Mutations Associated with Reduced Susceptibility to NNRTIs

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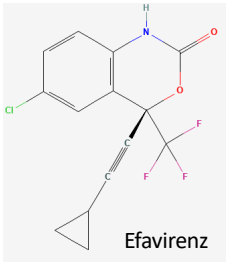
Disclosures

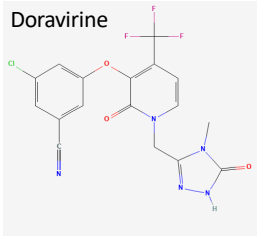
- Gilead Sciences (2022): Advisory board and speaking honorarium.
- ViiV Healthcare (2022): Speaking honorarium.

These are my disclosures.

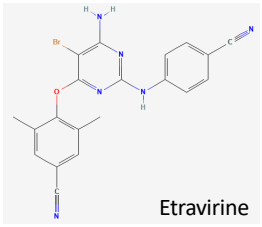
NNRTIs



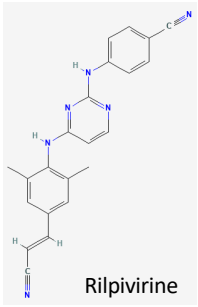
Efavirenz



Doravirine

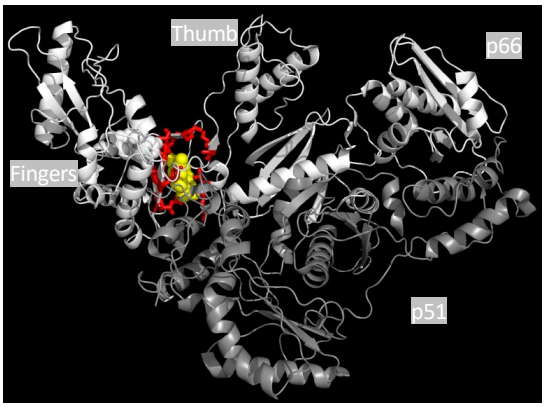


Etravirine



Rilpivirine

NNRTI Resistance Mutations



Active site Inhibitor DRMs

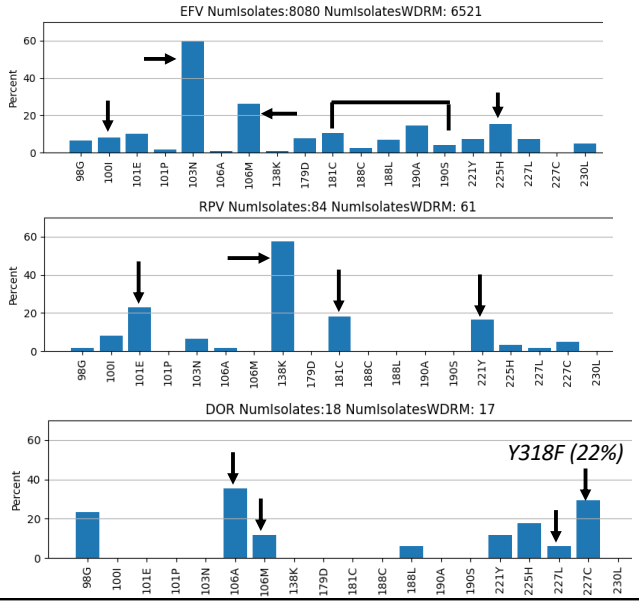
1. NNRTIs are characterized by having diverse chemical structures, which have been optimized to bind to a pocket in the RT enzyme that is close to but distinct from the enzyme's active site.
2. The NNRTI-binding pocket is highly adaptable and therefore the NNRTIs can differ dramatically in their structure.
3. This figure on the right shows an XR crystal structure of the HIV-1 RT bound to an NNRTI shown in yellow. The NNRTI binding pocket lies beneath the enzyme's active site.
4. When bound to the RT enzyme, the NNRTI restricts the movement of the enzymes thumb and fingers.
5. DRMs shown in red exclude the NNRTI from its binding pocket.

