# Mutations Associated with Reduced Susceptibility to NNRTIs

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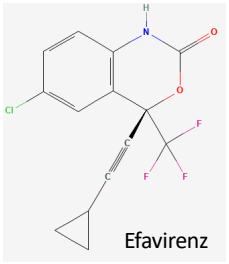
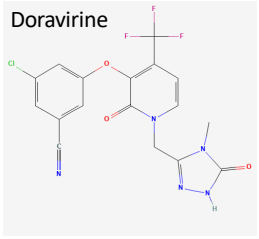
## Disclosures

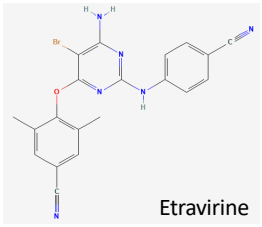
- Gilead Sciences (2022): Advisory board and speaking honorarium.
- ViiV Healthcare (2022): Speaking honorarium.

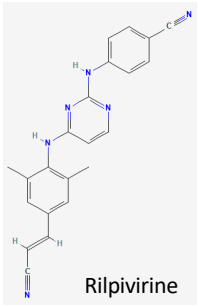
These are my disclosures.

## NNRTIs

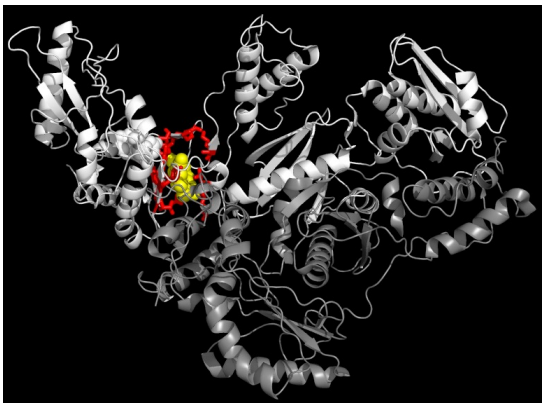



## NNRTI Resistance Mutations

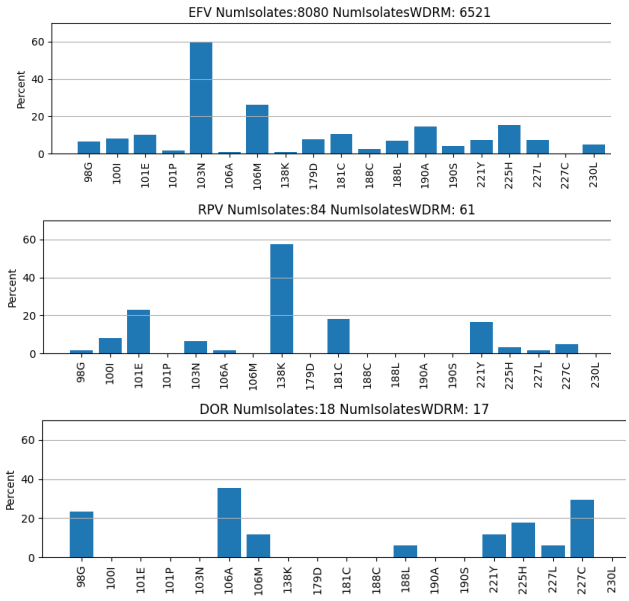


Active site Inhibitor DRMs

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 | 9,167 |
| RPV | 67 |
| DOR | 17 |

In vitro (RPV; ≥2 times): L100I, K101E, E138K, Y181C, H221Y, F227C, M230I

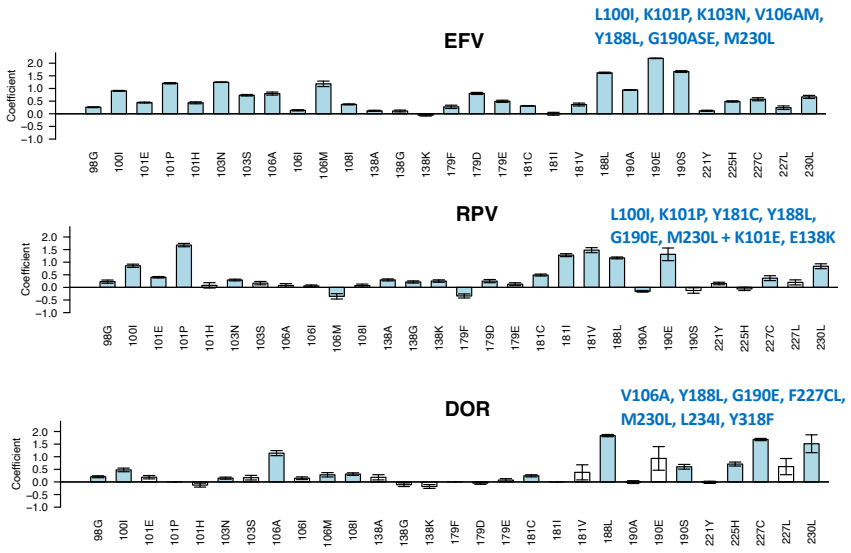
In vitro (DOR; ≥2 times): V106A/M, F227C/L, L234I, Y318F

