NORTHWEST AIDS EDUCATION AND TRAINING CENTER

NNRTI Resistance

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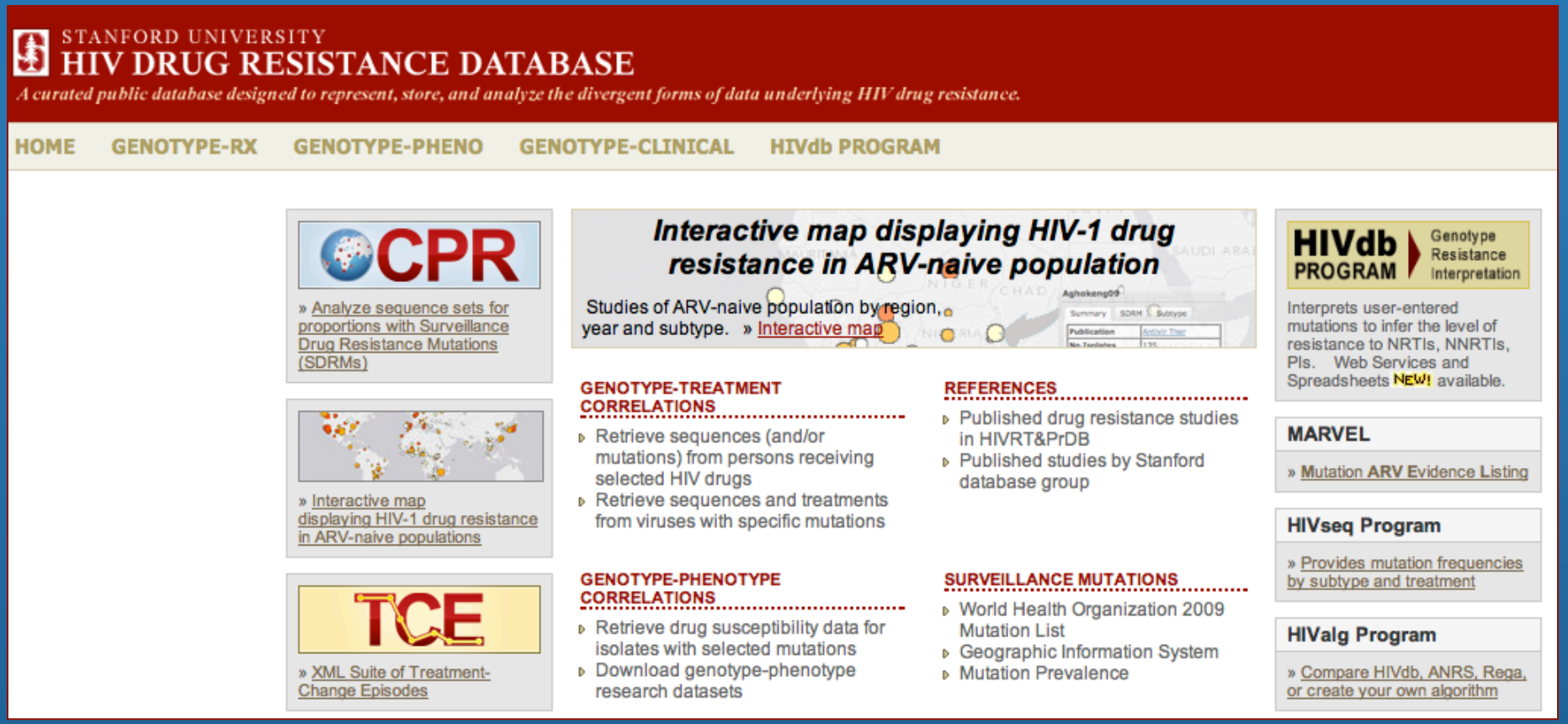
NNRTI Resistance