Active site Inhibitor

NNRTI-Selected Mutations in Patients

Genotype-Treatment

Drug	# Pts
EFV	8080
RPV	64
DOR	18



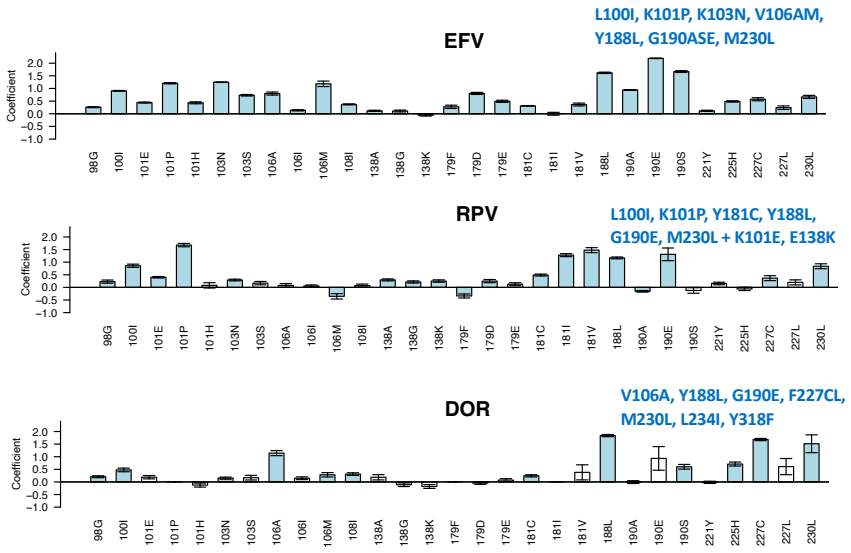
1. We have collected a large amount of sequence data from patients developing VF while receiving the first-generation NNRTIs nevirapine and efavirenz.
2. However, much less data are available for the second generation NNRTIs, in particular doravirine.
3. The few sequence data available for ETR are in patients who had a history of VF on a first-generation NNRTI.
4. Nonetheless sufficient data are available to show that the NNRTIs select for different DRMs in patients.
5. <><><><>K103N and V106M are the most common EFV-selected DRMs. V106M occurs commonly in subtype C isolates. L100I and P225H often occur in combination with K103N. Y181C, Y188L, and G190AS are other commonly selected DRMs.
6. <><>E138K, K101E, Y181C, and H221Y are the most common RPV-selected DRMs. Additional mutations that have occurred in patients and during in vitro passage experiments include L100I and F227C
7. <>Mutations at positions 106, 227, and 318 are the most common DOR-selected mutations.
8. Y318F is associated with a greater than 10-fold reduced DOR susceptibility. Therefore, it is important to know whether this position was sequenced because

not all genotypic assays sequence beyond RT position 300.

NNRTI Susceptibilities

Genotype-Phenotype

Drug	# Phenotypes
EFV	4,089
RPV	498
DOR	184

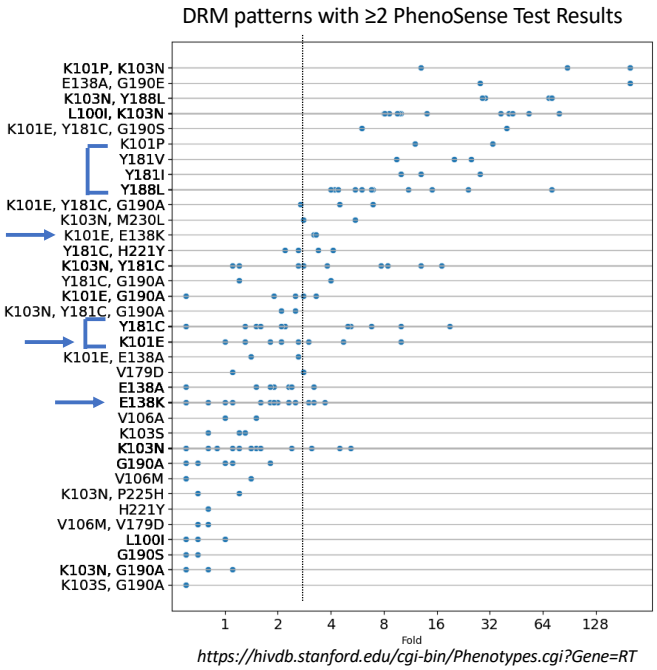


Accessory DRMs: A98G, V106I, V108I, V179DELF, H221Y, P225H

1. Extensive phenotypic data are available for EFV but much less for RPV and DOR
2. This figure on the right shows the results of a regression analyses for EFV in which each DRM is an explanatory variable and the fold reduction in susceptibility is the outcome variable.
3. The height of the bars are proportional to the mutations impact on susceptibility.
4. The most common single mutation with the greatest effect on EFV susceptibility include K103N, V106M, Y188L, and G190AS. Other less common mutations reduce susceptibility are shown at the upper right including L100I, K101P, G190E, and M230L.
5. <>The most common DRMs with the greatest effect on RPV susceptibility are L100I, Y181CIV, Y188L, and M230L,
6. Although K101E, and E138K are the most common RPV-selected DRMs, they have a minimal effect on RPV susceptibility suggesting that HIV-1 does not need to accumulate much reduced susceptibility to cause VF on an RPV-containing regimen.
7. <>The most common DRMs with the greatest effect on DOR susceptibility are V106A, Y188L, F227CL, M230L and two DRMs that are not shown in the figure -- L234I and Y318F.
8. There are several accessory DRMs that are associated with reduced susceptibility

only when they occur in combination with other NNRTI DRMs.