1. We have collected a large amount of sequence data from patients developing VF while receiving a first-generation NNRTIs including nevirapine and efavirenz.
2. However, much less data are available for the second generation NNRTIs, in particular doravirine.
3. Nonetheless sufficient data are available to show that the NNRTIs select for different DRMs in patients
4. 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.
5. E138K, K101E, and Y181C are the most common RPV-selected DRMs. The DRMs selected in patients are similar to those selected in vitro.
6. Mutations at positions 106 and 227 are the most common DOR-selected DRMs. L234I and Y318F, which are selected uncommonly by other NNRTIs, have been selected in patients and in vitro.
7. The few sequencedata available for ETR are in patients who had a history of VF on a first-generation NNRTI.

## NNRTI Susceptibilities

**Genotype-Phenotype**

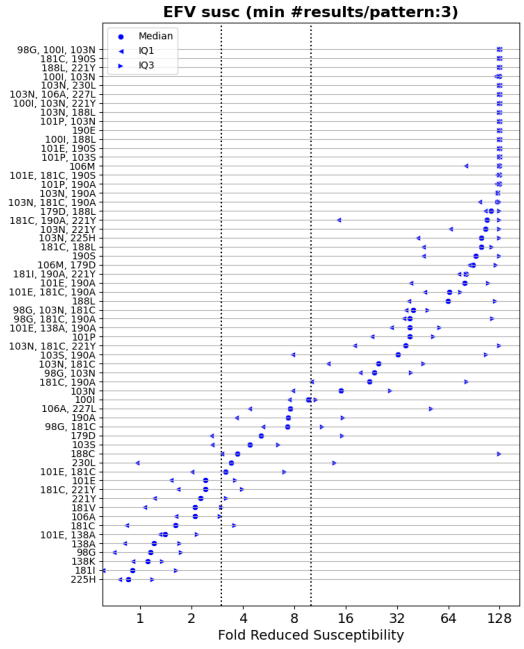
| Drug | # Phenotypes |
|---|---|
| EFV | 4,089 |
| RPV | 498 |
| DOR | 184 |




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 regression analyses for EFV, RPV, and DOR in which each DRM is an explanatory variable and the fold reduction in susceptibility is the outcome variable.
3. Individual NNRTI DRMs can have markedly different effects on different NNRTIs.
4. However, when 2 or 3 NNRTI combinations occur in combination, there are often high levels of NNRTI cross-resistance.
5. The most common single DRMs with the greatest effect on EFV susceptibility include K103N, V106M, Y188L, and G190AS. Other DRMs less common DRMs that have a large impact on susceptibility are shown at the upper right.
6. The most common DRMs with the greatest effect on RPV susceptibility are L100I, Y181CIV, Y188L, and M230L,
7. 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.
8. The most common DRMs with the greatest effect on DOR susceptibility are V106A, Y188L, F227CL, M230L and two DRMs that are not shown here L234I and Y318F.

9. K101P is an uncommon DRM that markedly reduces susceptibility to EFV and RPV. It is uncommon because it requires at least two base pair changes and usually occurs with at least one other NNRTI DRM.
10. G190E is an uncommon DRM that markedly reduces susceptibility to each of the NNRTIs. It is uncommon because if is associated with greatly reduced replication fitness. It also occurs in viruses that have been affected by APOBEC-mediated G-to-A hypermutation. Therefore, if it is presents, it is necessary to check for evidence of G-to-A hypermutation.
11. There are several accessory DRMs that are associated with reduced susceptibility only when they occur in combination with other NNRTI DRMs.

