ARV Resistance and why it still matters

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GreenShoots FOUNDATION

Resistance…

Outline

- Theory
- Relevance
- How to manage without a resistance test

- Please interact….

What is resistance..

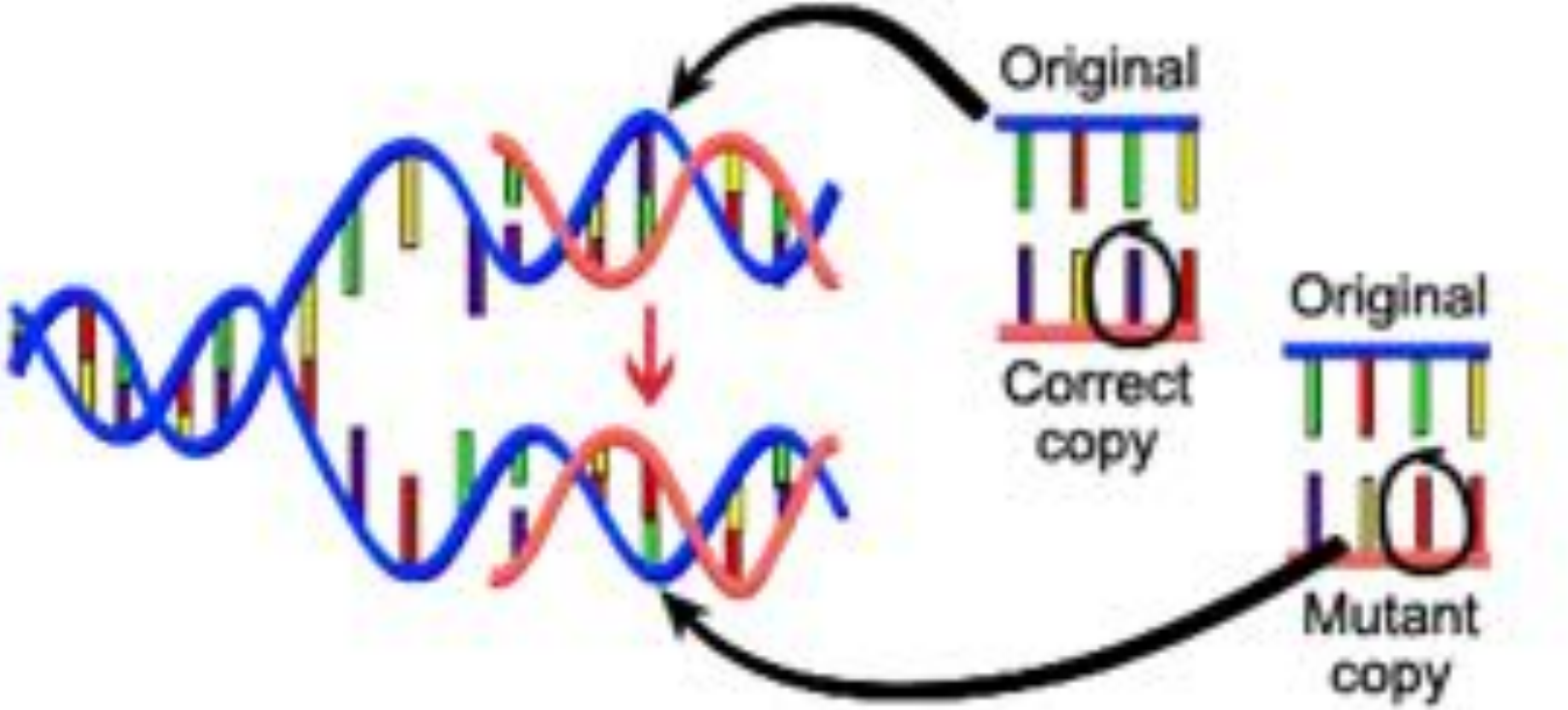
What happens..

How does it occur?

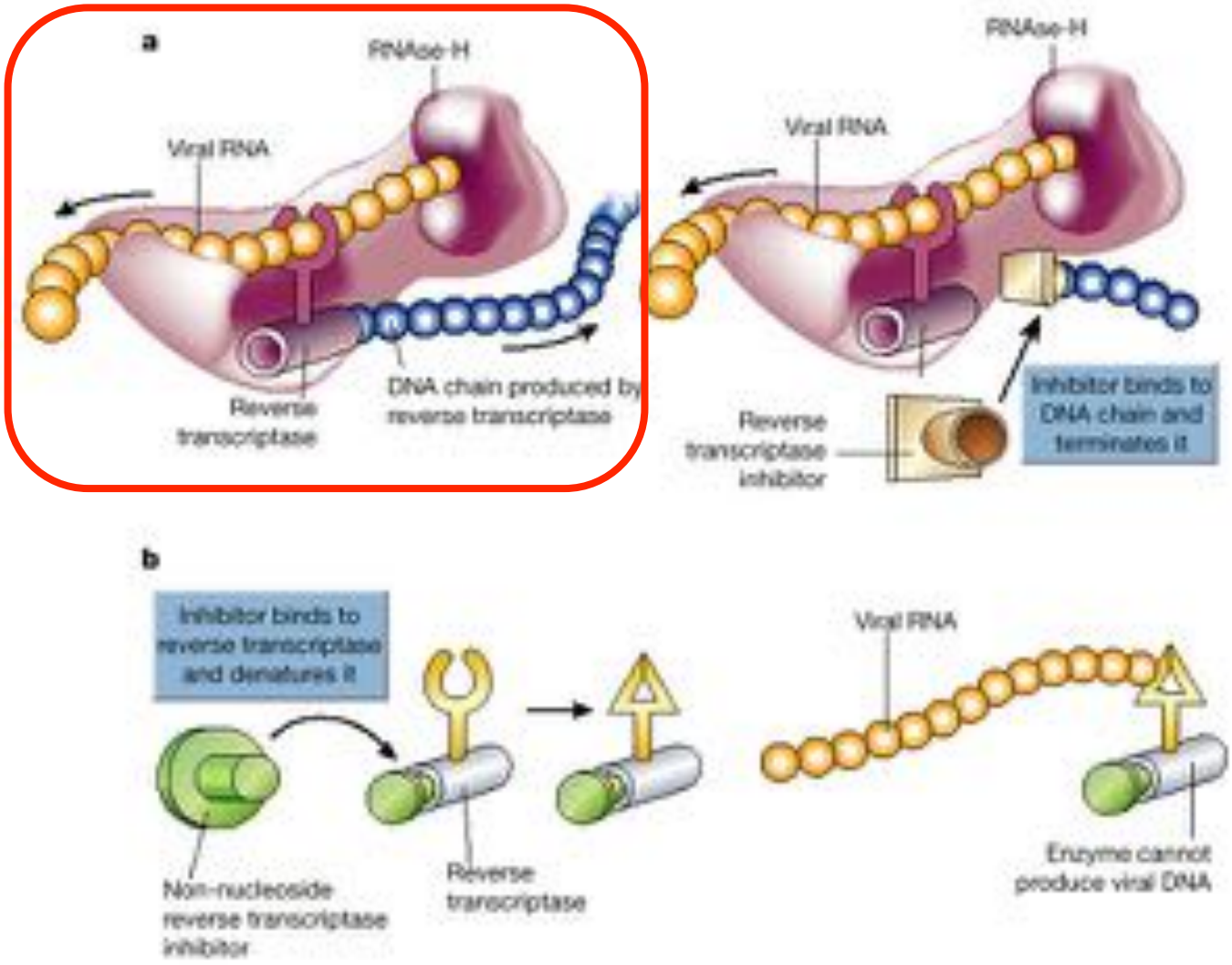
- **A mutation of the *viral genetic material***

And in HIV….

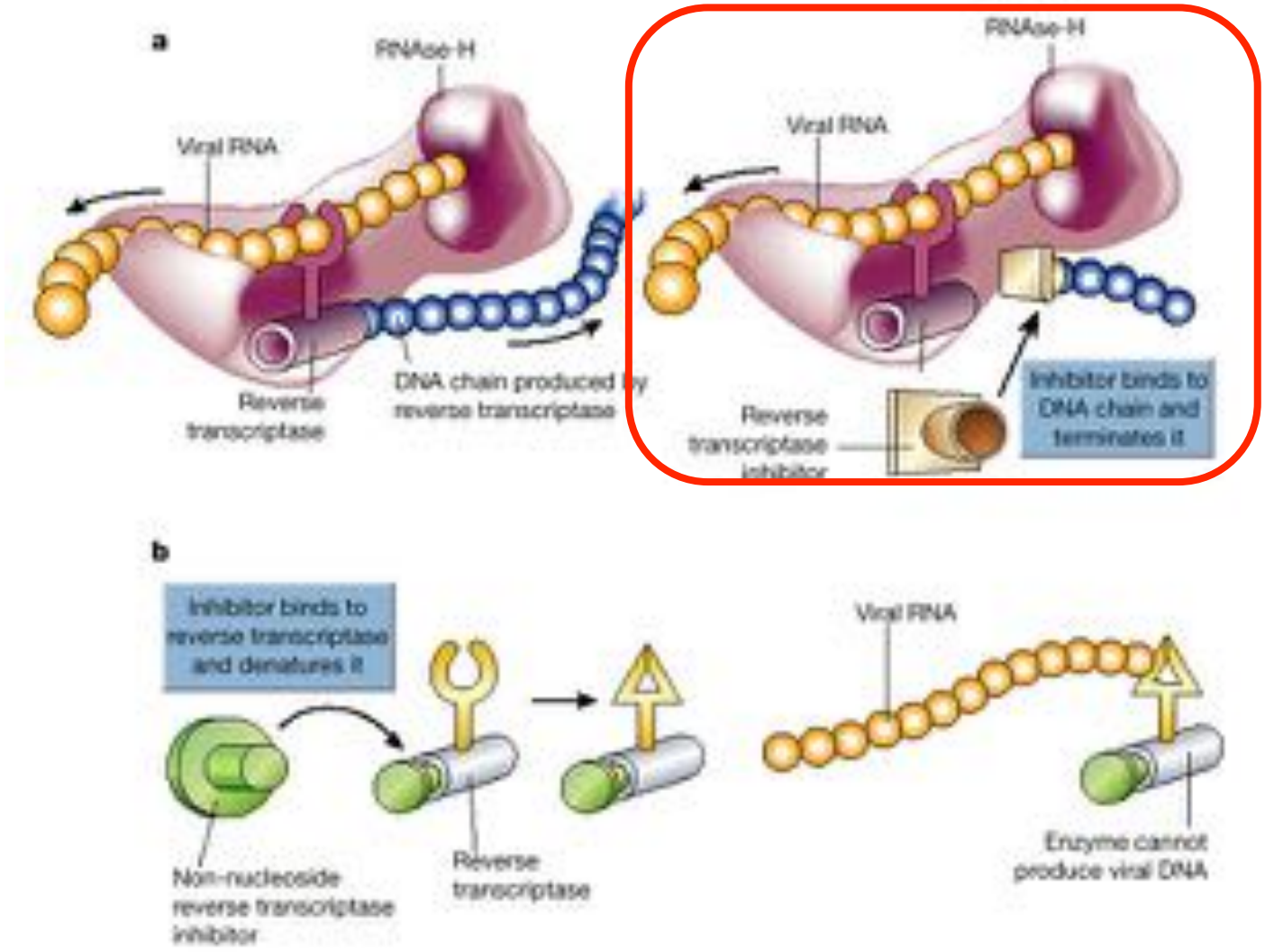
- **A mutation of the *viral genetic material*** that results in the drug no longer being able to block viral replication



