



NORTHWEST AIDS EDUCATION AND TRAINING CENTER

NNRTI Resistance

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Presentation prepared by:

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NNRTI Resistance

- Efavirenz
- Nevirapine
- Rilpivirine
- Etravirine

Stanford Database



STANFORD UNIVERSITY

HIV DRUG RESISTANCE DATABASE

A curated public database designed to represent, store, and analyze the divergent forms of data underlying HIV drug resistance.

HOME GENOTYPE-RX GENOTYPE-PHENO GENOTYPE-CLINICAL HIVdb PROGRAM



» [Analyze sequence sets for proportions with Surveillance Drug Resistance Mutations \(SDRMs\)](#)



» [Interactive map displaying HIV-1 drug resistance in ARV-naive populations](#)



» [XML Suite of Treatment-Change Episodes](#)

Interactive map displaying HIV-1 drug resistance in ARV-naive population

Studies of ARV-naive population by region, year and subtype. » [Interactive map](#)



GENOTYPE-TREATMENT CORRELATIONS

- » Retrieve sequences (and/or mutations) from persons receiving selected HIV drugs
- » Retrieve sequences and treatments from viruses with specific mutations

GENOTYPE-PHENOTYPE CORRELATIONS

- » Retrieve drug susceptibility data for isolates with selected mutations
- » Download genotype-phenotype research datasets

REFERENCES

- » Published drug resistance studies in HIVRT&PrDB
- » Published studies by Stanford database group

SURVEILLANCE MUTATIONS

- » World Health Organization 2009 Mutation List
- » Geographic Information System
- » Mutation Prevalence

HIVdb PROGRAM

Genotype Resistance Interpretation

Interprets user-entered mutations to infer the level of resistance to NRTIs, NNRTIs, PIs. Web Services and Spreadsheets **NEW!** available.

MARVEL

» [Mutation ARV Evidence Listing](#)

HIVseq Program

» [Provides mutation frequencies by subtype and treatment](#)

HIValg Program

» [Compare HIVdb, ANRS, Rega, or create your own algorithm](#)

Stanford Database

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Stanford Database

Drug Resistance Interpretation: RT

NRTI Resistance Mutations: None
 NNRTI Resistance Mutations: **K103N**
 Other Mutations: None

Nucleoside RTI		Non-Nucleoside RTI	
lamivudine (3TC)	Susceptible	efavirenz (EFV)	High-level resistance
abacavir (ABC)	Susceptible	etravirine (ETR)	Susceptible
zidovudine (AZT)	Susceptible	nevirapine (NVP)	High-level resistance
stavudine (D4T)	Susceptible	rilpivirine (RPV)	Susceptible
didanosine (DDI)	Susceptible		
emtricitabine (FTC)	Susceptible		
tenofovir (TDF)	Susceptible		

RT Comments

NNRTI

- K103N causes high-level resistance to NVP, and EFV. it has no effect on ETR or RPV susceptibility.

Mutation Scoring

RT	3TC	ABC	AZT	D4T	DDI	FTC	TDF	EFV	ETR	NVP	RPV
K103N	-	-	-	-	-	-	-	<u>60</u>	<u>0</u>	<u>60</u>	<u>0</u>
Total:	0	0	0	0	0	0	0	60	0	60	0

Case #1

- A 32-year-old man presents after several missed visits. He reports imperfect adherence to tenofovir-emtricitabine-efavirenz (*Atripla*). HIV RNA level (viral load) has increased from undetectable to 3,410 copies/mL.
- Genotype resistance assay shows: K103N
- Are other NNRTI's an option for this patient?

Efavirenz Resistance

- Most common mutation: **K103N**
- May be followed by: G190A/S, Y188L/H/C, K101E, L100I, accessory mutations
- *Efavirenz has long half-life and low barrier to resistance, so K103N often the first mutation with *Atripla* failure

K103N

	Efavirenz	Nevirapine	Rilpivirine	Etravirine
K103N	60	60	0	0

*Key points:

- K103N knocks out efavirenz and nevirapine
- Rilpivirine remains active *in vitro*; clinical data limited
- Etravirine still works unless additional mutations present

Penalty score

≥60: high-level resistance

30-60: intermediate-level resistance

10-30: low-level resistance

Less than 0: hypersusceptible

Case #2

- A 55-year-old man has had poor adherence to tenofovir-emtricitabine (*Truvada*) and nevirapine (*Viramune*). HIV RNA level has risen to 1,250 copies/mL.
- What is the most likely nevirapine-associated resistance mutation?

