NORTHWEST AIDS EDUCATION AND TRAINING CENTER

NRTI Resistance

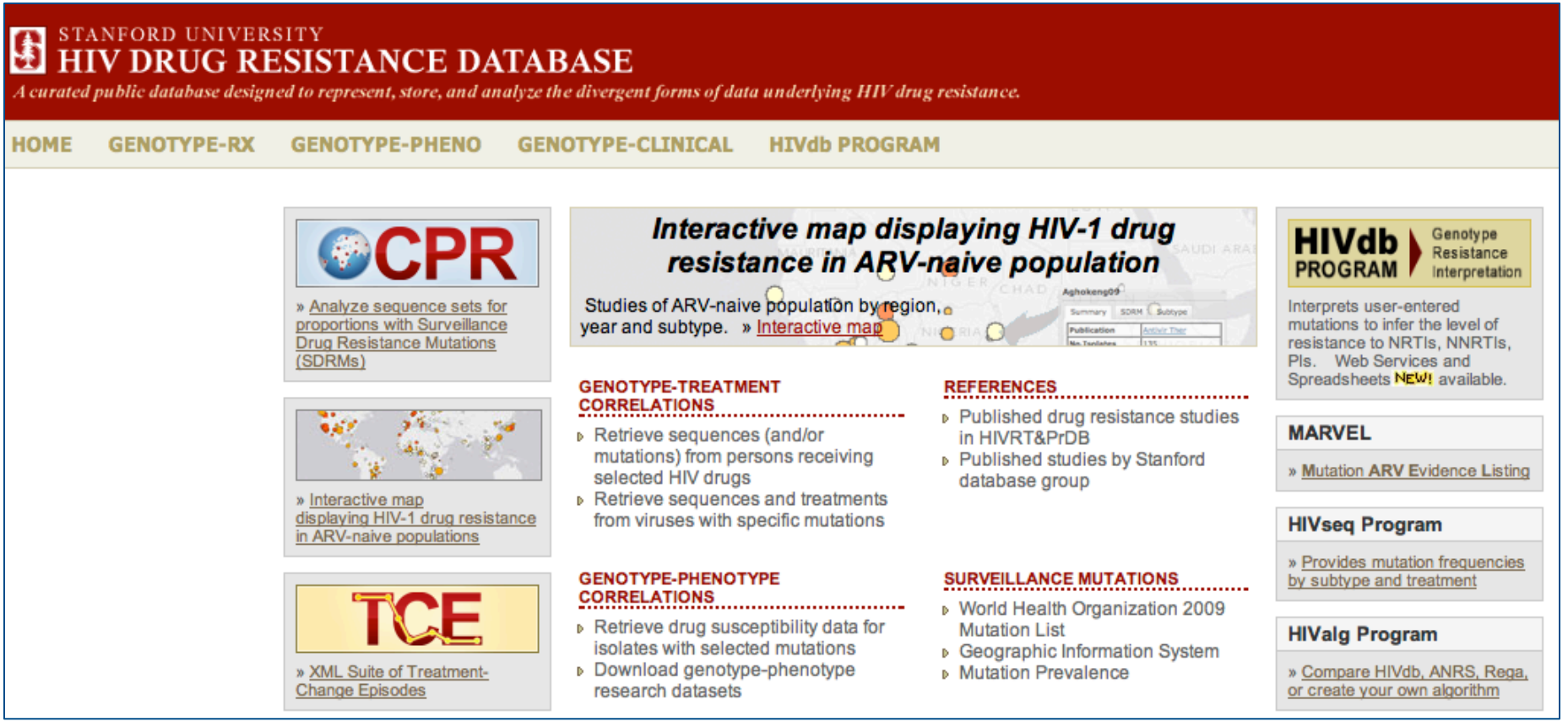
Brian R. Wood, MD
Medical Director, NW AETC ECHO
Assistant Professor of Medicine, University of Washington

Presentation prepared by:
Brian R. Wood, MD
Last Updated: 5/9/13

NRTI Resistance: Outline

- M184V
- K65R
- TAM's (Thymidine Analogue Mutations)
- L74V
- Q151 mutation complex
- T69 insertion complex

Stanford Database



http://hivdb.stanford.edu

NW AETC | echo

Stanford Database

Reverse Transcriptase

Enter Mutation List:

m184V

OR

Use The Pulldown Menus:

41 ---	44 ---	62 ---	65 ---
67 ---	69 ---	70 ---	74 ---
75 ---	77 ---	90 ---	98 ---
100 ---	101 ---	103 ---	106 ---
108 ---	115 ---	116 ---	118 ---
138 ---	151 ---	179 ---	181 ---
184 V	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 ---

Stanford Database

Drug Resistance Interpretation: RT

NRTI Resistance Mutations:	**M184V**
NNRTI Resistance Mutations:	None
Other Mutations:	None

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

RT Comments

NRTI

- M184V/I cause high-level resistance to 3TC and FTC and low-level resistance to ddI and ABC. However, M184V/I are not contraindications to continued treatment with 3TC or FTC because they increase susceptibility to AZT, TDF, and d4T and are associated with clinically significant decreased HIV-1 replication.