- Efavirenz
- Nevirapine
- Rilpivirine
- Etravirine

Stanford Database



http://hivdb.stanford.edu

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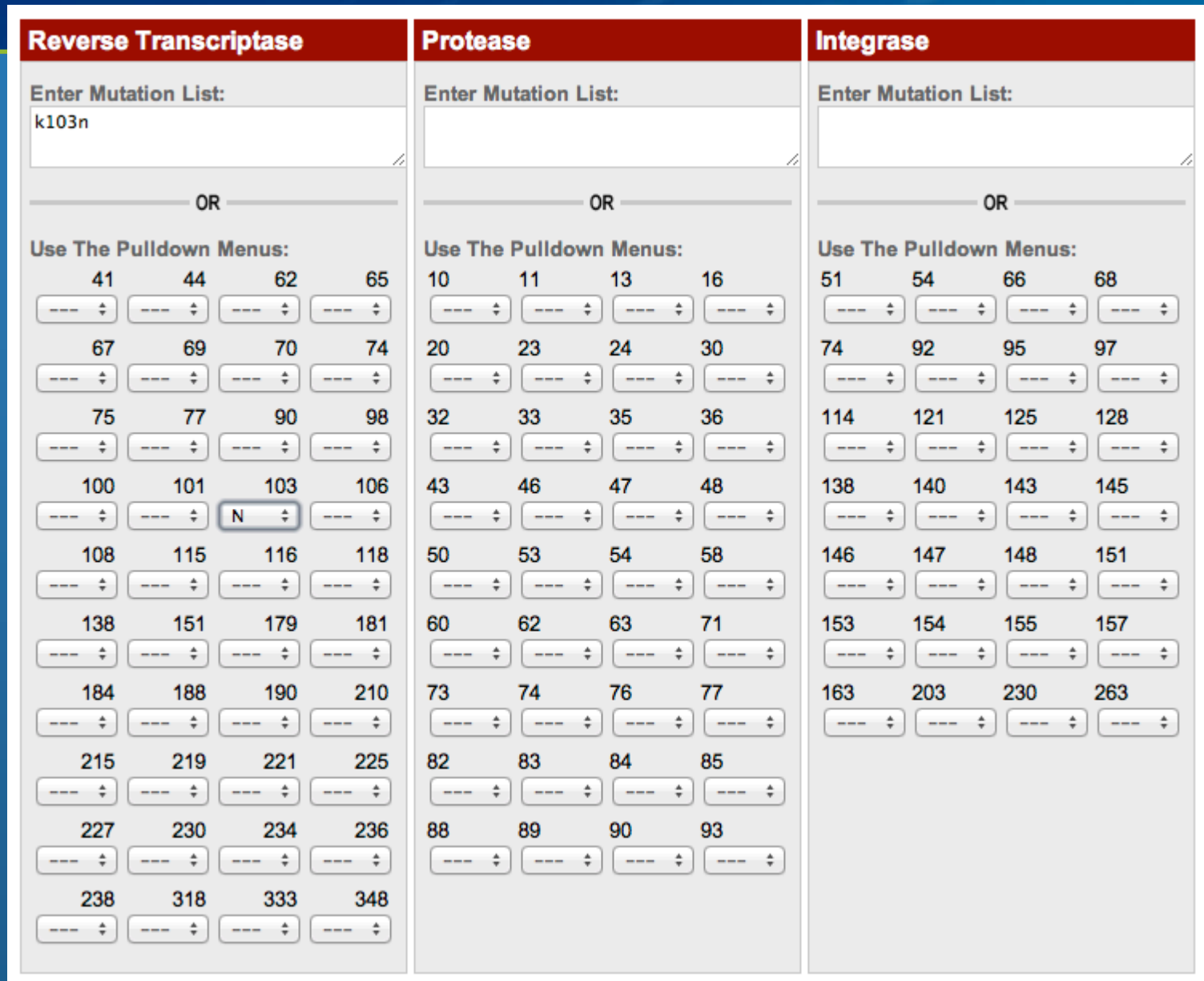
Stanford Database



Reverse Transcriptase

Enter Mutation List:

k103n

OR

Use The Pulldown Menus:

41	44	62	65
---	---	---	---
67	69	70	74
---	---	---	---
75	77	90	98
---	---	---	---
100	101	103	106
---	---	N	---
108	115	116	118
---	---	---	---
138	151	179	181
---	---	---	---
184	188	190	210
---	---	---	---
215	219	221	225
---	---	---	---
227	230	234	236
---	---	---	---
238	318	333	348
---	---	---	---

Protease

Enter Mutation List:

OR

Use The Pulldown Menus:

10	11	13	16
---	---	---	---
20	23	24	30
---	---	---	---
32	33	35	36
---	---	---	---
43	46	47	48
---	---	---	---
50	53	54	58
---	---	---	---
60	62	63	71
---	---	---	---
73	74	76	77
---	---	---	---
82	83	84	85
---	---	---	---
88	89	90	93
---	---	---	---

Integrase

Enter Mutation List:

OR

Use The Pulldown Menus:

51	54	66	68
---	---	---	---
74	92	95	97
---	---	---	---
114	121	125	128
---	---	---	---
138	140	143	145
---	---	---	---
146	147	148	151
---	---	---	---
153	154	155	157
---	---	---	---
163	203	230	263
---	---	---	---

echo

Stanford Database

Drug Resistance Interpretation: RT

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

Nucleoside RTI	
lamivudine (3TC)	Susceptible
abacavir (ABC)	Susceptible
zidovudine (AZT)	Susceptible
stavudine (D4T)	Susceptible
didanosine (DDI)	Susceptible
emtricitabine (FTC)	Susceptible
tenofovir (TDF)	Susceptible

Non-Nucleoside RTI	
efavirenz (EFV)	High-level resistance
etravirine (ETR)	Susceptible
nevirapine (NVP)	High-level resistance
rilpivirine (RPV)	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	-	-	-	-	-	-	-	60	0	60	0
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

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

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.

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E138K

	Efavirenz	Nevirapine	Rilpivirine	Etravirine
E138K	10	10	30	10

***Key point:** NNRTI cross-resistance is more common with rilpivine 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?

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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
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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/I/V**
- Best way to determine susceptibility: phenotype
  - Methods to estimate susceptibility:
    - *DUET (Tibotec) weighted scoring system*
    - *Monogram Biosciences weighted scoring system*

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

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)

Rathbun RC et al. Infections in Medicine. 2009;29(4).

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)

Vingerhoets J et al. CROI 2010.

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