9. In the next two slides, I will dive somewhat deeper into RPV and DOR resistance because they are being used with increasing frequency.



https://hivdb.stanford.edu/cgi-bin/Phenotypes.cgi?Gene=RT

RPV Resistance

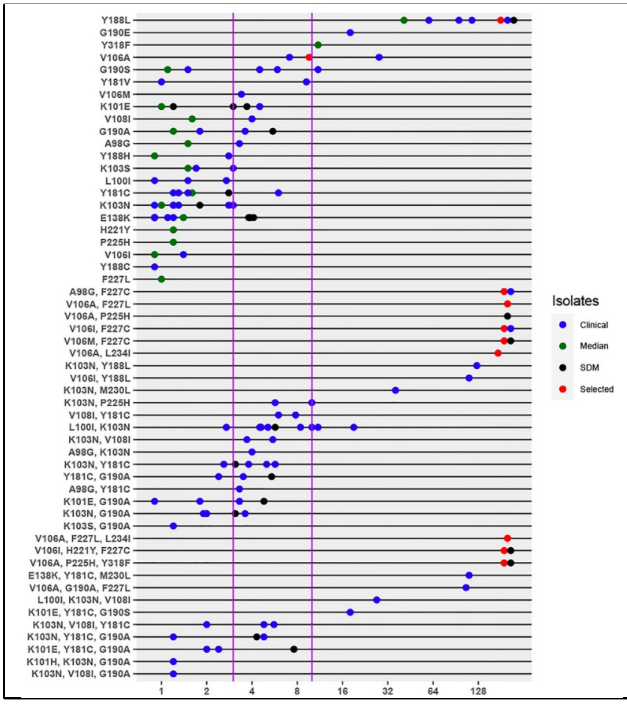
- Biological cut-off considered to be 2.0 to 2.5-fold.
- DRMs with the greatest effect: K101P, Y181IV, Y188L, G190E, L100I+K103N, K101E+Y181C.
- E138K +/- K101E
- Effect of combinations not entirely predictable.
- Variability caused by additional NNRTI DRMs which increase resistance.
- E138 mutations
  - K: 1.5-fold
  - A: 1.9-fold
  - Q: 2.6-fold
  - G: 2.7-fold

Haddad M. Impact of HIV-1 Reverse Transcriptase E138 Mutations on Rilpivirine Drug Susceptibility. HIVDR Workshop 2011

1. This figure shows those patterns of DRMs that were present in at least two isolates undergoing susceptibility testing.
2. The X-axis shows the fold reduction in susceptibility on a log 2 scale.
3. <>A line is drawn at 2.5-fold because wildtype isolates nearly always have a fold reduction in susceptibility that is less than 2 to 2.5-fold.
4. This upper limit of the fold reduction in susceptibility is referred to as the technical biological cut-off.
5. <><>Most of the DRMs associated with the highest reductions in susceptibility such as K101P, Y181I/V, and G190E are uncommon while Y181C and Y188L are common.
6. <><>Interestingly the most commonly occurring DRMs, E138K and K101E either alone or even together are generally not associated with marked reductions in susceptibility.
7. <>There is variability in the fold reduction in susceptibility for each pattern because some rare NNRTI DRMs were not considered when defining the DRMs to include in a pattern, because some backbone mutations can influence NNRTI susceptibility, and several NRTI-resistance DRMs can reduce the effect of NNRTI-resistance DRMs if they are associated with reduced replication fitness.
8. RPV is unique because mutations at position 138 are common and can cause low-

level reductions in RPV susceptibility.

9. E138A is a polymorphic mutation which occurs in 2% to 5% of persons depending on viral subtype. Its clinical significance is not known. It is listed as an RPV associated DRM in the FDA package insert and patients with E138A were excluded from the RPV clinical trials. Our interpretation reports it as being associated with low-level resistance.



DOR Resistance

- Biological cut-off is 3-fold. Clinical cut-off is not known.
- Canonical DRMs: V106A, Y188L, F227C/L, M230L, Y318F
  - >30-100-fold reduced susceptibility
  - V106IAM usually occur with F227CL
  - L234I has not been sufficiently studied
- Combinations of non-canonical mutations
  - 2 mutations 3-10-fold reduced susceptibility
  - 3 mutations >10-fold reduced susceptibility

Asante-Appiah E. Impact of HIV-1 associated mutations on susceptibility to doravirine: analysis of real-world clinical isolates. AAC 2021
Rhee SY. Potential Role of Doravirine for the Treatment of Patients with Transmitted Drug Resistance. AIDS Res Ther 2023