Mutation Scoring

RT	3TC	ABC	AZT	D4T	DDI	FTC	TDF	EFV	ETR	NVP	RPV
M184V	60	15	-10	-10	10	60	-10	-	-	-	-
Total:	60	15	-10	-10	10	60	-10	0	0	0	0

Case #1

- A 50-year-old HIV-infected woman presents to clinic for follow-up. She has struggled with adherence to tenofovir-emtricitabine (*Truvada*) and nevirapine (*Viramune*).
- HIV RNA has increased to 2,450 copies/mL.
- Resistance assay demonstrates an M184V mutation.

M184V

- High-level resistance to emtricitabine (FTC) & lamivudine (3TC); low-level resistance to abacavir (ABC) and didanosine (DDI)
- Increased susceptibility to tenofovir (TDF), zidovudine (AZT), and stavudine (D4T)
- Reduced viral fitness

Stanford Database: M184V/I

Mutation	3TC	FTC	ABC	DDI	AZT	D4T	TDF
M184V/I	60	60	12	5	-8	-5	-8

Penalty score
≥60: high-level resistance
30-60: intermediate-level resistance
10-30: low-level resistance
Less than 0: hypersusceptible

HIV1GENO

HIV-1 Genotyping

See Note

NRTI DRUGS

EPIVIR, (lamivudine, 3TC)	Resistance
EMTRIVA, (emtricitabine, FTC)	Resistance
RETROVIR, (zidovudine, AZT)	None
VIDEX, (didanosine, ddI)	None
ZERIT, (stavudine, d4T)	None
ZIAGEN, (abacavir, ABC)	None
VIREAD, (tenofovir, TDF)	None

NRTI associated resistance mutations found: M184V

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, E138K, Y188L

Protease inhibitors

SUMMARY REPORT

	DRUGS		FOLD CHANGE[1]	CUT-OFF[2]		RESISTANCE ANALYSIS[3]	CLINICAL NOTES (see p2 for details)
	NRTI / NtRTI mutations[4]: 118wt/I 184V, 335D						
NRTI/NtRTI	Retrovir®	Zidovudine	0.6	1.5	11.4	MAXIMAL RESPONSE	
NRTI/NtRTI	Epivir®	Lamivudine	48.7	*2.1*	4.6	MINIMAL RESPONSE	
NRTI/NtRTI	Videx®	Didanosine	1.4	0.9	2.6	REDUCED RESPONSE	
NRTI/NtRTI	Zerit®	Stavudine	0.6	1.0	2.3	MAXIMAL RESPONSE	
NRTI/NtRTI	Ziagen®	Abacavir	1.7	0.9	3.5	REDUCED RESPONSE	
NRTI/NtRTI	Emtriva®	Emtricitabine	41.1	*3.1*		RESISTANT	
NRTI/NtRTI	Viread®	Tenofovir DF	0.4	1.0	2.3	MAXIMAL RESPONSE	
	NNRTI mutations[4]: 106wt/I/M, 179D						
NNRTI	Viramune®	Nevirapine	28.2	*6.0*		RESISTANT	
NNRTI	Sustiva® , Stocrin®	Efavirenz	287.8	*3.3*		RESISTANT	
NNRTI	Intelence™	Etravirine	1.3	*3.2*	27.6	SUSCEPTIBLE	Note 2,3
	PI mutations[4]: 16E, 62V, 77I						
PI	Crixivan ®; boosted	Indinavir/r	0.8	2.3	27.2	MAXIMAL RESPONSE	
PI	Viracept®	Nelfinavir	0.7	2.2	9.4	SUSCEPTIBLE	Note 1
PI	Invirase®; boosted	Saquinavir/r	0.6	3.1	22.6	MAXIMAL RESPONSE	
PI	Lexiva®,Telzir®; boosted	Fosamprenavir/r	0.7	1.5	19.5	MAXIMAL RESPONSE	
PI	Kaletra®	Lopinavir/r	0.7	6.1	51.2	MAXIMAL RESPONSE	
PI	Reyataz®; boosted	Atazanavir/r	0.6	2.5	32.5	MAXIMAL RESPONSE	
PI	Aptivus®; boosted	Tipranavir/r	0.9	1.5	7.0	MAXIMAL RESPONSE	Note 2
PI	Prezista™; boosted	Darunavir/r	1.8	10.0	106.9	MAXIMAL RESPONSE	