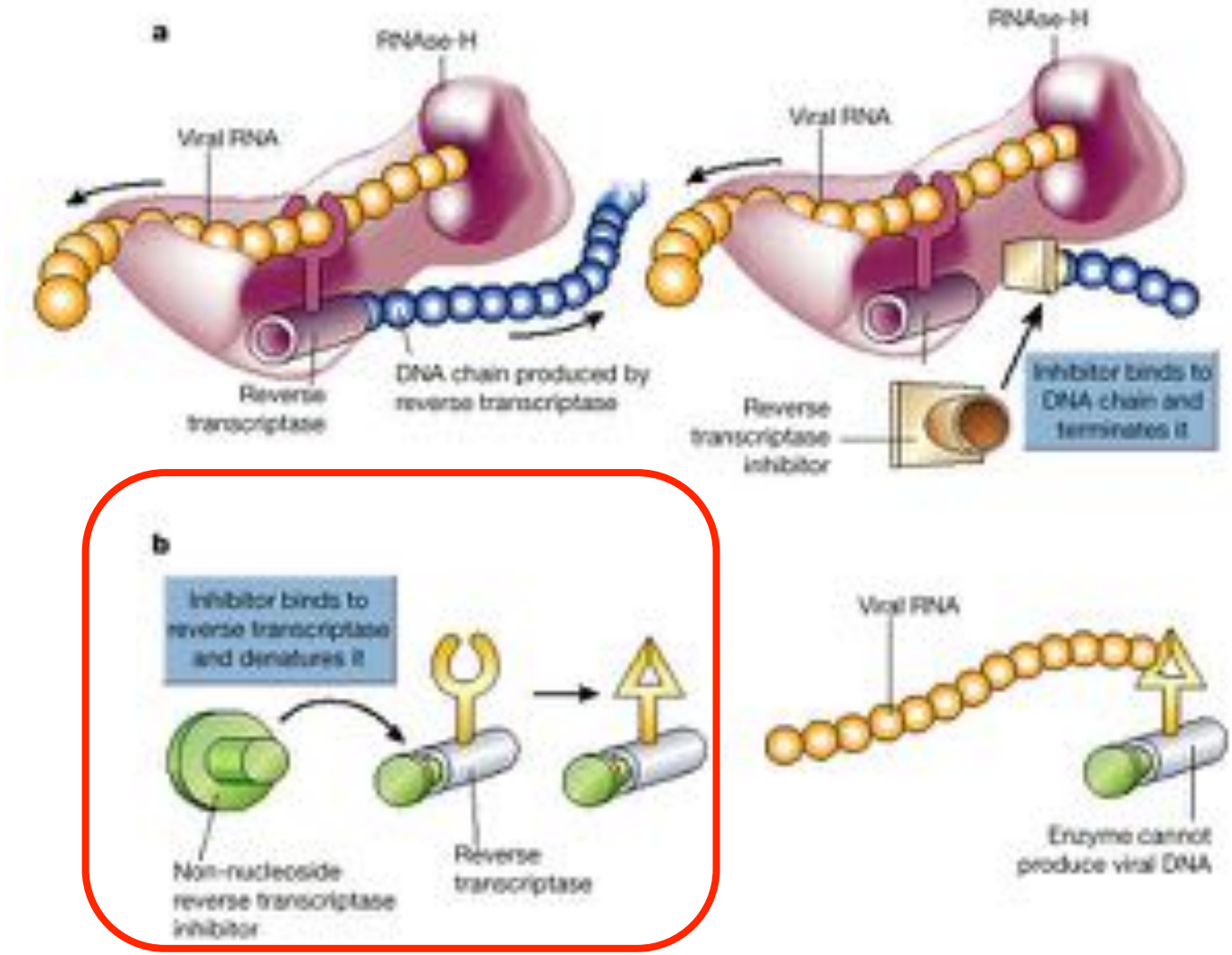
What happens…



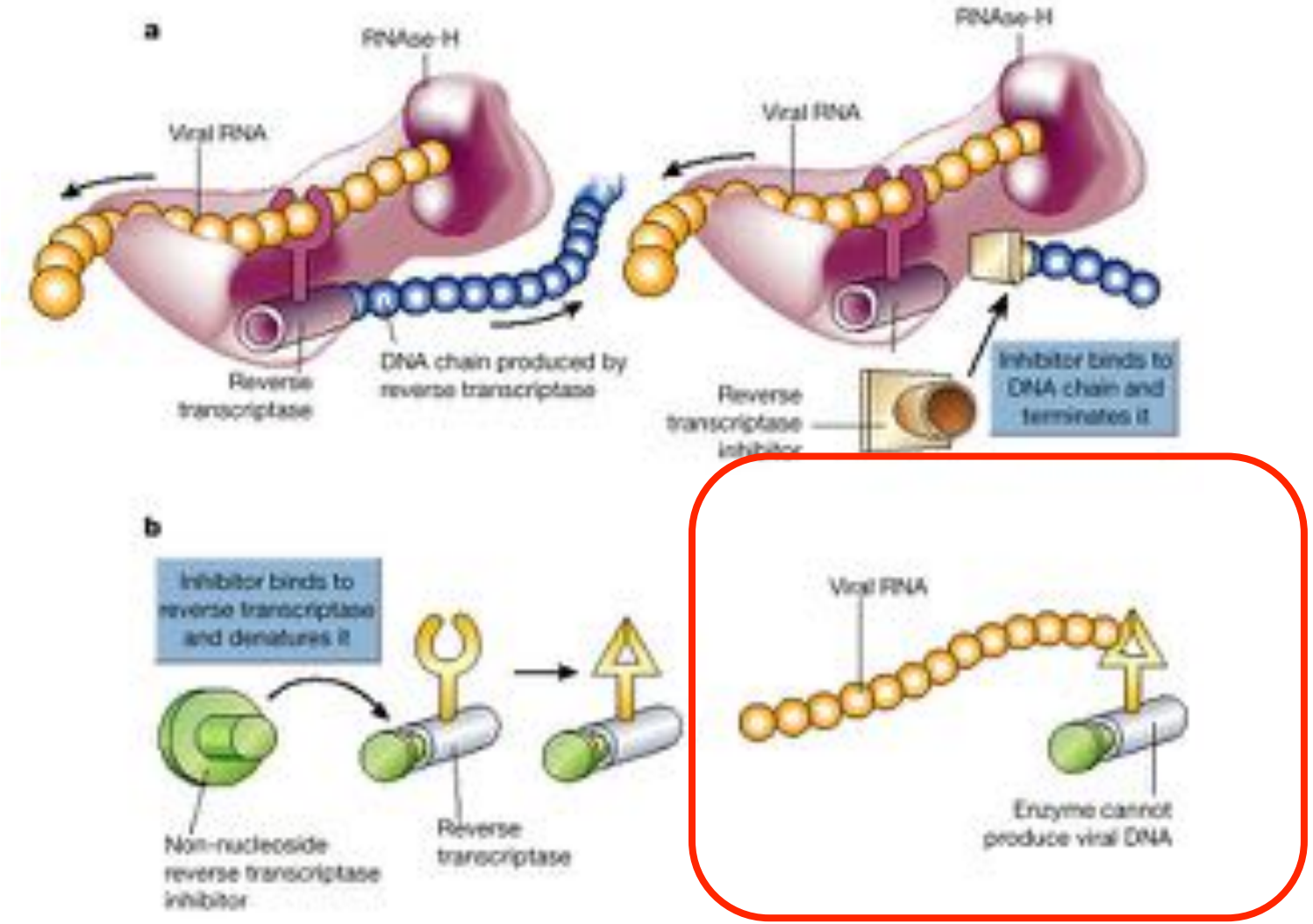
What happens…



What happens…



What happens…



Why does it occur?

- High mutation rate
  - HIV is 'poor' at replicating itself accurately
    - Many mistakes occur
  - Therefore lots of potential to develop resistance
    - In untreated patient: >1 billion viral particles made/day, with at least one mutation per 1000 viruses → 1-10 million mutations/day.
    - In a patient with a moderate viral load, every single mutation is possible in the HIV genome, every single day…

- Low barrier to resistance
  - It doesn't take many resistance mutations to knock out a drug
  - These mutations not 'lethal' or significantly hampering for the virus

Why does it occur?