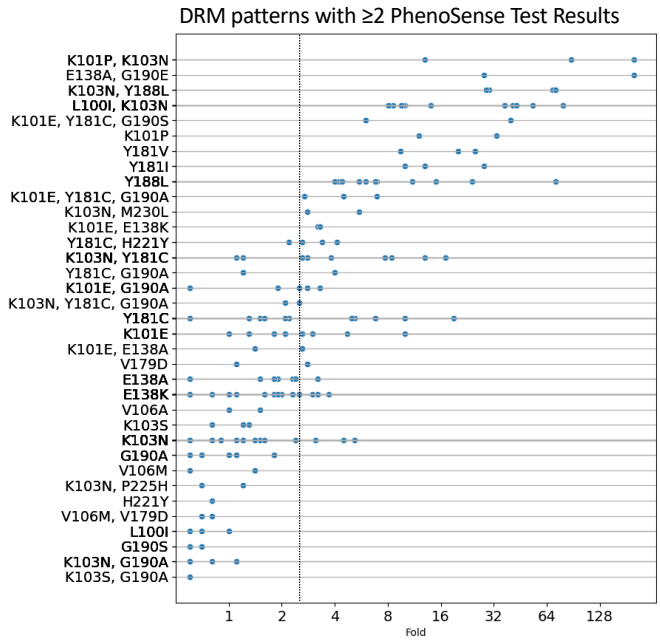



*https://hivdb.stanford.edu/cgi-bin/Phenotypes.cgi?Gene=RT*

## EFV Resistance

- Biological cut-off 3.0-fold.
- DRMs with the greatest effect: K103N, V106M, Y188L, G190S
- DRM combinations with the greatest effect: K103N + (L100I, K101P, P225H), G190A + (K101E, Y181C)
- Rare DRMs: K101P, G190E, M230L
- Variability caused by additional accessory NNRTI DRMs which increase resistance and by NRTI DRMs which increase susceptibility.

1. This figure shows the median and IQR of the fold reduced EFV susceptibility associated with NNRTI DRMs for which 3 or more phenotypic results are available.
2. The biological cut-off for EFV in the PhenoSense assay is 3-fold, meaning that it is unusual for viruses without any DRMs to have a ≥3-fold reduced susceptibility..
3. In addition to indicating which DRMs have the greatest effect on susceptibility, the figure indicates which DRM combinations appear to be particularly synergistic. For example, K103N alone is associated with about 15-fold reduced susceptibility, while K103N plus several other DRMs can be associated with >100-fold reduced susceptibility.
4. The variability associated with each pattern is often the result of additional accessory NNRTI DRMs which were not considered when creating the patterns shown in this figure and by NRTI DRMs which have been shown to increase the susceptibility to EFV and other NNRTIs.



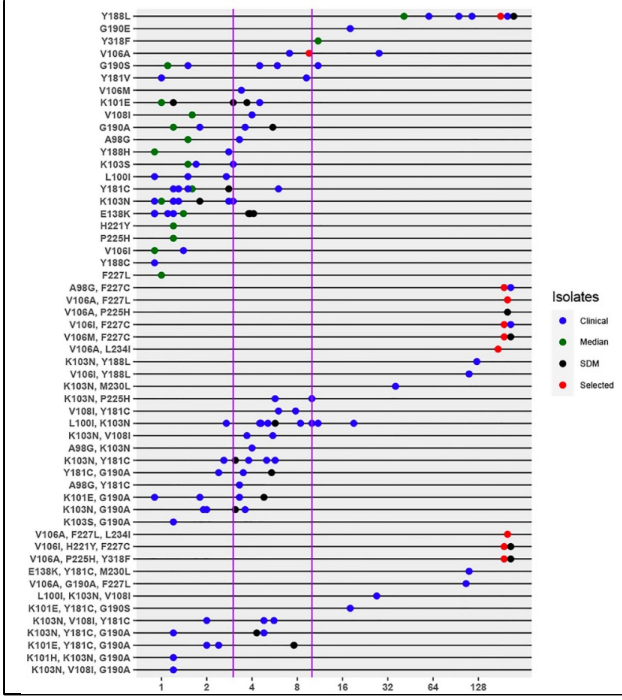

*https://hivdb.stanford.edu/cgi-bin/Phenotypes.cgi?Gene=RT*

## 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. Wildtype isolates nearly always have a fold reduction in susceptibility that is less than 2 to 2.5-fold.
3. 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.
4. Interestingly the most commonly occurring DRMs, E138K and K101E either alone or together generally associated reductions in susceptibility below 4-fold.
5. 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.
6. RPV is unique because mutations at position 138 are common and can cause low-level reductions in RPV susceptibility.
7. E138A is a polymorphic mutation which occurs in 2% to 5% of persons according to subtype with the the 5% being in subtype C viruses. Its clinical significance is not known but it is listed as an RPV associated DRM in the FDA package insert and patients with E138A were excluded from the RPV clinical trials.