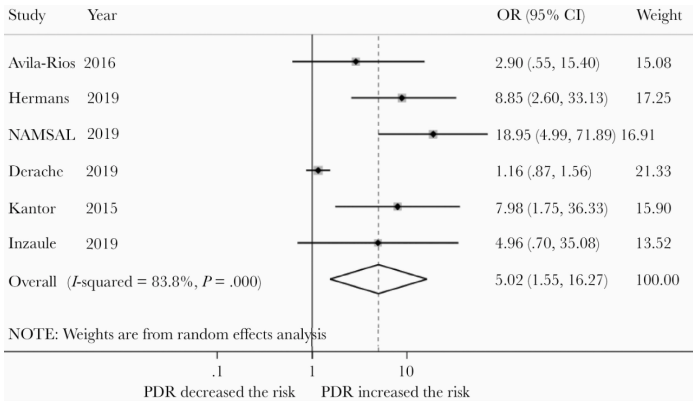
1. There have been about 200 published DOR susceptibility results performed using the Monogram BioSciences PhenoSense assay or by the Merck Research Lab which seems concordant with the PhenoSense assay.
2. This figure shows those patterns of DRMs that were present in at least one isolate undergoing susceptibility testing.
3. The X-axis shows the fold reduction in susceptibility on a log 2 scale.
4. <>Lines are drawn at 3-fold which it the technical biological cutoff of the PhenoSense assay and at 10-fold primarily because this is a convenient benchmark.
5. <> Six DRMs have consistently been associated with >10-fold reduced susceptibility including V106A, Y188L, M230L, and Y318F. F227C/L have been associated with >100-fold reduced susceptibility when they occur in combination with V106I/A/M.
6. Certain DRMs require further study such as L234I which has been selected in vitro and which in combination with V106A has been associated with >100-fold reduced susceptibility.
7. <>Certain combinations of 2 non-canonical DOR-associated DRMs such as K103N in combination with L100I or P225H are associated with 3-10 fold reduced susceptibility and at least two 3-mutation combinations lacking canonical DOR-

associated DRMs have been associated with >10-fold reduced susceptibility.

8. The fact that most patients who develop VF while receiving DOR have high levels of resistance may suggest that DOR retains activity against viruses with lower levels of reduced susceptibility such as those in the 3-10 fold range.

Clinical Significance of NNRTI-Resistance Mutations

Effect of PDR on the risk of VF in PLWH receiving TDF/XTC/EFV



Bertagnolio S. Clinical impact of pre-treatment HIVDR in people initiating NNRTI-containing ART: A systematic review and meta-analysis. JID 2021

- Risk of VF is higher for PLWH with PDR with previous ART experience than those who are ART-naïve.
- PDR in PLWH with ART-experience is associated with more NNRTI and NRTI DRMs.
- PDR in PLWH with ART-experience may be a marker for nonadherence.

Inzaule, S. C. et al. Previous antiretroviral drug use compromises standard first-line HIV therapy and is mediated through drug-resistance. Sci. Rep. 2018

1. What is the clinical significance of reduced NNRTI susceptibility?
2. A systematic review on the impact of pre-treatment NNRTI DRMs on the risk of VF on a first-line NNRTI-containing regimen was recently published.
3. People living with HIV with NNRTI-associated PDR had an increased risk of VF on a first-line TDF/XTC/EFV containing regimen based on a meta-analysis of 4 clinical trials and 2 cohort studies.
4. <>The risk of VF was particularly high for PLWH who had prior ART-experience -- such as those re-initiating ART after an interruption in therapy -- as compared to those who had been ART-naïve in part <> because those re-initiating therapy were more likely to have had NRTI as well as NNRTI-associated DRMs. Moreover, PDR in persons with ART-experience may be a marker for nonadherence.

NNRTI-experienced PLWH with NNRTI DRMs have a quasispecies containing more DRMs compared with ART-naïve PLWH with NNRTI DRMs

TABLE 2. Clinical Characteristics and UDPS Results in 20 NNRTI-Treated Patients With Plasma Samples Containing the RT Mutation K103N

PID	NNRTI	CD4 Count, Cells/μL	HIV-1 RNA, Log Copies/mL	Mutations Detected by Direct PCR Sequencing	Mutations Detected Only by UDPS	ETR Mutations†	Other NNRTI Mutations
6584	EFV	464	5.7	**103NK**, 118IV, 123E, 165IT, 174E, 214L	90I*(8.2), **101E*(3.8)**, **101N(2.4)**, 104N(3.1), 179D*(3.4), **188C(1.5)**, 189I(2.3), **190A*(4.9)**	2 (2)	2
6455	EFV	463	4.5	**74LV**, 101R, 102Q, **103N**, 135V, 142V, 162A, 174H, **184V**, 211K, **221HY**, 234IL	20R(13), **65R(9.7)**, **67N(2.4)**, **75I(14)**, **100I*(32)**, **108I(4.8)**, **190A*(5.4)**, **219N(2.7)**, 224V(5.8), **225H(11.2)**, 228R(5.0)	2	2
1872	NVP	239	4.5	20R, **41L**, 42AE, 43KN, 64KR, **103N**, 122E, 169D, 179I, **184MV**, **215Y**	36D(18), **181C*(3.5)**, **190A*(3.2)**, 196E(6.1), **210W(6.3)**, 237N(5.9)	2	0
26423	EFV	27	5.7	35I, 75LV, **103N**, 121Y, 122E, 135T, 176S, 200E, 211K, **225HP**	62V(1.4), 69N(1.1), **74V(8.5)**, **101E*(4.0)**, 106I*(1.0), **190S*(4.8)**, **H221Y(1.1)**	2 (1)	1
1838	DLV	91	4.9	20R, 35MI, **67N**, 102Q, **103N**, 122E, 162C, **184V**, 200A, 203K, 207E, **210W**, 211K, **215Y**, 223E	6K(8.6), 53K(2.0), **74V(12)**, 83K(58), **108I(28)**, 111I(3.5), 118I(73), **181C*(7.0)**, **219E(7.9)**, **236L(1.2)**	1	2
5248	EFV	120	5.3	**103N**, 122E, **184V**, 207E, **225H**	6K(2.7), **74V(13)**, **100I*(14)**, **108I(2.3)**, **219E(1.1)**	1	1
8350	EFV	261	4.5	41L, 101KQ, **103N**, **108IV**, 122E, 135T, 142V, 166R, 207E, **215Y**	**184V(1.2)**, **190S*(3.1)**, T200A(8.5), **225H(1.2)**	1	1