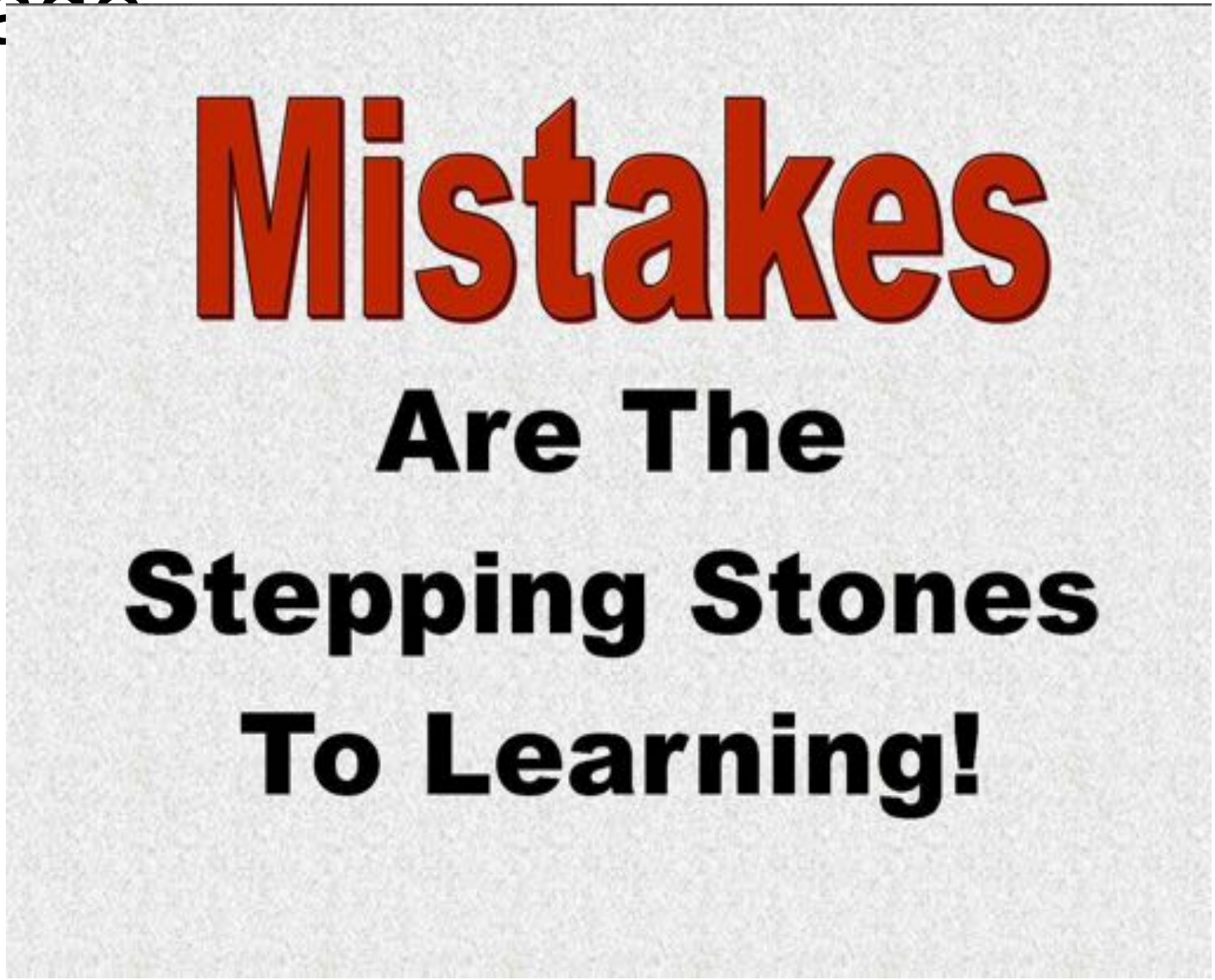
- Viral replication in presence of detectable drug(s)
  - Inadequate combination of drugs
    - **Not potent enough**

Resistance will develop with suboptimal treatment

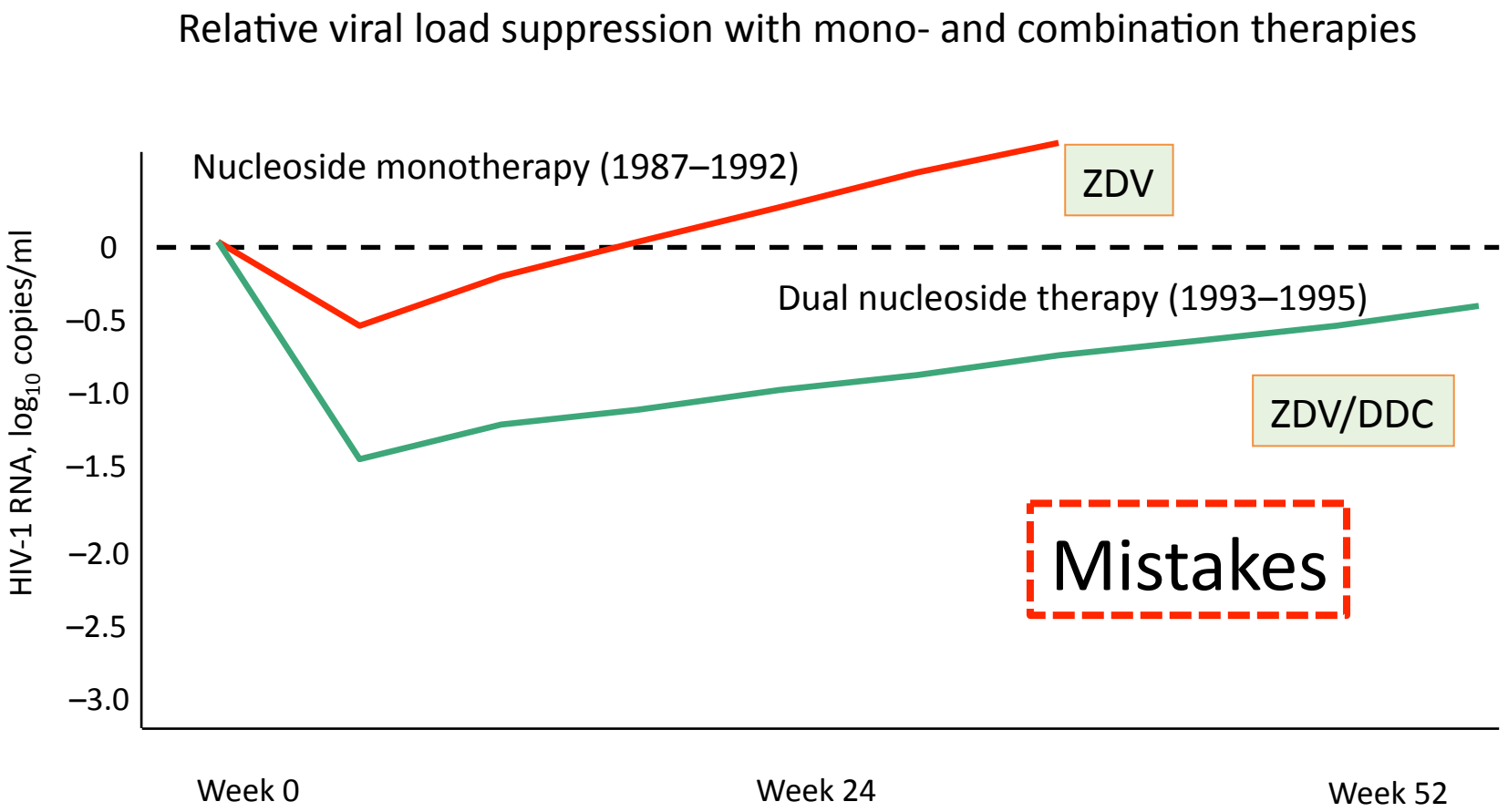
Inevitable consequence of pre-ART therapy

At a time when treatment was for survival

And mistakes were being ma



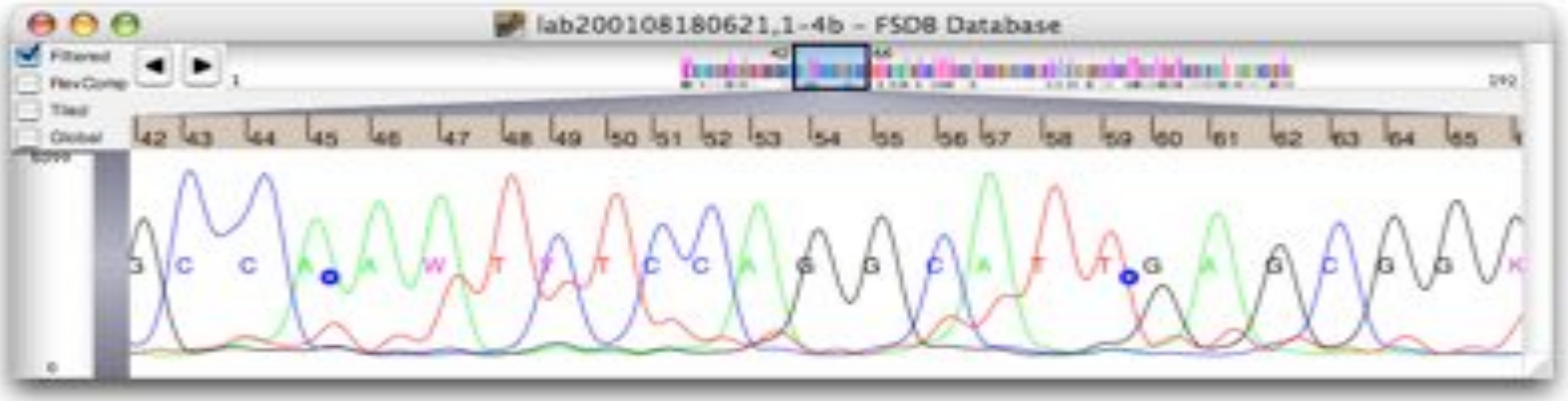
2NRTI therapy failed



Adapted from Facui, AS. Nat. Med 2003. 6: 839–843

Resistance testing became available…

Nucleotide sequencing



TRUGENE® HIV-1 Genotyping Test
GuideLines™ Rules 13.0
RESISTANCE REPORT

State Central Labs
22 State St. Statesville, ST 56789

Sample ID: 18SC060124
Patient ID: 1013drew
Patient Name: John Doe
Date Drawn: 20030606
Physician: Dr. Jane Doe
Institution: City Hospital
Report Date: 2007/11/12

Bayer Reference Testing Laboratory
Example Report
725 Potter Street (APC3)
Berkeley, CA 94710
Tel: 800-434-2447
Fax: 510-705-5902

