

Patterns of Resistance to Antiretrovirals: Do We Need Different Approaches?

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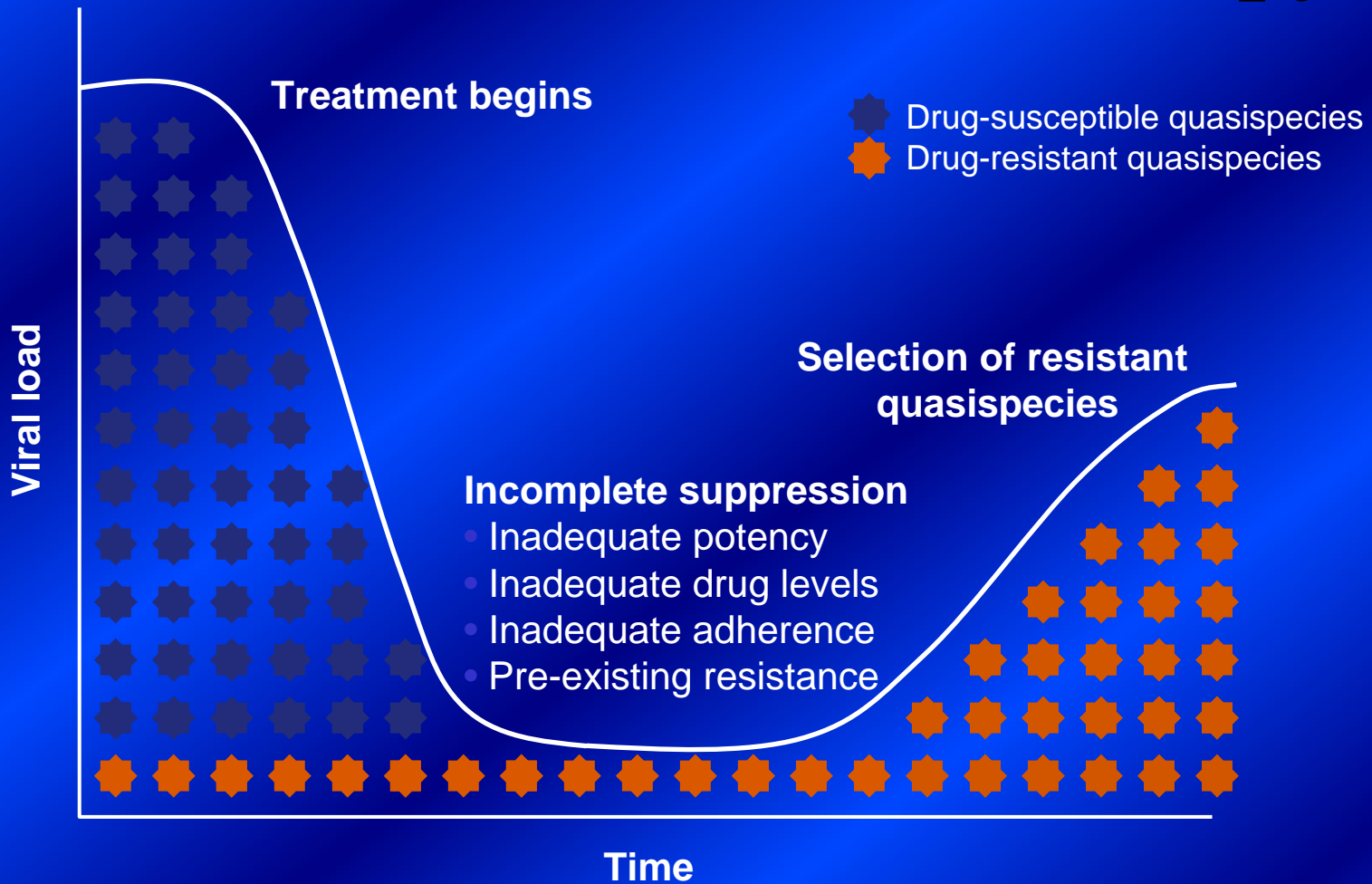
¿Which one of the following statements about antiretroviral resistance patterns is correct?