## DOR Resistance

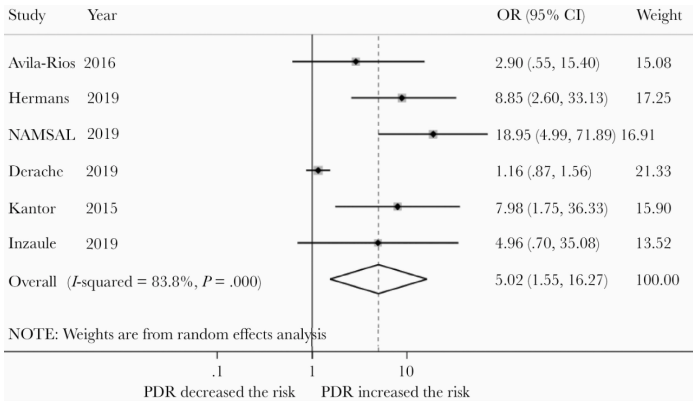
- Biological cut-off is 3-fold. Clinical cut-off is not known.
- Canonical DRMs: V106A, Y188L, F227C/L, M230L, Y318F
  - >30-100-fold reduced susceptibility
  - V106IAM usually occur with F227CL
  - L234I has not been sufficiently studied
- Combinations of non-canonical mutations
  - 2 mutations 3-10-fold 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. 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.
3. 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.
4. 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.
5. 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 patients 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. Silvia Bertagnolio from the WHO published a systematic review on the impact of pre-treatment NNRTI DRMs on the risk of VF on a first-line NNRTI-containing regimen.
3. Patients with NNRTI PDR included all patients with NNRTI DRMs who present for initial therapy including those who were ART-naïve as well as those in whom ART was interrupted and those who received ART to prevent MTCT.
4. This surveillance strategy reflects the programmatic reality of the WHO's public health approach that initiates HIV treatment in all people without a documented history of VF on a first-line regimen.
5. The figure shows that pre-therapy NNRTI DRMs were associated with an increased risk of VF on a first-line TDF/XTC/EFV containing regimen in 4 clinical trials and 2 cohort studies.
6. Several factors, however, are important to keep in mind regarding patients with PDR.
7. The risk of VF was higher for those patients with PDR who had previous ART experience compared with those who were ART naïve.
8. This may be because, PDR in PLWH with ART-experience is associated with more NNRTI and NRTI DRMs and because PDR in patients with ART-experience

may be a marker of nonadherence..

## NNRTI-experience patients with NNRTI DRMs have a quasispecies containing more DRMs compared with ART-naïve persons with NNRTI DRMs