Resistance associated RT Mutations: L100I, K103N, T215S*/Y

Nucleoside and Nucleotide RT Inhibitors	Resistance Interpretation
abacavir (ABC)	No Evidence of Resistance
didanosine (ddI)	No Evidence of Resistance
lamivudine (3TC)/emtricitabine (FTC)	No Evidence of Resistance
stavudine (d4T)	Resistance
tenofovir (TDF)	No Evidence of Resistance
zidovudine (AZT)	Resistance
NonNucleoside RT Inhibitors	**Resistance Interpretation**
efavirenz (EFV)	Resistance
nevirapine (NVP)	Resistance

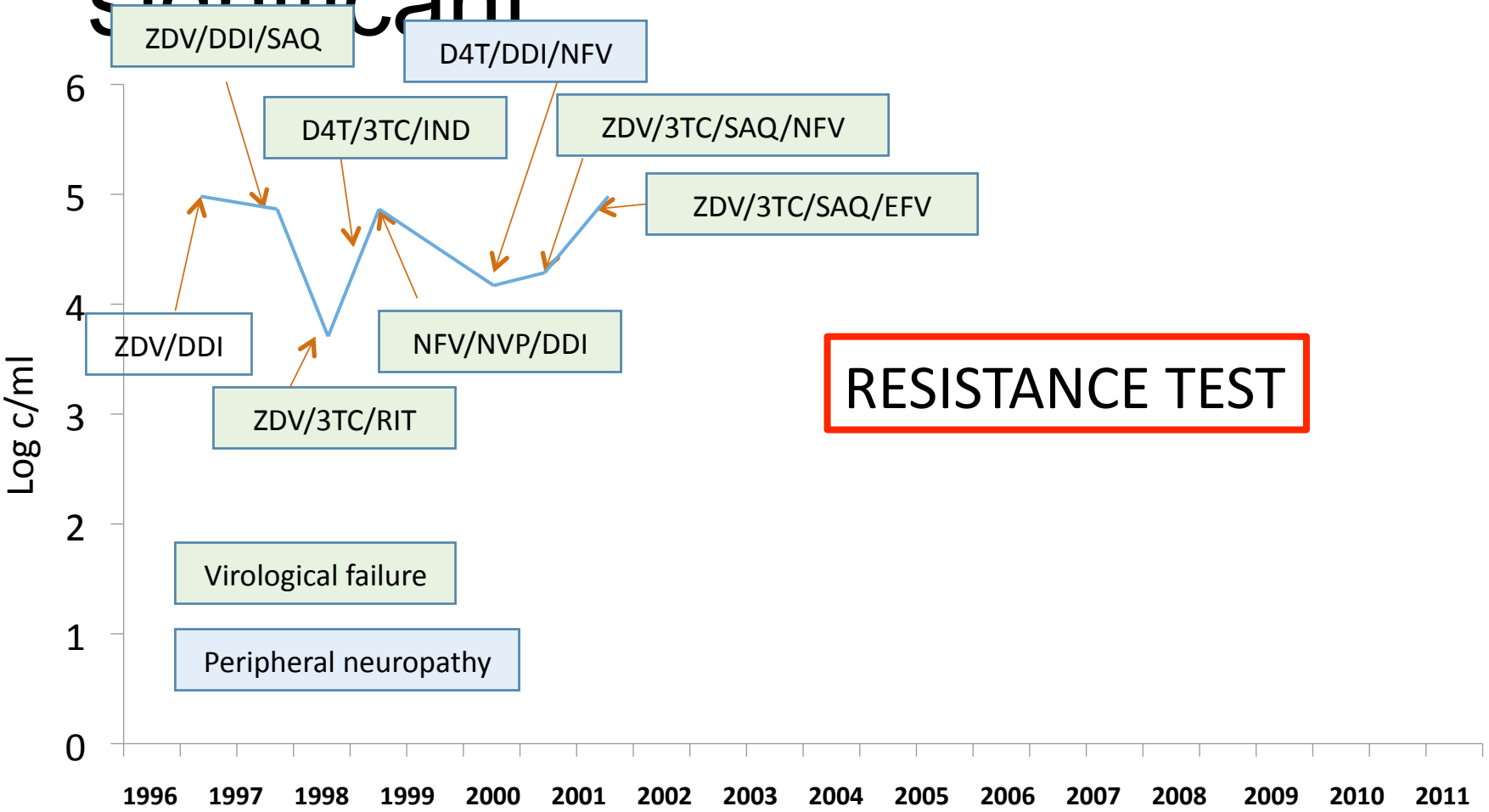
Resistance associated PR Mutations: L19I, M46L*, L63P, A71T

Protease Inhibitors	Resistance Interpretation
amprenavir (APV)/fosamprenavir (FPV)	Resistance
APV/r or FPV/r **	Resistance
atazanavir (ATV)	No Evidence of Resistance
ATV/r **	No Evidence of Resistance
darunavir + ritonavir (DRV/r)	No Evidence of Resistance
indinavir (IDV)	Resistance
IDV/r **	Possible Resistance
lopinavir + ritonavir (LPV/r)	No Evidence of Resistance
nelfinavir (NFV)	Possible Resistance
saquinavir + ritonavir (SQV/r)	No Evidence of Resistance
tipranavir + ritonavir (TPV/r)	No Evidence of Resistance

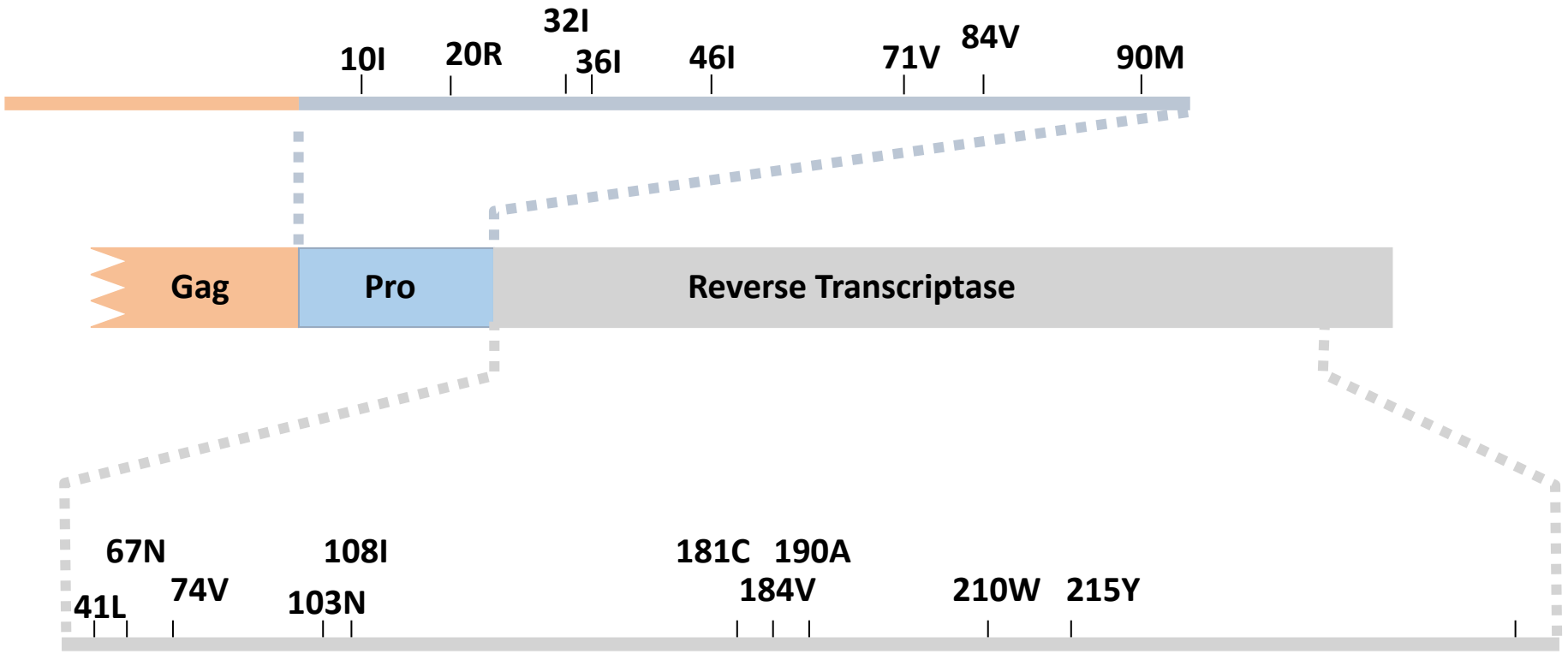
** Protease Inhibitors administered with low-dose ritonavir for pharmacological boosting.

Resistance interpretation is based upon interpretation by an international expert panel (The Consensus Panel) of in vitro and in vivo data including phenotypic and virologic response data available as of June 2007 for correlation of Protease and RT sequences to antiretroviral drug resistance. These include primary and secondary mutations.

Consequences were significant



GT resistance test



Why does it occur?

- Viral replication in presence of detectable drug(s)
  - Inadequate combination of drugs
    - Not potent enough
    - **Pre-existing resistance**

Case 1

- 33 year old heterosexual male
- Presents with oropharyngeal and oesophageal candidiasis
- CD4 142 cells/mL
- Viral load 37,567 copies/ml
- Started on Septrin

So what are you going to choose..

1. AZT and 3TC
2. TDF and FTC
3. TDF and 3TC
4. TDF and AZT
5. Other

Audience vote

So what are you going to choose..