- Resistance mutations may also be associated with enhanced susceptibility to some antiretroviral drugs.
- Resistance mutations generally increase the rate of viral replication.
- The K103N mutation markedly reduces the replication rate of the virus.
- TAMs, thymidine analogue mutations, tend to be specific for the thymidine analogue used.
- Antiviral resistance patterns are simple to interpret and apply to patient care.
- I do not know, I'm coming to learn.

Dynamics of HIV Drug Resistance

- Mutations occur at 10^{-5}
- HIV genome is $\sim 10^4$
- Rate of replication is $\sim 10^{10}$
- Thus, at any one time, one resistance-conveying mutation is present.
- > 100 mutations known to be associated with alterations in susceptibility to drugs.

Selective Pressures of Therapy



The Initial Regimen

- Factors to consider in selecting the first regimen:
 - Presence of resistance-conveying mutations
 - Potential toxicities
 - Co morbid diseases
 - Drug interactions
 - Ability of the patient to adhere with multidrug regimens

HIV Resistance Assays

- **Genotypic assays**
- **Phenotypic assays**
- **Recombinant phenotypic assays**
- **“Virtual” phenotypic assays**

Types of Resistance Assays

- **Phenotypic HIV drug resistance assays**
 - Viral isolates or recombinant viruses derived from patient plasma sequences analyzed in culture-based assay
 - Quantitation of drug concentration needed to inhibit HIV replication
- **Genotypic HIV drug resistance assays**
 - Identify whether specific mutations are present
 - Resistance inferred through an algorithm or database analysis

Mutations in HIV-1 RT Commonly Associated with Resistance to NRTIs

Drug(s)	Common RT Resistance Mutations
Abacavir	K65R, L74V, Y115F, M184V
Didanosine	K65R, L74V
Lamivudine	E44A/D, V118I, M184I/V
Stavudine	M41L, E44A/D, D67N, K70R, V118I, L210W, T215Y/F, K219Q/E
Tenofovir DF	K65R
Zalcitabine	K65R, T69D, L74V, M184V
Zidovudine	M41L, E44A/D, D67N, K70R, V118I, L210W, T215Y/F, K219Q/E
Thymidine analogue mutations (TAMs)	M41L, D67N, K70R, L210W, T215Y/F, and K219Q
Multinucleoside resistance	<i>Q151M resistance complex</i> : A62V, V75I, F77L, F116Y, Q151M
	<i>69XXX insertion</i> : Usually seen with TAMs