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

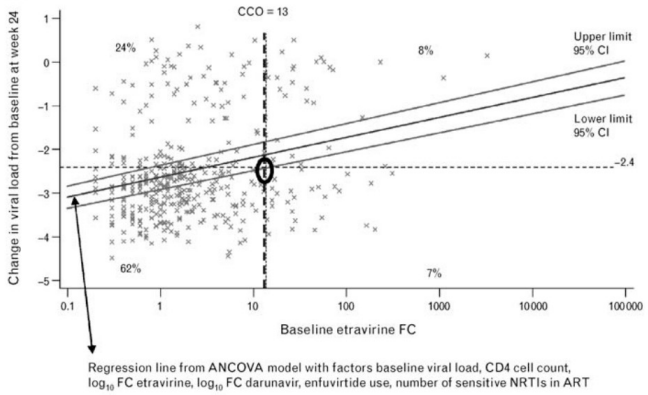
| PID | NNRTI | CD4 Count, Cells/μL | HIV-1 RNA, Log Copies/mL | Mutations Detected by Direct PCR Sequencing | Mutations Detected Only by UDPS | ETR Mutations† | Other NNRTI Mutations |
|---|---|---|---|---|---|---|---|
| 6584 | EFV | 464 | 5.7 | **103NK**, 118IV, 123E, 165IT, 174E, 214L | 90I*(8.2), **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 in which we compared standard Sanger sequencing with deep sequencing in ART-naïve patients with K103N and in ART-experienced patients with K103N.
2. Among 13 ART-naïve patients with K103N detected by Sanger sequencing, none had additional mutations detectable by deep sequencing that would cause cross-resistance to the 2nd-generation NNRTIs ETR or RPV.
3. By contrast, among 20 ART-experienced patients with K103N, likely acquired by NNRTI therapy, 7 patients -- shown on this slide -- had additional NNRTI DRMs detected by deep sequencing that are associated with cross-resistance to ETR and RPV. These additional mutations are shown in the second column of mutations. They are in bold and are underlined and their proportions in the sample are indicated in parentheses.
4. This suggests that a 2nd-generation NNRTI may be active against patients with NNRTI-associated TDR provided no DRMs associated with that inhibitor are present.
5. Indeed, in a very small study, which had trouble with enrollment, showed that TDF/3TC/DOR was highly effective in 8 patients with TDR associated with K103N, Y181C, or G190A.
6. However, acquired NNRTI resistance is often associated with additional DRMs that

may only be detectable by more sensitive methods. On average, nearly 3 additional NNRTI associated mutations were present by deep sequencing at proportions above 1%. Similar findings have been reported in patients with VF on NVP-containing regimens including those receiving single dose NVP to prevent MTCT.

## 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. The DUET clinical trial was the only trial in which a large number of patients with acquired NNRTI resistance were randomized to a second generation NNRTI, specifically ETR.
2. The study, which recruited patients between 2005 and 2006, compared ETR to placebo in patients with VF who had at least one NNRTI DRM and at least 3 PI DRMs. All patients also received DRV/r and two other investigator selected ARVs.
3. The study found that patients receiving etravirine were significantly more likely to attain a VL <50 copies at week 48 - 61% vs 40%.
4. A follow-up study examined genotypic and phenotypic predictors of response to ETR in this trial.
5. A scatter plot -- shown in this figure examined the fold reduction in etravirine susceptibility at baseline versus the change in VL from baseline to week 24.
6. Two models were used to determine the level of fold change at which ETR did not reduce VL.
7. The models controlled for the fold change of DRV at baseline and the predictive activity of the background regimen.
8. The figure shows that there was an inverse relationship between the ETR FC and the reduction in VL but that there is much variability not explained by the model.
9. However, when the fold change was above 13-fold, there was no longer a

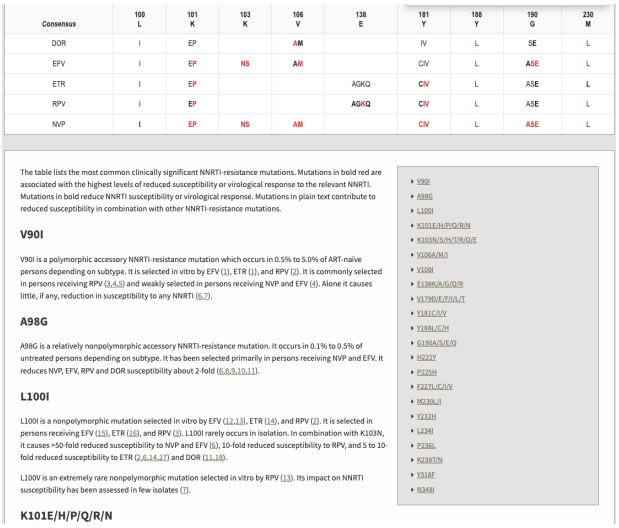
relationship between fold change and virological response with approximately 8% having little or no response and 7% having a VL reduction >=2.4 logs likely explained by DRV/r and other drugs in the regimen.

10. 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 no-ncanonical 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 patients 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/I/V + G190A/C/S/T/V | 10 | 0 | 10 | 0 | 10 |
| Y181C/I/V + H221Y | 10 | 0 | 0 | 0 | 10 |
| A98G + Y181C | 5 | 5 | 5 | 5 | 5 |
| A98G + F227C/L | 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 + F227C/L | 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:
hivdbteam@lists.Stanford.edu

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