1. NVP
2. EFV
3. ATAZ/r
4. LOP/r
5. Other

Audience vote

Case 1

- 33 year old heterosexual male
- Presents with oropharyngeal and oesophageal candidiasis
- CD4 142 cells/mL
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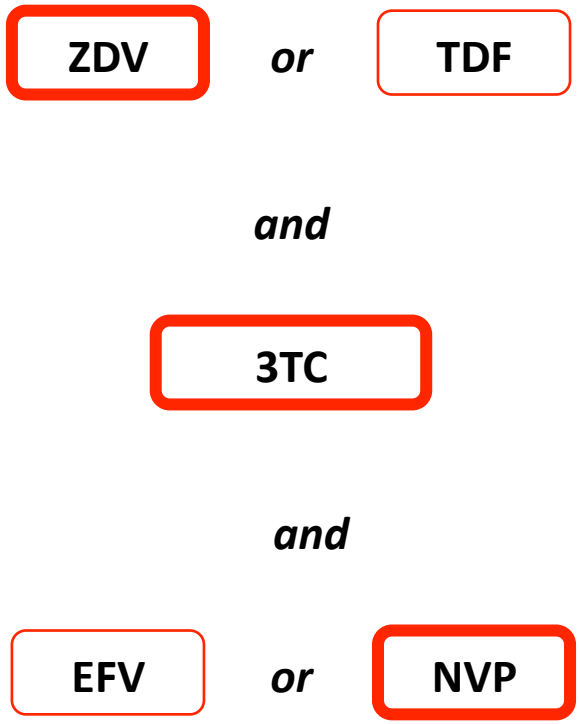
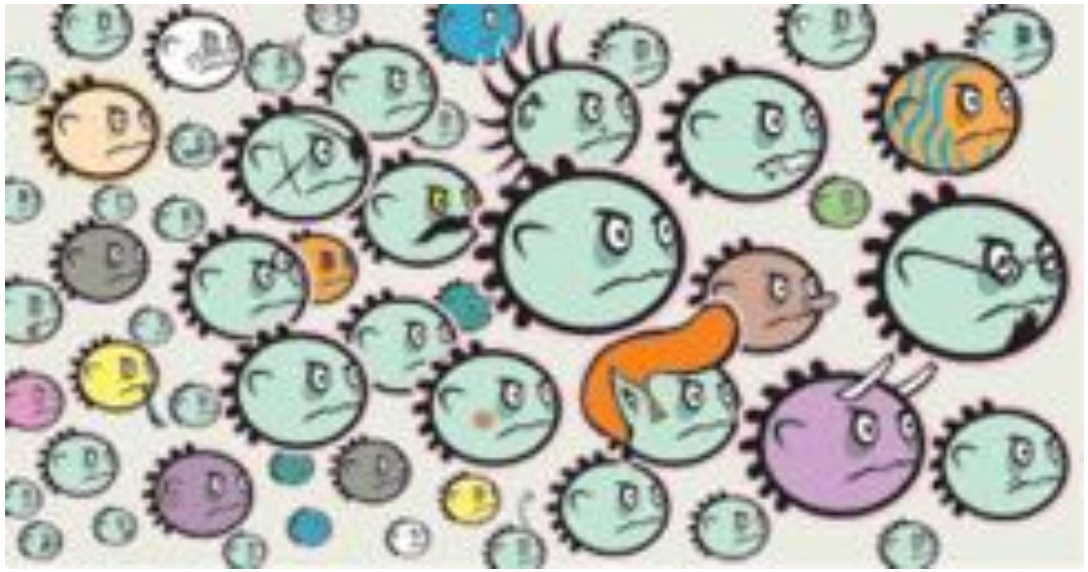
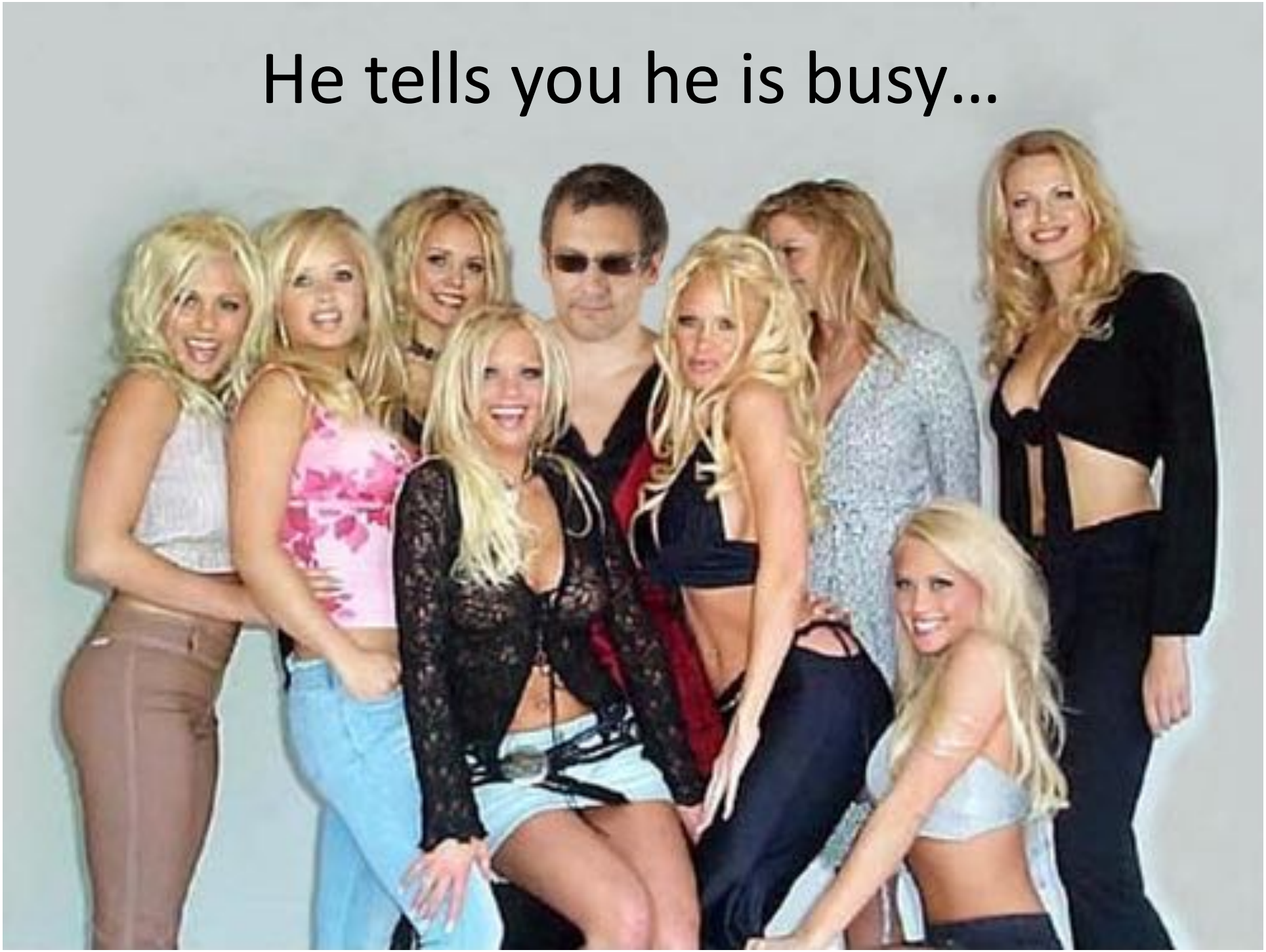


Ask professor for help in getting/ interpreting a resistance test…



He tells you he is busy…



And he is!

