure shows the top of the table sorted by # sequences in which the most common DRM patterns are shown ranging in number from about 2400 to 560 and a section of the table somewhat lower down showing those patterns occurring in 58 to 54 sequences.

Mutations Associated with Reduced Susceptibility to PIs

For questions and suggestions:
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1. Thank you for your attention.
2. If you have any questions or suggestions don't hesitate to email us.