Second-Line Regimens after M184V

- **Background:**
  - N = 117 patients with documented M184V +/- NNRTI mutations
  - No PI mutations and no other NRTI mutations
  - Setting: British Columbia
- **2nd-Line Regimens:**
  - A) 2 NRTI's (including 3TC or FTC) + Boosted PI
  - B) 2 NRTI's (including 3TC or FTC) + Boosted PI + ≥1 active agent
  - C) 2 NRTI's (excluding 3TC or FTC) + Boosted PI +/- ≥1 active agent
- **Results**: No significant difference between groups A, B & C

Hull M, et al. 49th ICAAC. 2009; Abstract H-916.

NW AETC | echo

Case #2

- A 33-year-old man with HIV-HCV coinfection is being considered for HCV treatment to include an HCV PI. Current ARV's include: zidovudine-lamivudine (AZT-3TC, *Combivir*) plus atazanavir (*Reyataz*) and ritonavir (*Norvir*).
- HIV RNA is undetectable.
- Past resistance assay showed a K65R mutation.

K65R

- Signature **tenofovir (TDF) mutation**
  - Less common with abacavir (ABC) or didanosine (DDI)
  - Abacavir → L74V > K65R
- Resistance to most NRTI's but **increased susceptibility to zidovudine (AZT)**
- Other data:
  - K65R and TAM's tend to be mutually exclusive
  - K65R + M184V decreases viral fitness > M184V alone
  - Greater likelihood of K65R with subtype C virus

Stanford Database: K65R

Mutation	3TC	FTC	D4T	ABC	DDI	TDF	AZT
K65R	30	30	30	45	45	45	-10

Penalty score
≥60: high-level resistance
30-60: intermediate-level resistance
10-30: low-level resistance
Less than 0: hypersusceptible

K65R

HIV-1 GenotypR™ PLUS

Resistance associated RT Mutations: K65R, L100I, K103N, V108I, M184V*

zidovudine (AZT)	No Evidence of Resistance
didanosine (ddI)	*Possible Resistance*
zalcitabine (ddC)	**Resistance**
lamivudine (3TC)/emtricitabine (FTC)	**Resistance**
stavudine (d4T)	*Possible Resistance*
abacavir (ABC)	**Resistance**
tenofovir (TDF)	**Resistance**

Case #3

- A 43-year-old heavily treatment-experienced woman presents to restart ART after a lapse in adherence due to drug use.
- Past genotype demonstrated: M184V, M41L and T215Y

TAM's (Thymidine Analogue Mutations)

- Pathway 1: M41L, L210W, T215F/Y
- Pathway 2: D67N, K70R, K219E/Q
- Emerge sequentially with **AZT or D4T**
- Confer some degree of resistance to **all NRTI's**
  - In general, pathway 1 is worse
  - As more accumulate, resistance increases
  - May protect against NNRTI resistance