Nevirapine Resistance

- Most common: **Y181C**
- Also possible: Y181I/V, G190A/S/E/Q, Y188L/H/C, K103N/S/T, K101E, A98G, accessory mutations

Libre JM, Schapiro JM, Clotet B. CID. 2010;(50),872-881.

Y181C

	Efavirenz	Nevirapine	Rilpivirine	Etravirine
Y181C	30	60	30	30

***Key point:** the most common nevirapine mutation affects all NNRTI's, including etravirine

Penalty score

≥60: high-level resistance

30-60: intermediate-level resistance

10-30: low-level resistance

Less than 0: hypersusceptible

Case #3

- A 35-year-old woman has imperfect adherence to tenofovir-emtricitabine-rilpivirine (*Complera*). HIV RNA level is 4,950 copies/mL.
- What is the most likely rilpivirine-associated resistance mutation?

Rilpivirine Resistance

- Most common rilpivirine mutation: **E138K**
- With *Complera* failure, most often see: **E138K + M184I**
 - M184I enhances rilpivirine resistance and causes emtricitabine resistance at the cost of viral fitness
- Other mutations: V90I, K101E/P/T, V179I/D/L, Y181C/I/V, V189I, H221Y, F227C/L, M230I/L

<http://hivdb.stanford.edu>

Kulkarni R et al. *JAIDS*; 59(1): 47-54.

E138K

	Efavirenz	Nevirapine	Rilpivirine	Etravirine
E138K	10	10	30	10

***Key point:** NNRTI cross-resistance is more common with rilpivirine than efavirenz

Penalty score

≥60: high-level resistance

30-60: intermediate-level resistance

10-30: low-level resistance

Less than 0: hypersusceptible

Case #4

- A 45-year-old woman presents for an initial visit. She doesn't recall the names of the ARV's she was taking most recently and has been off of them for 4 weeks.
- You perform a genotype resistance assay and find the following NNRTI mutations: K103N, Y181I and P225H.
- Is etravirine an option for this patient?

NNRTI DRUGS

RESCRIPTOR, (delavirdine, DLV)	Resistance***
SUSTIVA, (efavirenz, EFV)	Resistance***
VIRAMUNE, (nevirapine, NVP)	Resistance***
INTELENCE, (etravirine, ETR)	Possible Resistance***

NNRTI associated resistance mutations found: K103N,
Y181I, P225H

Etravirine Resistance

- Etravirine may retain activity even if resistance develops to other NNRTI's
- Depends on # of mutations and which specific mutations
- Most significant: **Y181C//V**
- Best way to determine susceptibility: phenotype
 - Methods to estimate susceptibility:
 - *DUET (Tibotec) weighted scoring system*
 - *Monogram Biosciences weighted scoring system*

Etravirine: DUET Score

Weight	Mutations
3	Y181I/V
2.5	L100I, K101P, Y181C, M230L
1.5	V106I, E138A, V179F, G190S
1	V90I, A98G, K101E/H, V179D/T, G190A

*Response rates based on total score:
0-2: 74% (highest response)
2.5-3.5: 52% (intermediate response)
≥4.0: 38% (progressively reduced response)

Etravirine: Monogram “Enhanced” Score

Weight	Mutation
4	L100I, K101P, Y181C/I/V
3	E138A/G, V179E, G190Q, M230L, K238N
2	K101E, V106A/I, E138K, V179L, Y188L, G190S,
1	V90I, A98G, K101H, K103R, V106M, E138Q, V179D/F/I/M/T, Y181F, V189I, G190A/E/T, H221Y, P225H, K238T

Total score ≥ 4 correlates with fold-change on phenotype that indicates resistance (90% sensitivity, 85% specificity)

Summary of Key Mutations

- Efavirenz: K103N, also knocks out nevirapine
- Nevirapine: Y181C, more etravirine cross-resistance
- Rilpivirine: E138K +/- M184I, more NNRTI cross-resistance
- Etravirine: scoring systems estimate degree of resistance