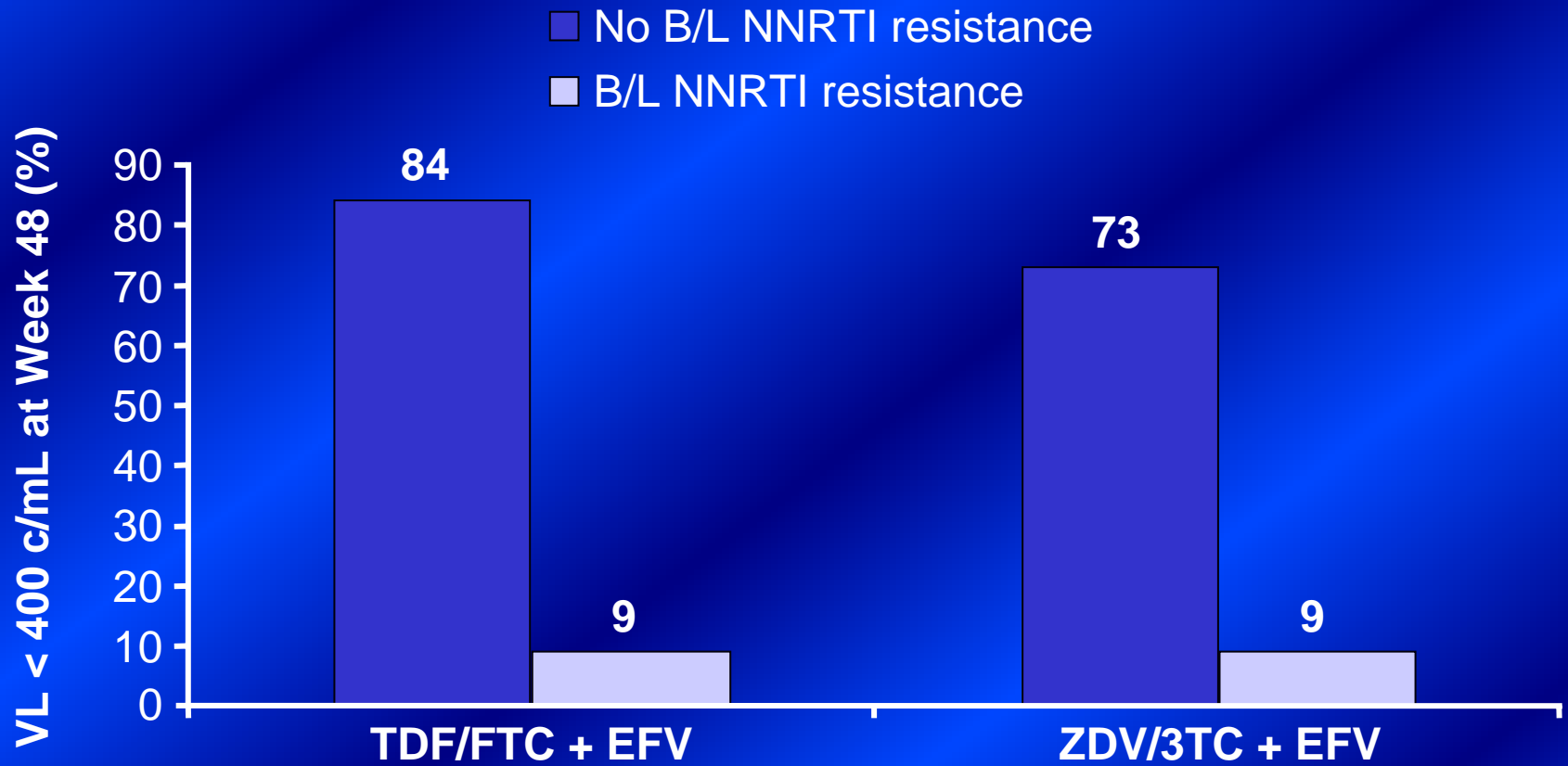
TAMs

- Comprise a group of 6 drug resistance mutations
 - M41L, D67N, K70R, L210W, T215Y/F, and K219Q
- Associated with resistance to d4T and AZT
- Result in moderate levels of resistance to other NRTIs
 - Including ABC, ddI, TDF, and ddC
 - Depends on the mutational pattern present
- Can increase the likelihood of further mutations
- TDF is active against HIV-1 with up to 3 TAMs
 - Unless TAMs include M41L or L210W
 - Can be used to treat individuals previously treated with a variety of NRTI-based regimens