TAM's

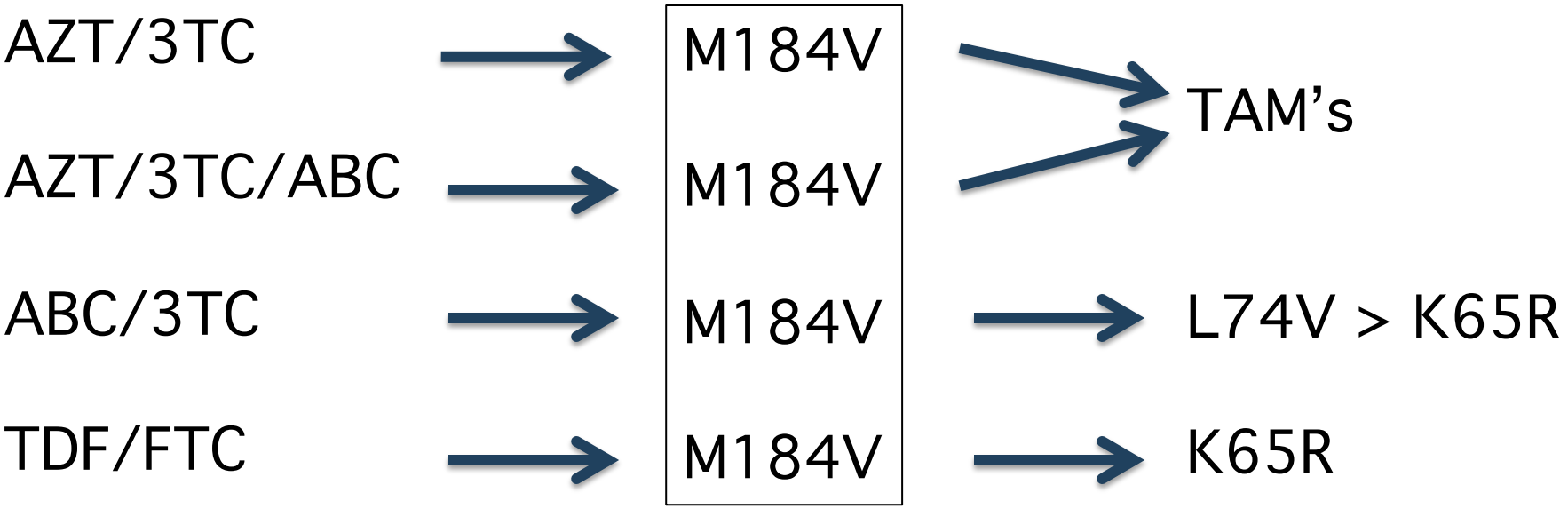
1st Pathway

RT	3TC	ABC	AZT	D4T	DDI	FTC	TDF
M41L	5	5	15	15	5	5	5
L210W	5	5	15	15	5	5	5
T215Y	5	15	45	45	15	5	15
All three	**15**	**55**	**105**	**105**	**55**	**15**	**55**

2nd Pathway

RT	3TC	ABC	AZT	D4T	DDI	FTC	TDF
D67N	0	5	15	15	5	0	5
K70R	0	0	30	15	0	0	10
K219E	0	5	10	10	5	0	5
All three	**0**	**10**	**55**	**40**	**10**	**0**	**20**