His football club need him

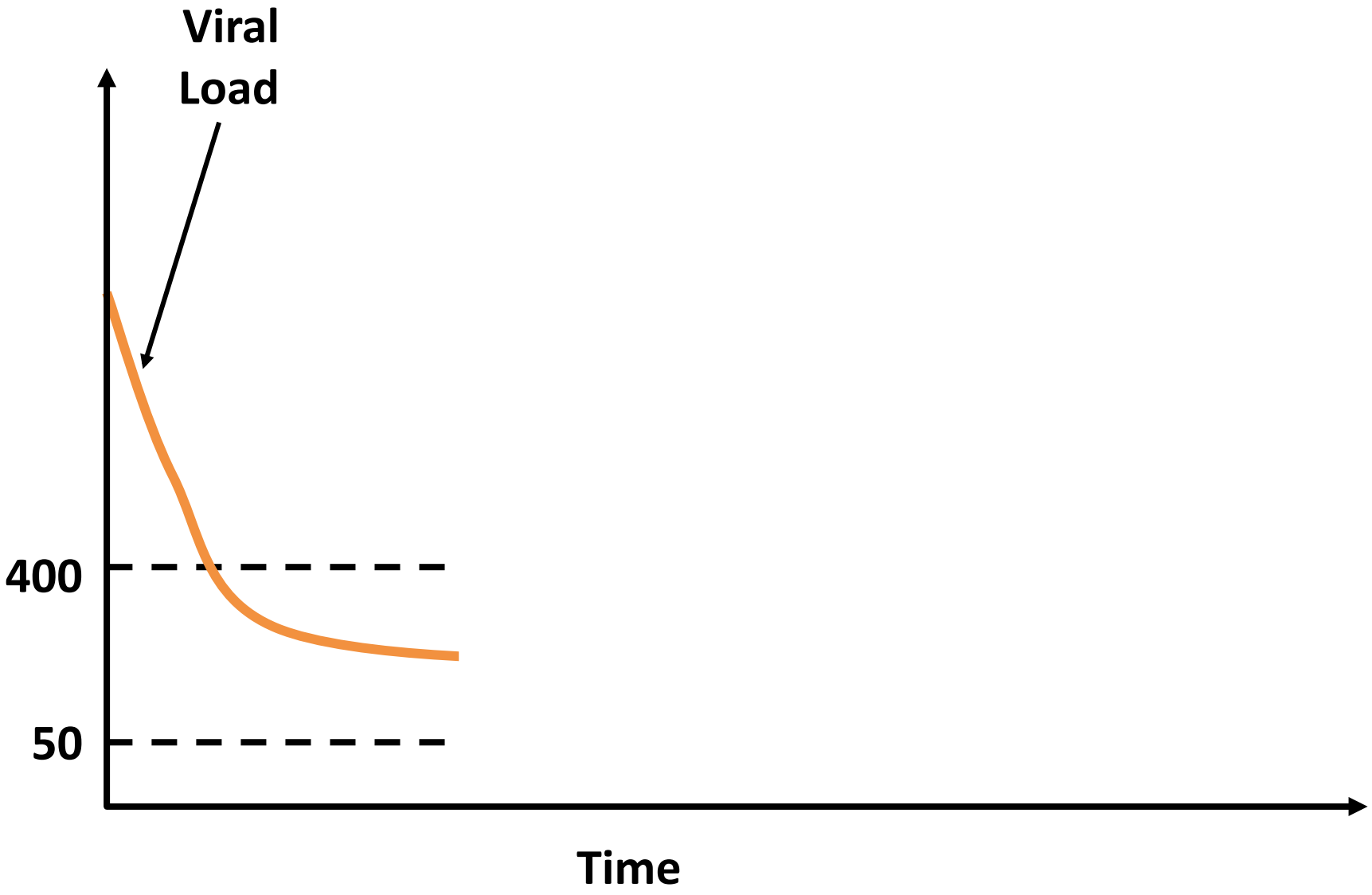
Man Utd 2 Chelsea 1

Barclays Premier League table

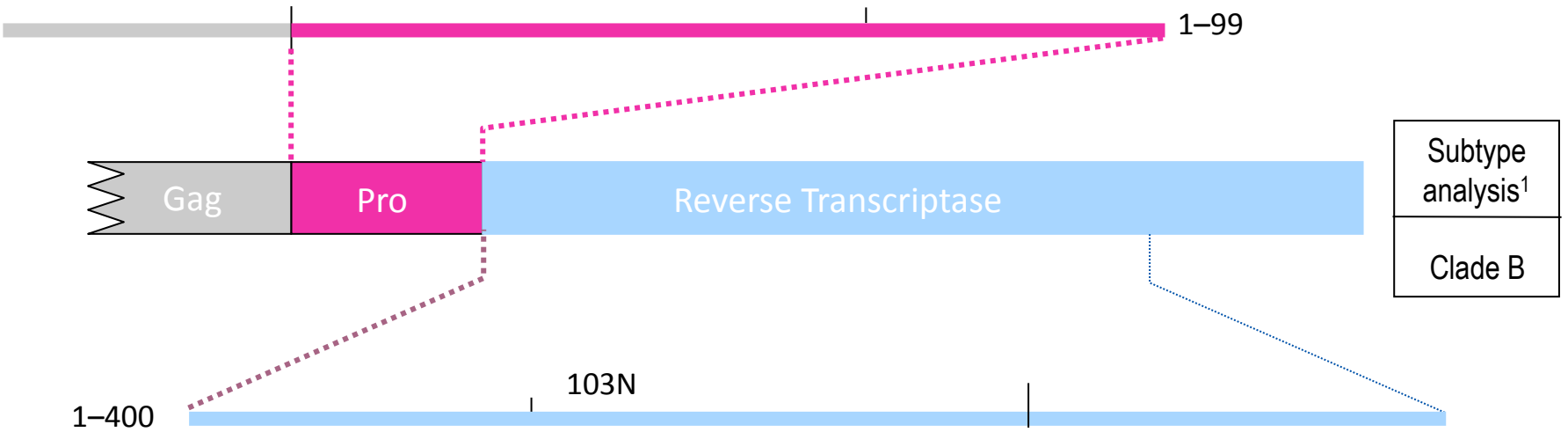
Sunday, 8 May 2011 6:00 pm

	Team	P	GD	PTS
1	Man Utd	35	39	76
2	Chelsea	35	37	71
3	Arsenal	35	30	67
4	Man City	35	31	62
5	Tottenham	35	7	56
6	Liverpool	35	18	55
7	Everton	35	9	51
8	Stoke	35	2	46
9	Bolton	34	-1	44
10	Fulham	35	7	43
11	Newcastle	34	-1	44
12	Sunderland	35	-12	44
13	West Brom	34	-14	43
14	Aston Villa	34	-13	42
15	Blackburn	35	-14	39
16	Birmingham	34	-18	39
17	Wolves	35	-21	37
18	Blackpool	35	-23	36
19	Wigan	35	-23	36
20	West Ham	34	-29	33

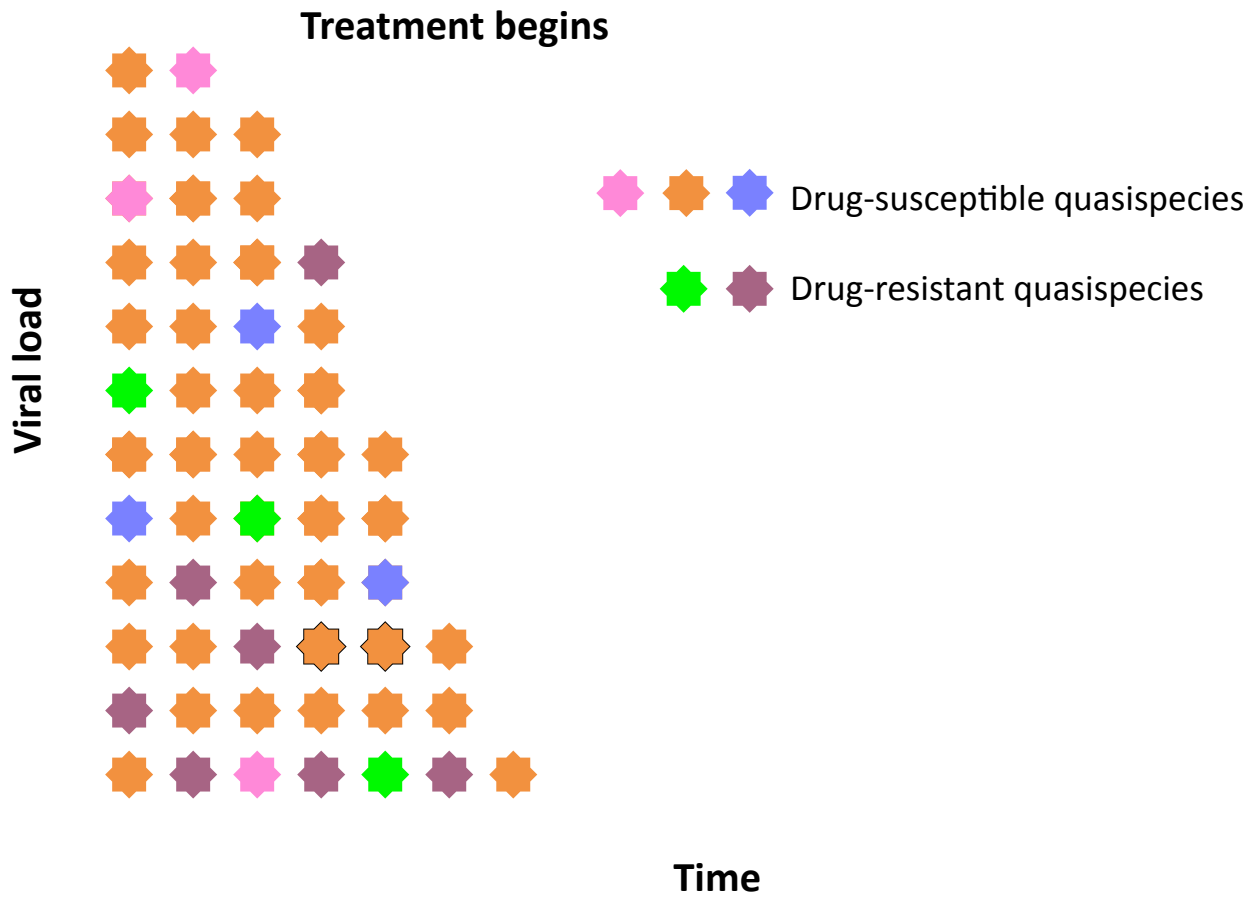
Response to therapy – case 1



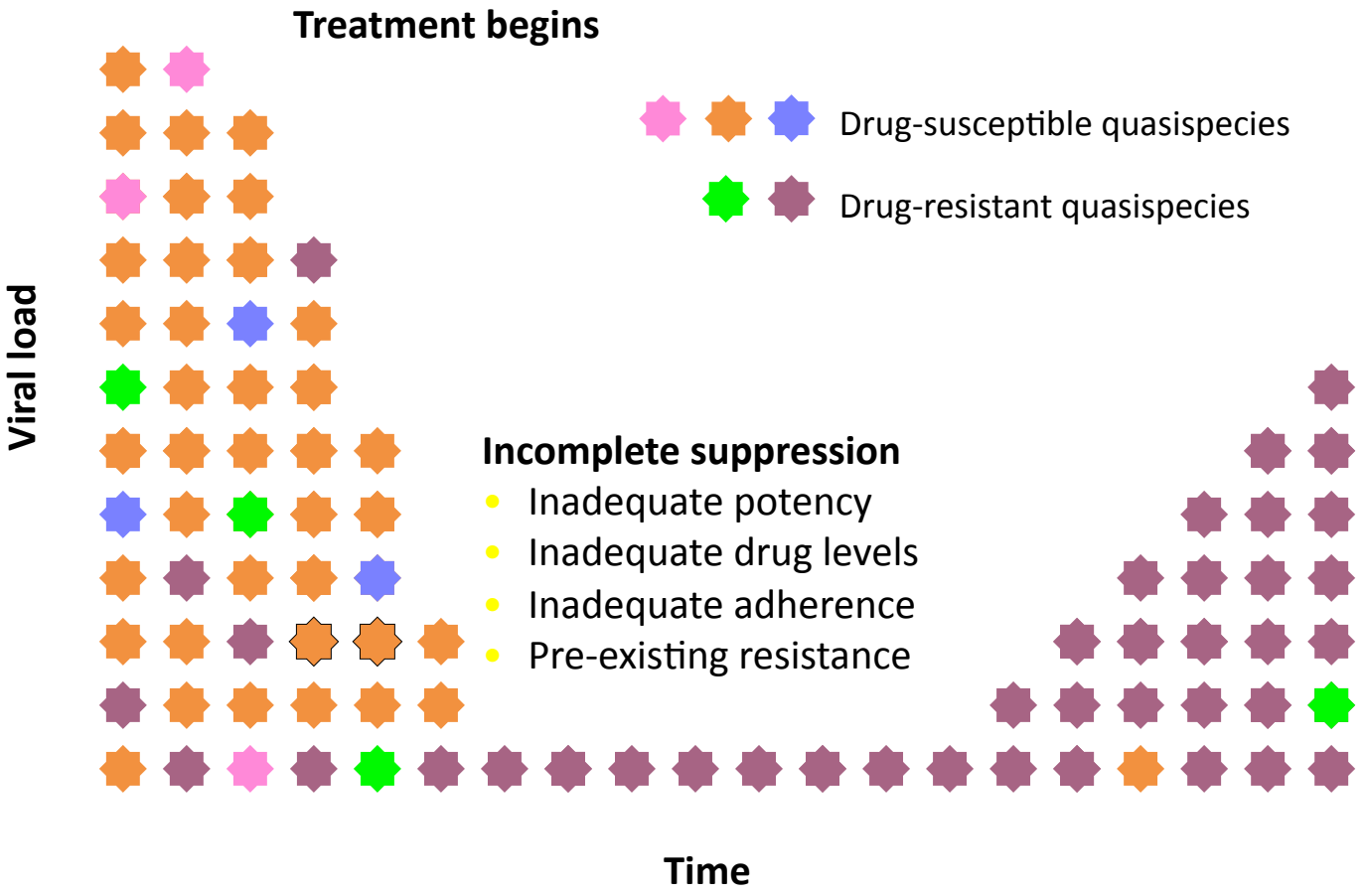
Resistance-associated mutation identified on baseline test