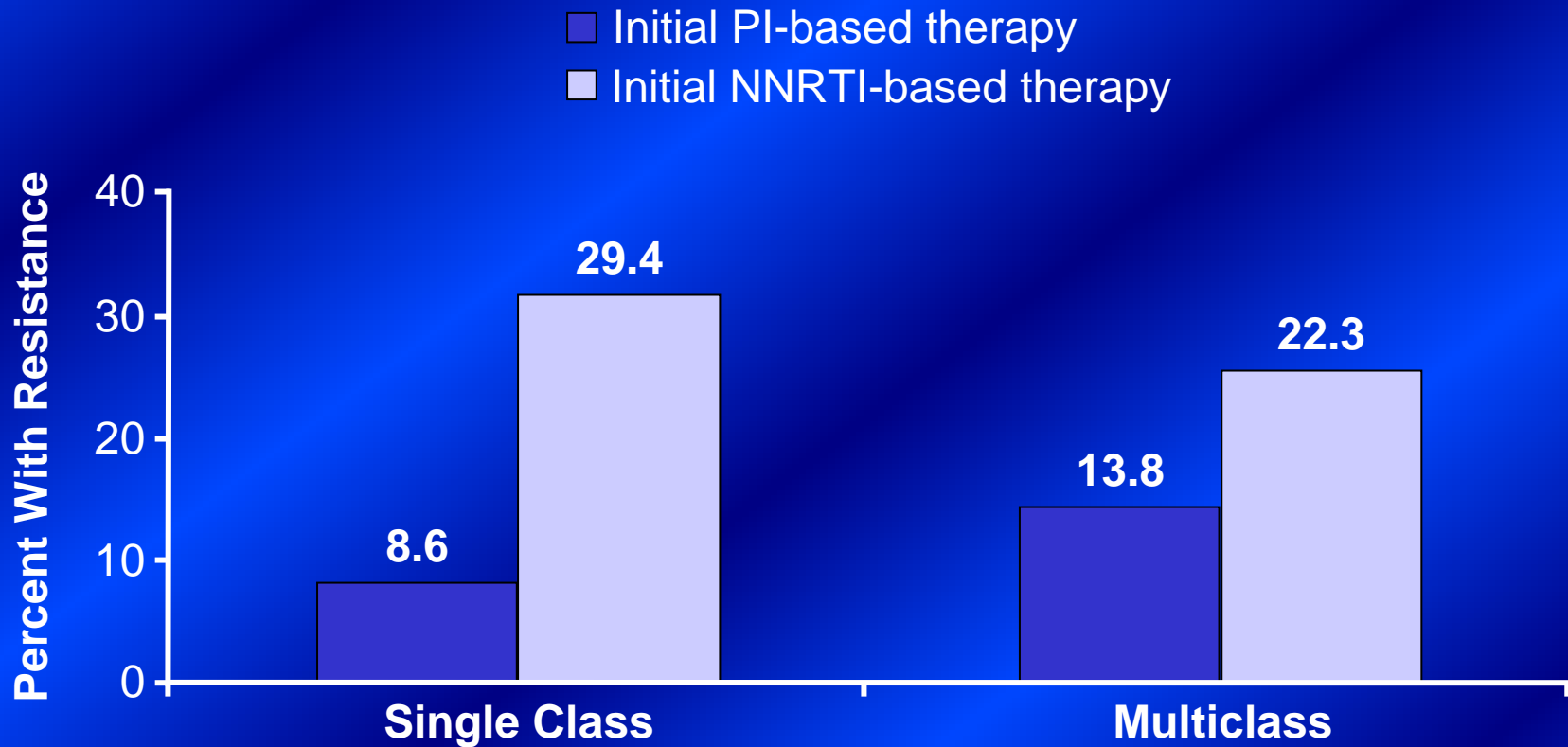
Summary of Effects of Common Mutational Patterns

Mutation	Effects
TAMs	<ul style="list-style-type: none"> • Decrease susceptibility to all NRTIs • More TAMs = more NRTI cross-resistance
K65R	<ul style="list-style-type: none"> • Decreases susceptibility to TDF, ABC, 3TC, ddI, and ddC • Hypersusceptibility to AZT • Maintains susceptibility to d4T
L74V	<ul style="list-style-type: none"> • Decreases susceptibility to ddI, TDF, ABC, 3TC • Hypersusceptibility to AZT
M184V	<ul style="list-style-type: none"> • Confers high-level resistance to 3TC and lower level resistance to ABC • No major effect on ddI or TDF • Hypersusceptibility to ZDV
Multi-NRTI resistance	<ul style="list-style-type: none"> • Q151M complex: resistance to all NRTIs (but not TDF) • T69 insertion: Resistance to all NRTIs + TDF