M184V Occurs First

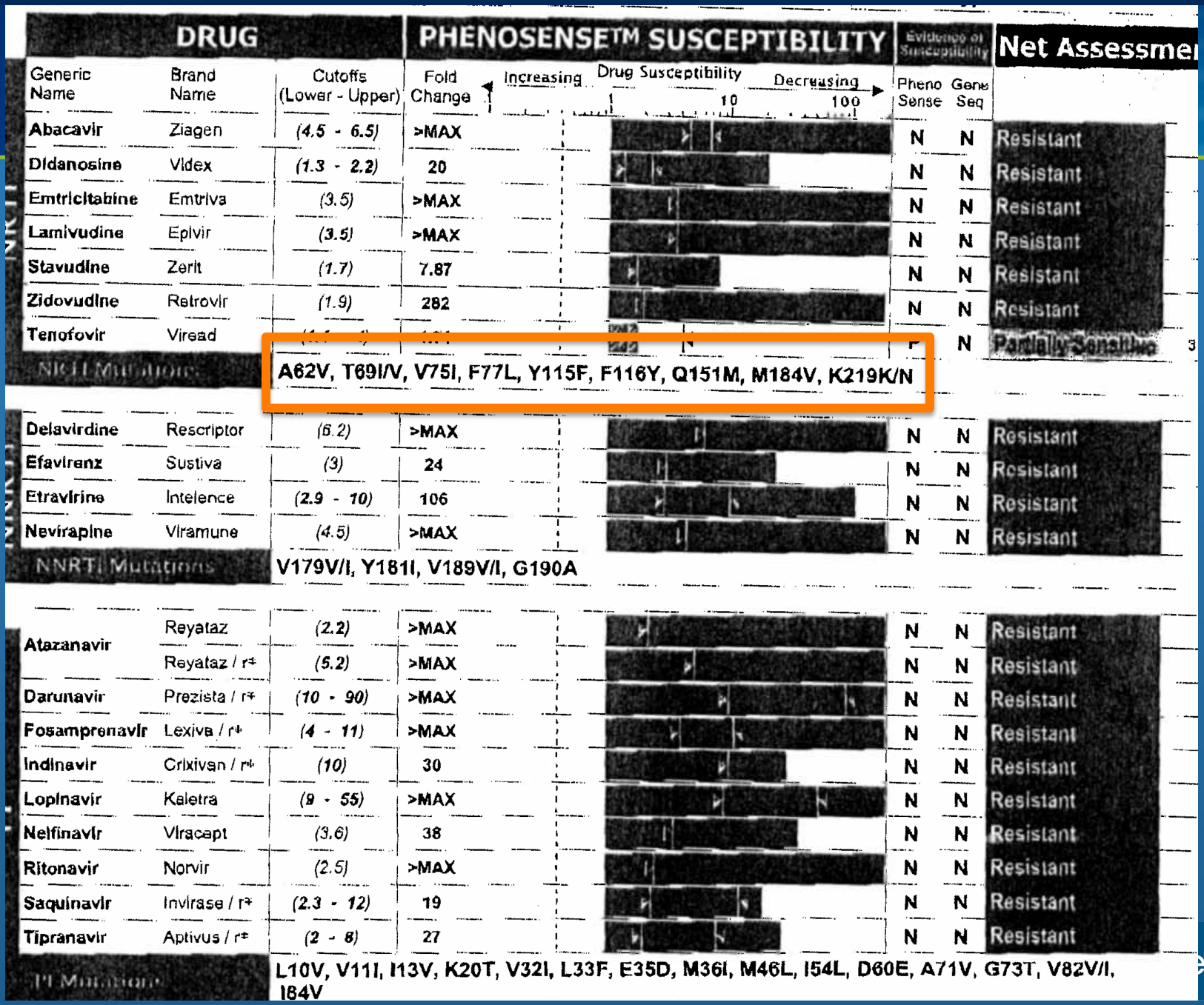


*Key point: stop meds early if signs of resistance to prevent accumulation of mutations

Gallant JE. Top HIV Med. 2005 Dec-2006 Jan;13(5):138-42.

Other NRTI Mutations

- **Q151 mutation complex:**
  - Q151M: Intermediate-to-high resistance to AZT, ddI, d4T, and ABC; low resistance to TDF, 3TC, and FTC
  - Worse if add: A62V, V75I, F77L, F116Y
- **T69 insertion complex (T69i or T69ins):**
  - High resistance to AZT, d4T, ddI, ABC, and TDF
  - Intermediate-to-high resistance to 3TC and FTC


DRUG
PHENOSENSE™ SUSCEPTIBILITY
Net Assessme
Generic Name
Brand Name
Cutoffs (Lower - Upper)
Fold Change
Increasing Drug Susceptibility Decreasing
1
10
100
Pheno Sense
Geno Seq
Abacavir Ziagen (4.5 - 6.5) >MAX N N Resistant
Didanosine Videx (1.3 - 2.2) 20 N N Resistant
Emtricitabine Emtriva (3.5) >MAX N N Resistant
Lamivudine Epivir (3.5) >MAX N N Resistant
Stavudine Zerit (1.7) 7.87 N N Resistant
Zidovudine Retrovir (1.9) 282 N N Resistant
Tenofovir Viread N N Partially Sensitive
A62V, T69I/V, V75I, F77L, Y115F, F116Y, Q151M, M184V, K219K/N
Delavirdine Rescriptor (6.2) >MAX N N Resistant
Efavirenz Sustiva (3) 24 N N Resistant
Etravirine Intelence (2.9 - 10) 106 N N Resistant
Nevirapine Viramune (4.5) >MAX N N Resistant
V179V/I, Y181I, V189V/I, G190A
Atazanavir Reyataz (2.2) >MAX N N Resistant
Reyataz / r* (5.2) >MAX N N Resistant
Darunavir Prezista / r* (10 - 90) >MAX N N Resistant
Fosamprenavir Lexiva / r* (4 - 11) >MAX N N Resistant
Indinavir Crixivan / r* (10) 30 N N Resistant
Lopinavir Kaletra (9 - 55) >MAX N N Resistant
Nelfinavir Viracept (3.6) 38 N N Resistant
Ritonavir Norvir (2.5) >MAX N N Resistant
Saquinavir Invirase / r* (2.3 - 12) 19 N N Resistant
Tipranavir Aptivus / r* (2 - 8) 27 N N Resistant
L10V, V11I, I13V, K20T, V32I, L33F, E35D, M36I, M46L, I54L, D60E, A71V, G73T, V82V/I, I84V

Summary

- M184V:
  - Resistance to 3TC/FTC; increased susceptibility to TDF, AZT and D4T; reduced viral fitness
- K65R:
  - Resistance to most NRTI's but increased susceptibility to AZT
- TAM's:
  - Resistance to AZT and D4T, also TDF (especially with first pathway)
  - As they accumulate, things get worse
- L74V:
  - Most common abacavir-associated mutation
- Q151 mutation complex and T69 insertion complex:
  - Near class-wide resistance