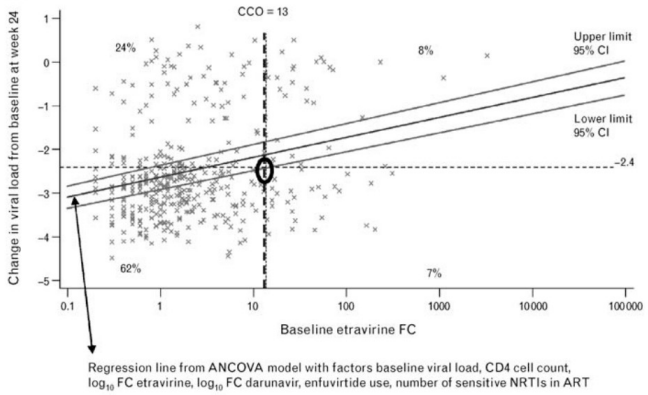
Varghese V. Minority variants associated with transmitted and acquired HIV-1 NNRTI resistance: Implications for 2nd-generation NNRTIs. JAIDS 2009

1. We published a study 15 years ago providing a likely explanation for why NNRTI DRMs are likely to be associated with a higher risk of VF in in persons who are NNRTI-experienced compared with persons who are ART-naïve and have TDR.
2. We performed direct PCR Sanger sequencing and deep sequencing in 13 ART-naïve persons and 20 NNRTI-experienced persons who had K103N.
3. Among 13 ART-naïve persons with K103N detected by direct PCR sequencing, none had additional mutations detectable by deep sequencing that would cause cross-resistance to the 2nd-generation NNRTIs ETR or RPV.
4. <><>By contrast, among 20 ART-experienced persons with K103N, sequences from the 7 persons shown in the table on this slide, had additional NNRTI DRMs that were only detected by deep sequencing.
5. These additional DRMs and their numbers are shown in the last three columns of the table. Those that would reduce susceptibility to ETR and RPV are in bold and are underlined. Their proportions in the sample are indicated in parentheses. On average, nearly 3 additional NNRTI associated mutations were present by deep sequencing at proportions above 1%.
6. A 2nd-generation NNRTI may be active against persons with NNRTI-associated TDR provided no DRMs associated with that inhibitor are present. Indeed, in a small study, which was terminated as a result of limited enrollment showed that

TDF/3TC/DOR was highly effective in 8 persons with TDR associated with K103N, Y181C, or G190A.

7. However, as the study on this slide and as other studies have shown acquired NNRTI resistance is often associated with additional DRMs that may not be detectable by standard sequencing.

Derivation of clinical cutoffs: the example of ETR



Vingerhoets J. Resistance profile of etravirine: combined analysis of baseline genotypic and phenotypic data from the randomized, controlled Phase III clinical studies. AIDS 2010

DRUG		
Generic Name	Brand Name	Cutoffs (Lower - Upper)
Doravirine	Pifeltro	*(3)* ←
Efavirenz	Sustiva	*(3)* ←
Etravirine	Intelence	***(2.9 - 10)*** ←
Nevirapine	Viramune	*(4.5)* ←
Rilpivirine	Edurant	*(2)* ←

PhenoSense Clinical Cutoffs for NNRTIs

1. There was only one clinical trial in which NNRTI-experienced persons were randomized to another NNRTI.
2. The DUET trial recruited participants between 2005 and 2006. It compared treatment with the 2nd generation NNRTI ETR with placebo in persons with VF who had at least one NNRTI DRM and at least 3 PI DRMs.
3. All participants also received b-DRM and two other investigator selected ARVs.
4. The study found that participants receiving ETR were significantly more likely to attain a VL <50 copies at week 48: 61% vs 40%.
5. <>A follow-up study examined the genotypic and phenotypic predictors of response to ETR in this trial.
6. A scatter plot, shown in this figure examined the fold reduction in ETR susceptibility at baseline versus the change in VL from baseline to week 24.
7. Two models were used to determine how phenotypic resistance predicted the virological response to ETR salvage therapy.
8. These models had to control for the baseline level of DRV resistance and for the predicted activity of the two other investigator selected ARVs.
9. The figure shows that there was an inverse relationship between the fold reduction in ETR susceptibility and the reduction in VL.
10. When the fold reduction in susceptibility was above 3-fold, there was a reduction

in response to ETR compared with those viruses that had <3-fold reduced susceptibility.