GS 934: Baseline NNRTI Resistance Reduces Virologic Response



FIRST: Risk of Resistance at Virologic Failure by Initial Regimen Strategy



Summary of Resistance Patterns and Treatment Strategies

Initial PI	Mutations After Early Failure	Additional Mutations	Impact on Second-line PIs	Potential PI-based Salvage Options*
APV	I50V	M46I/L, I84V	Susceptibility to PIs	Most other PIs
ATV	I50L		Susceptibility to PIs	Most other PIs
	I84V	I54L	Cross-resistance	TPV/r, LPV/r
fAPV/r	None identified		Susceptibility to PIs	Most other PIs
IDV	M46I / V82A	I54V, A71V/T	Cross-resistance	ATV/r, LPV/r, TPV/r
LPV/r	None identified		Susceptibility to PIs	Most other PIs
NFV	D30N	Rare; N88S	Susceptibility to PIs	Most other PIs
	L90M		Cross-resistance	SQV/r, ATV/r, LPV/r, TPV/r
RTV	V82F	I54V/L, A71V, M36I→M46I→I84V	Cross-resistance	SQV/r, ATV/r, LPV/r, TPV/r
SQV	L90M > G48V	V82A	Cross-resistance	FPV/r, ATV/r, LPV/r, TPV/r

* Decisions should be individualized according to specific resistance testing results; if available, therapeutic drug monitoring may be helpful to ensure that adequate PI trough concentration levels are achieved

New Agent – Etravirine - New Mutations

- Resistance associated mutations: V96I, A98G, L100I, K101E/I, V106I, V179D/F, Y181C/I/V, G190A/S
- Three or more mutations associated with high level resistance
- But Not to K103N and most other common NNRTI resistance mutations

New Agents – Raltegravir & Elvitegravir - New Mutations

- Two Resistance Patterns:
 - N155H plus E92Q, V151I, T97A, G163K, & L64M
 - Q148K/R/H plus G120?S/A & E138K
- Cross resistance within class demonstrated.

THE DILEMMA: An extensively treated patient with aids has failed his second salvage regimen. His resistance genotype demonstrates resistance to all agents but darunavir. You expect that raltegravir or possibly etravirine will be available within the next six months.

- **What do think is the best course of action?**
 - **Continue the current failing regimen until one of the new agents is available.**
 - **Add boosted darunavir to his failing regimen**
 - **Stop all but lamivudine**
 - **Stop all antiretrovirals until you have two active agents?**
 - **Does it matter if his CD4 count is 50? 500?**

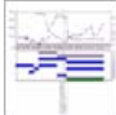
Resistance Testing

- **Expensive, difficult to interpret, measure only major species of virus present.**
- **Recommended for anyone failing an initial or subsequent regimen.**
- **Recommended for newly infected persons living in areas where resistance is known to be present.**
- **CDC has surveillance network to assay for HIV genotypic resistance mutations for all newly diagnosed persons.**
- **Interpretation? Try <http://hivdb.stanford.edu/>**

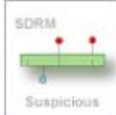
Genotype-Treatment, Genotype-Phenotype, and Genotype-Clinical Correlations

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

Three new programs launched: ART-AiDE, eCARE, and CPR



Antiretroviral Therapy - Acquisition and Display Engine (ART-AiDE) makes it possible to generate a permanent electronic and graphical record of a patient's antiretroviral treatment (ARV) history, plasma HIV-1 RNA levels,... [More »](#)



HIVdb PROGRAM

Genotype Resistance Interpretation

This program interprets user-entered mutations to infer the level of resistance to NRTIs, NNRTIs, PIs. Web Service is available.

GENOTYPE-TREATMENT CORRELATIONS

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

[More »](#)

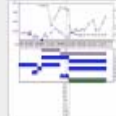
GENOTYPE-CLINICAL CORRELATIONS

- Summaries of genotype-clinical outcome studies
- Genotype-clinical outcome datasets (download)

[More »](#)

ART-AiDE

Antiretroviral Therapy - Acquisition & Display Engine
[» Go To Program](#)



HIVseq Program

Provides mutation frequencies by subtype.
[» Go To Program](#)

GENOTYPE-PHENOTYPE CORRELATIONS

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

[More »](#)

REFERENCES

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

[More »](#)


HIValg Program

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

ANALYSIS TOOLS

- Calibrated Population Resistance (CPR) [Version 2.0 beta](#)
- REGA HIV-1 Subtyping Tool [Version 1.0](#)

Drug Resistance Summaries

PI	
NRTI	
NNRTI	

HIVdb Genotypic Resistance Interpretation Program

A Reverse Transcriptase

Enter Mutation List:
67N, 70R, 75M, 179D, 184V, 215E, 219Q

OR

Use The Pulldown Menus:

41	---	44	---	62	---	65	---
67	N	69	---	70	R	74	---
75	M	77	---	98	---	100	---
101	---	103	---	106	---	108	---
115	---	116	---	118	---	151	---
179	D	181	---	184	V	188	---
190	---	210	---	215	F	219	Q
225	---	227	---	230	---	236	---
238	---	318	---	333	---		

Protease

Enter Mutation List:
10F, 20I, 46I, 73S, 84V, 90M

OR

Use The Pulldown Menus:

10	F	16	---	20	I	23	---
24	---	30	---	32	---	33	---
36	---	46	I	47	---	48	---
50	---	53	---	54	---	63	---
71	---	73	S	77	---	82	---
84	V	88	---	90	M	93	---

Identifier (Optional)

Date (Optional)

Output Analysis:
 Mutation Scores Mutation Comments

RESET
ANALYZE

B Sequences

A Text Input
Paste sequence text in the text box below.

```

>NC4172-1997|AY031148
CCTCAGATCACTCTTTGGCAACGACCCATCGTCACAGTAAAGATAGGGGGCACTAATG
GAAGCTCTATTAGATACAGGAGCAGATGATACAGTATTAGAAGAAATAAATTTGCCAGGA
AGATGGAAACCAAAATGATAGGGGGAATGGAGGTTTTTTCRAAGTAAGACAGTATGAT
CAGRTACCCATAGAAATCTGTGGACATAAAGTTGTAAGTACAGTATTAGTAGGCCTACA
CCTGTCAACGTAATTGGAAAGGAATCTGATGACTCAGATTGGTTGCACCTTAAATTTTCCC
            
```

B Text File Upload
Choose a file to upload from your computer using the file selection box below.

C GRF File Upload
Choose a GRF (Bayer Diagnostics) file to upload from your computer using the file selection box below.

Identifier (Optional)

Date (Optional)

Output Analysis:
 QA Analysis Mutation Comments
 Mutation Scores

RESET
ANALYZE

HIVdb Genotypic Resistance Interpretation Program - <http://hivdb.stanford.edu>

A Drug Resistance Interpretation

NRTI Resistance Mutations: D67N, K70R, V75M, M184V, T215F, K219Q
 NNRTI Resistance Mutations: V179D
 RT Other Mutations: None

Nucleoside RTI		Non-Nucleoside RTI	
3TC	High-level resistance	DLV	Potential low-level resistance
ABC	Intermediate resistance	EFV	Potential low-level resistance
AZT	High-level resistance	NVP	Potential low-level resistance
D4T	High-level resistance		
DDI	Intermediate resistance		
FTC	High-level resistance		
TDF	Low-level resistance		

RT Comments

- D67N contributes some degree of resistance to each of the NRTIs except 3TC and FTC. It usually occurs with mutations at positions 70 or 215. D67E/G occur in heavily treated patients and probably have a similar effect as D67N.
- K70R causes low-level AZT and probably d4T resistance but appears to have little effect on the other NRTIs. K70E reduces TDF susceptibility. K70G/N are rare variants of unknown significance
- V75I increases multinucleoside resistance caused by Q151M when present with F77L and F116Y; its effect in the absence of Q151M is not known. V75T/M/A cause d4T and possibly ddi resistance. The significance of V75S and L are not known, although the former only occurs in treated persons.

• M184V partially reverses AZT, d4T, and TDF resistance caused by other TAMs.

Mutation Scoring

	3TC	ABC	AZT	D4T	DDI	FTC	TDF	DLV	EFV	NVP
D67N	0	8	15	12	8	0	5	-	-	-
K70R	0	0	18	10	0	0	8	-	-	-
V75M	0	5	5	20	10	0	5	-	-	-
V179D	-	-	-	-	-	-	-	10	10	10
M184V	60	12	-8	-5	5	60	-8	-	-	-
T215F	4	20	35	30	20	4	10	-	-	-
K219Q	0	0	15	10	0	0	0	-	-	-
Total:	64	45	80	77	43	64	20	10	10	10

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- Antiviral resistance patterns are simple to interpret and apply to patient care.
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