So what happens when resistance is present? Selective Pressure of Therapy



Selective Pressure of Therapy

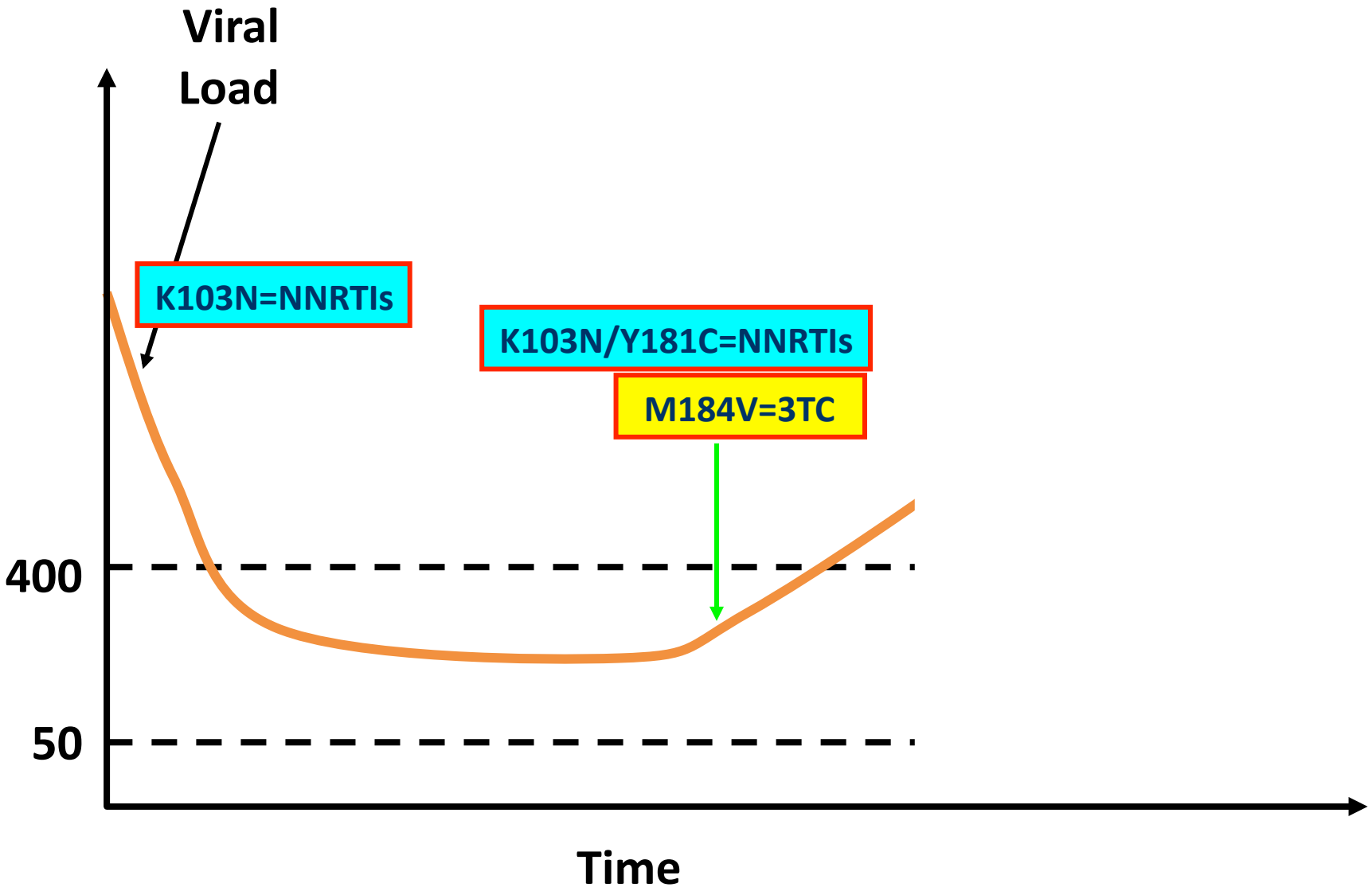


Patient – CD4 falls to 230 from 501 – what would you do?

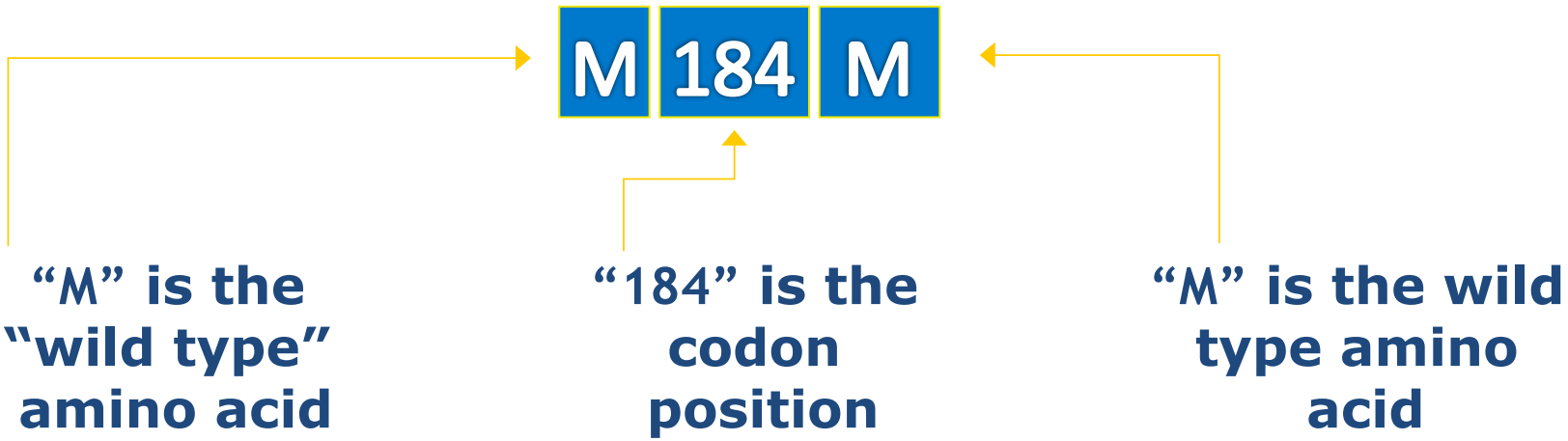
1. Carry on with NVP/AZT/3TC
2. Switch to EFV/TDF/FTC
3. Switch to ATAZ/r/TDF/FTC
4. Persuade Dr Nelson to organise another resistance test
5. Repeat CD4 and wait till fall further
6. Other