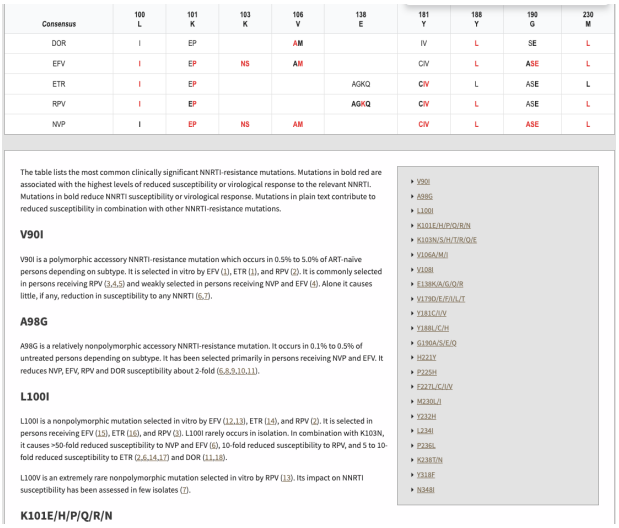
11. And when the fold reduction in susceptibility was above 10-13-fold, there was no longer any virological response that could be attributed to ETR.
12. Although ETR is now used infrequently, this study demonstrates the complexity of correlating resistance to a drug with response to that drug in salvage therapy regimens containing multiple drugs.
13. <>Nonetheless, based on this study, the PhenoSense assay provides some guidance on how to interpret ETR susceptibilities.
14. <>Of note, for the remaining NNRTIs, the only cut-off provided is the upper limit for the fold reduction in susceptibility of wildtype isolates lacking NNRTI-resistance mutations, a cut-off referred to as the technical biological cutoff.

15. change was above 13-fold, there was no longer a relationship between fold change and virological response with approximately 8% having little or no response and 7% having a VL reduction >=2.4 logs likely explained by DRV/r and other drugs in the regimen.
16. Although ETR is no longer widely used, this is one of the few papers show how clinical cut-offs for several drugs have been derived.

Conclusions

- EFV, RPV, and DOR select for largely non-overlapping DRM.
- NNRTI DRMs often have different effects on these NNRTIs.
- VF on an RPV-containing regimen is often associated with DRMs causing low-level RPV resistance suggesting that RPV has a low genetic barrier to resistance.
- In contrast, VF on EFV and especially DOR-containing regimens is usually associated with DRMs associated with high levels of reduced susceptibility.
- Although a small set of canonical DRMs cause high levels of DOR resistance, several combinations of 2 non-canonical DRMs can reduce DOR susceptibility by 3-10-fold while ≥3 non-canonical DRMs can reduce DOR susceptibility >10-fold.
- RPV and DOR may be successful in treating ART-naïve patients with DRMs that do not reduce their susceptibility but the use of these NNRTIs in persons with acquired NNRTI DRMs is likely to be risky.

NNRTI Notes and Handout



Consensus	100 L	101 K	103 K	106 V	138 E	181 Y	188 Y	190 G	230 M
DOR	I	EP		AM		IV	L	SE	L
EFV	I	EP	NS	AM		CIV	L	ASE	L
ETR	I	EP			AGKQ	CIV	L	ASE	L
RPV	I	EP			AGKQ	CIV	L	ASE	L
NVP	I	EP	NS	AM		CIV	L	ASE	L

The table lists the most common clinically significant NNRTI-resistance mutations. Mutations in bold red are associated with the highest levels of reduced susceptibility or virological response to the relevant NNRTI. Mutations in bold reduce NNRTI susceptibility or virological response. Mutations in plain text contribute to reduced susceptibility in combination with other NNRTI-resistance mutations.

V90I

V90I is a polymorphic accessory NNRTI-resistance mutation which occurs in 0.5% to 5.0% of ART-naive persons depending on subtype. It is selected in vitro by EFV (1), ETR (1), and RPV (2). It is commonly selected in persons receiving RPV (3,4,5) and weakly selected in persons receiving NVP and EFV (4). Alone it causes little, if any, reduction in susceptibility to any NNRTI (6,7).

A98G

A98G is a relatively nonpolymorphic accessory NNRTI-resistance mutation. It occurs in 0.1% to 0.5% of untreated persons depending on subtype. It has been selected primarily in persons receiving NVP and EFV. It reduces NVP, EFV, RPV and DOR susceptibility about 2-fold (6,8,9,10,11).

L100I

L100I is a nonpolymorphic mutation selected in vitro by EFV (12,13), ETR (14), and RPV (2). It is selected in persons receiving EFV (15), ETR (16), and RPV (3). L100I rarely occurs in isolation. In combination with K103N, it causes >50 fold reduced susceptibility to NVP and EFV (6), 10-fold reduced susceptibility to RPV, and 5 to 10-fold reduced susceptibility to ETR (2,6,14,17) and DOR (11,18).

L100V is an extremely rare nonpolymorphic mutation selected in vitro by RPV (13). Its impact on NNRTI susceptibility has been assessed in few isolates (7).

K101E/H/P/Q/R/N

- V90I
- A98G
- L100I
- K101E/H/P/Q/R/N
- K103N/S/H/T/R/Q/E
- V106A/M/I
- V108I
- E138K/A/G/Q/R
- V179D/E/F/I/L/T
- Y181C/I/V
- Y188L/C/H
- G190A/S/E/Q
- H221Y
- P225H
- F227L/C/I/V
- M230L/I
- Y232H
- L234I
- P236L
- K238T/N
- Y318F
- N348I

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

Major Non-Nucleoside RT Inhibitor (NNRTI) Resistance Mutations

	100	101	103	106	181	188	190	227	230
Cons	L	K	K	V	Y	Y	G	F	M
DOR	I	E		**AM**	IV	**L**	SE	**LC**	**L**
EFV	**I**	E**P**	**NS**	**AM**	CIV	**L**	**ASE**	LC	**L**
ETR	**I**	E**P**			**CIV**	L	ASE	**C**	**L**
RPV	**I**	**EP**			**CIV**	**L**	ASE	**C**	**L**
NVP	**I**	**EP**	**NS**	**AM**	**CIV**	**L**	**ASE**	**LC**	**L**

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

Abbreviations: Doravirine (DOR), efavirenz (EFV), etravirine (ETR), rilpivirine (RPV), nevirapine (NVP).

Additional Mutations: A98G (DOR, EFV, ETR, NVP, RPV); E138GQKR are nonpolymorphic mutations associated with intermediate/high-level RPV resistance. E138A is a polymorphic mutation associated with low-level RPV resistance. Y188CH are associated with intermediate / high-level resistance to EFV; G190Q is a rare mutation which may have an effect similar to G190E; P225H (DOR, EFV); L234I (DOR), Y318F (DOR, NVP).

Synergistic combinations: V179D+K103R reduce NVP and EFV susceptibility >10-fold. Y181C+V179F cause high-level ETR and RPV resistance.

DOR and ETR often require multiple mutations: DOR - high level with Y188L, V106A, F227L/C, M230L or any combination of V106 and F227 mutations. ETR: L100I, K101P, Y181C/I/V, M230L. But multiple non-DOR mutations at common positions such as Y181 and G190 can produce intermediate levels of reduced DOR susceptibility.

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.

Individual DRM Scores

Rule	DOR	EFV	ETR	NVP	RPV
A98G	15	15	10	30	15
L100I	15	60	30	60	60
L100V	10	30	10	30	15
K101E	15	15	15	30	45
K101P	10	60	60	60	60
V106A	60	45	0	60	0
V106I	10	0	10	10	10
V106M	30	60	0	60	0
V108I	10	10	0	15	0
E138K	5	10	10	10	45
V179F	10	10	15	15	15
Y181C	10	30	30	60	45
Y181I	20	30	60	60	60
Y181V	20	30	60	60	60
Y188C	5	60	0	60	0
Y188F	30	60	0	60	30
Y188H	5	30	0	60	0
Y188L	60	60	10	60	60
G190C	10	60	10	60	10
G190E	60	60	45	60	60
G190Q	30	60	45	60	45
G190S	20	60	10	60	15
G190T	10	60	10	60	10
G190V	10	60	10	60	10
H221Y	10	10	10	15	15
P225H	20	45	0	45	0
F227C	60	45	30	45	45

Rule	DOR	EFV	ETR	NVP	RPV
F227I	60	10	0	30	0
F227L	60	15	0	30	0
F227V	60	10	0	30	0
M230I	15	15	15	30	30
M230L	60	45	30	60	60
L234I	45	0	0	0	0
P236L	10	0	0	0	0
Y318F	60	10	0	30	0
K101H	0	10	10	15	10
K103H	0	60	0	60	0
K103N	0	60	0	60	0
K103S	0	45	0	60	0
K103T	0	15	0	60	0
E138G	0	10	10	10	15
E138Q	0	10	10	10	15
E138R	0	10	10	10	15
V179D	0	10	10	10	10
V179E	0	10	10	10	10
V179L	0	10	10	10	15
Y181F	0	15	15	60	30
Y181G	0	15	15	60	30
Y181S	0	15	15	60	30
G190A	0	45	10	60	15
K238N	0	10	0	10	0
K238T	0	30	0	30	0
E138A	0	0	10	0	15
N348I	0	0	0	15	0

Combination DRM Scores

Combination Rule	DOR	EFV	ETR	NVP	RPV
L100I + K103N	15	0	0	0	0
L100I + K103N + P225H	-10	0	0	0	0
K103N + Y181C	5	0	0	0	0
K103N + P225H	10	0	0	0	0
V106I + Y181C	5	0	0	0	10
V106I + G190S	5	0	0	0	0
V108I + Y181C	5	0	0	0	0
V108I + L234I	10	0	0	0	0
Y181C/V + G190ACSTV	10	0	10	0	10
Y181C/V + H221Y	10	0	0	0	10
A98G + Y181C	5	5	5	5	5
A98G + F227CL	15	15	15	15	15
K101E + G190A	5	0	5	0	0
K101E + G190S	5	0	5	0	0
K101E + Y181C	0	5	5	5	0
K103R + V179D	0	20	0	20	15
V106A + F227CL	0	15	0	0	0
K101E + Y188L	0	0	5	0	0
V179F + Y181C	0	0	15	0	15
V179T + Y181C	0	0	10	0	10
K101E + M184I	0	0	0	0	15
E138K + M184I	0	0	0	0	15

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

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.

NNRTI Comments

Condition	Comment/ Mutation Type	Comment
RPV=4		This virus is predicted to have intermediate-level reduced susceptibility to RPV. The use of the combination of CAB/RPV should be considered to be contraindicated.
RPV=3		This virus is predicted to have low-level reduced susceptibility to RPV. The use of the combination of CAB/RPV should be considered to be relatively contraindicated.
100I	NNRTI	L100I is a non-polymorphic mutation that usually occurs in combination with K103N. In this setting it confers high-level resistance to NVP, EFV, and RPV and intermediate resistance to ETR and DOR.
100V	NNRTI	L100I is a non-polymorphic mutation that usually occurs in combination with K103N. In this setting it confers high-level resistance to NVP, EFV, and RPV and intermediate resistance to ETR and DOR. L100V is a rare mutations that likely has effects similar to L100I.
101E	NNRTI	K101E is a non-polymorphic accessory mutation that confers intermediate resistance to NVP and RPV and low-level reductions in susceptibility to EFV, ETR, and DOR when it occurs with other NNRTI-resistance mutations.
101H	NNRTI	K101H is a non-polymorphic accessory mutation selected by NVP, EFV and ETR. When present with other NNRTI-resistance mutations, it contributes reduces susceptibility to these NNRTIs.
101NAT	Other	K101N/A/T are uncommon non-polymorphic NNRTI-selected mutation of uncertain phenotypic and clinical significance.
101P	NNRTI	K101P is a non-polymorphic mutation that confers high-level resistance to NVP, EFV, RPV, and ETR. Its does not appear to reduce DOR susceptibility.
101Q	Other	K101Q is a relatively non-polymorphic mutation that is weakly selected in persons receiving NVP and EFV. It is of uncertain phenotypic and clinical significance.
103EQ	NNRTI	K103E/Q are rare mutations that have not been associated with reduced NNRTI susceptibility.
103H	NNRTI	K103H is a rare non-polymorphic mutation that confers high-level resistance to NVP and EFV.
103N	NNRTI	K103N is a non-polymorphic mutation that confers high-level reductions in NVP and EFV susceptibility. It is the most commonly transmitted DRM.
103R	Other	K103R is a polymorphic mutation that alone has no effect on NNRTI susceptibility. However, in combination with V179D, it reduces NVP and EFV susceptibility about 15-fold.
103S	NNRTI	K103S is a non-polymorphic mutation that causes high-level reductions in NVP susceptibility but intermediate reductions in EFV susceptibility. Because K103S is a 2-bp change from the wildtype K and a 1-bp change from K103N, persons with K103S may be likely to have once had K103N.

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

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	DOR	EFV	ETR	NVP	RPV
K103N	13309	0	60	0	60	0
E138A	5243	0	0	10	0	15
V106I	4861	10	0	10	10	10
K103R	3905	0	0	0	0	0
V179D	3277	0	10	10	10	10
Y181C	2411	10	30	30	60	45
K103N + P225H	2398	30	105	0	105	0
V179E	2102	0	10	10	10	10
L100I + K103N	2012	30	120	30	120	60
K103N + Y181C	1737	15	90	30	120	45
K103R + V106M + V179D	170	30	90	10	90	25
L100I + K103N + H221Y	167	40	130	40	135	75
A98G + K103N + V108I	164	25	85	10	105	15
L100I + K103N + P225H	159	50	165	30	165	60
K101H + G190A	158	0	55	20	75	25
K103N + V108I + K238T	152	10	100	0	105	0
K101E + Y181C	151	25	50	50	95	90
G190Q	151	30	60	45	60	45
K103N + V108I + Y181C	149	30	100	30	135	45
K103N + E138G	148	0	70	10	70	15
A98G + K101E + G190A	147	35	75	40	120	75

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

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 an NNRTI.
3. It is very useful 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 1700 to 13,000 and a section of the table somewhat lower down showing those patterns occurring in 147 to 170 sequences

Mutations Associated with Reduced Susceptibility to NNRTIs

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.