Audience vote

Response to therapy – case 1

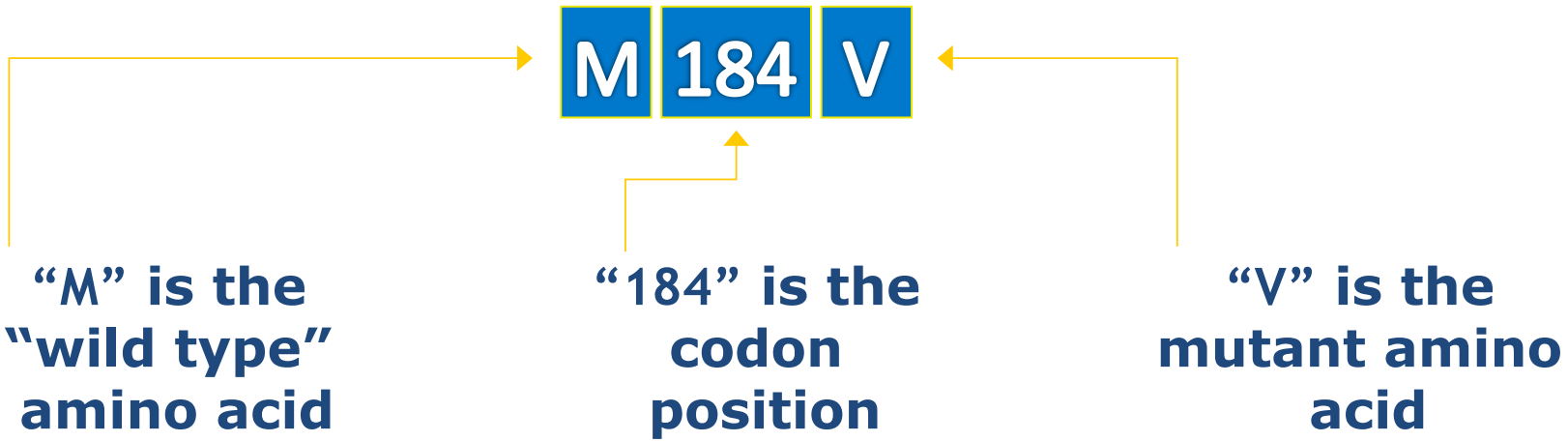


What do these mean…..
Before 3TC



After 3TC and resistance…

- **How do we identify a resistance mutation?**



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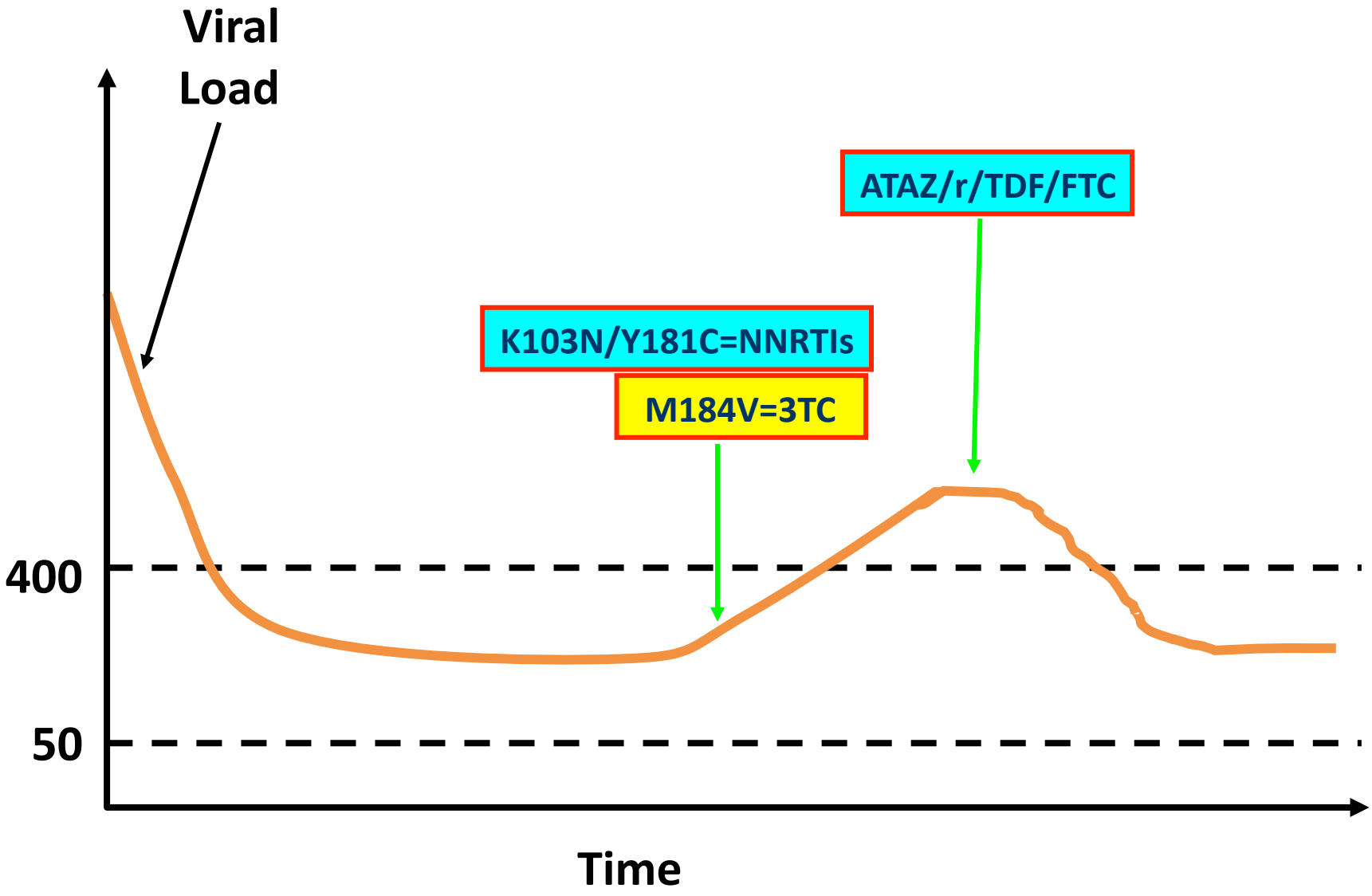
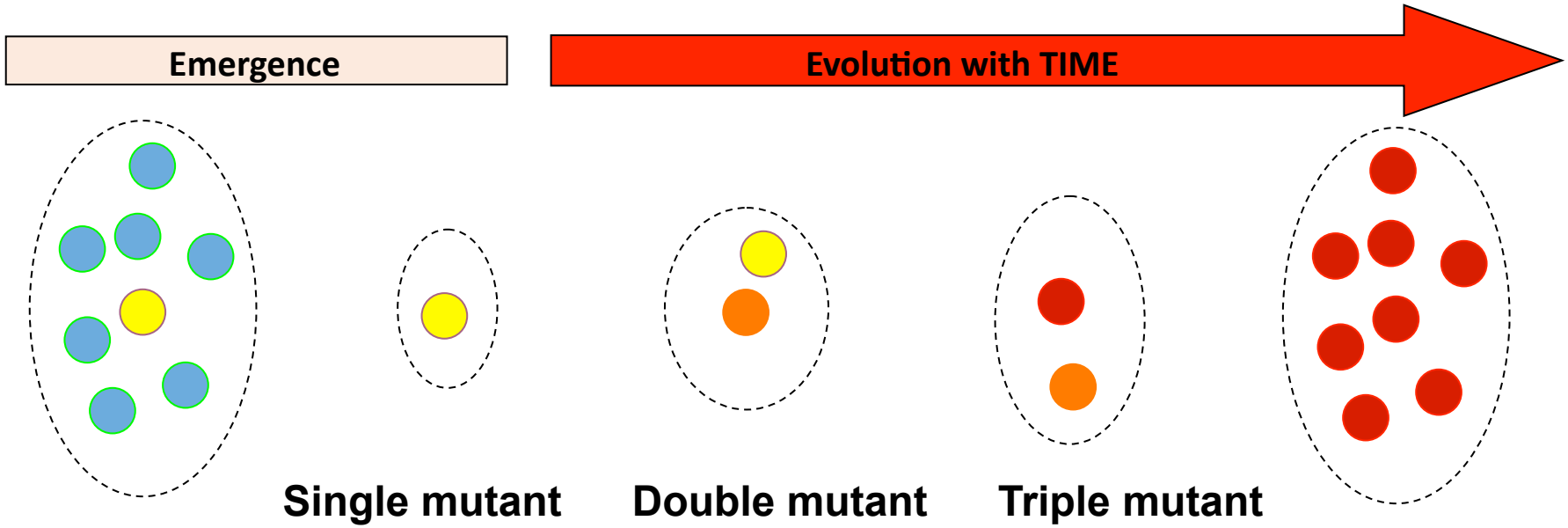
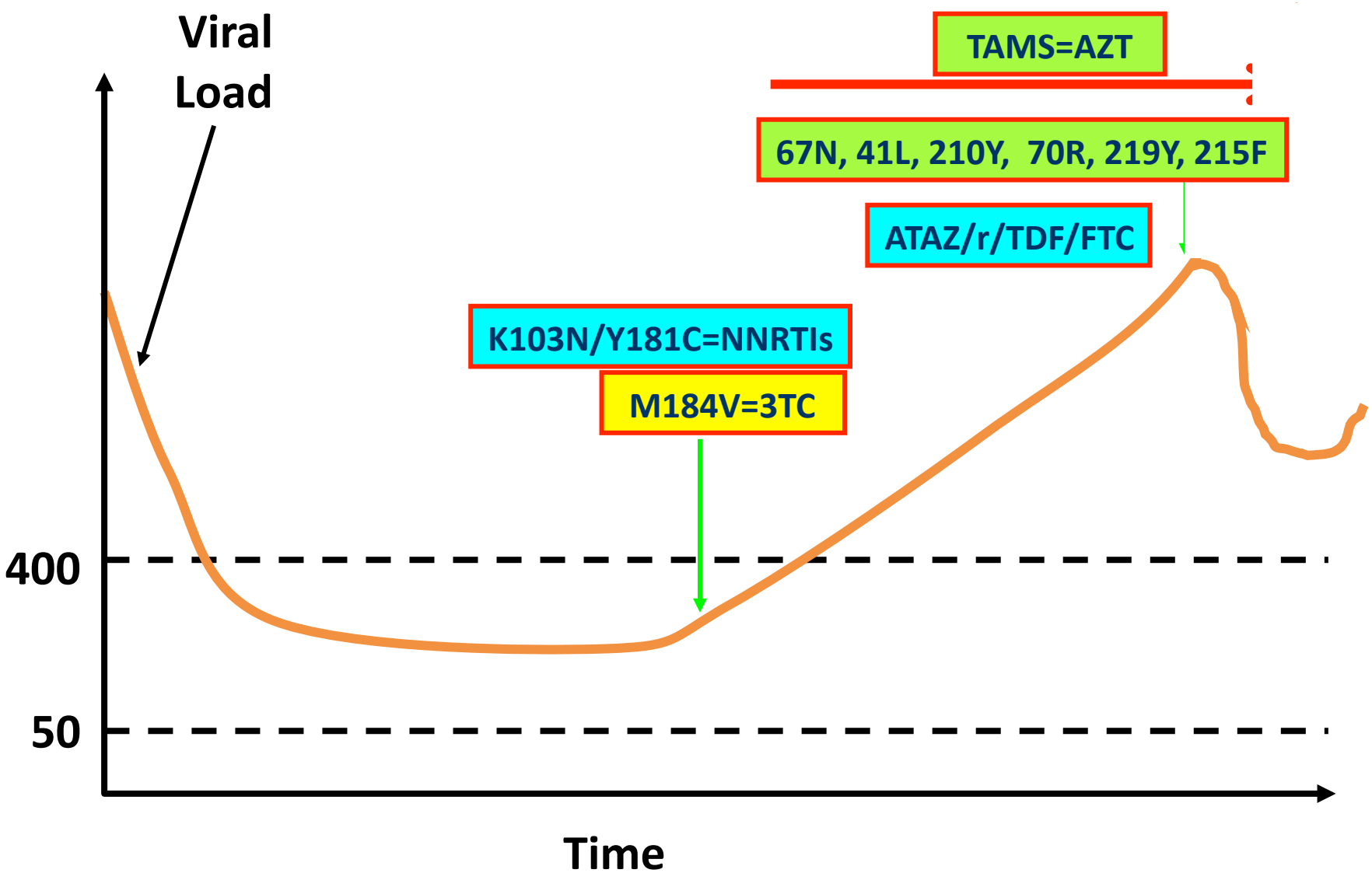


Emergence and evolution of resistance



- Increasing number of mutations
- Accumulation of mutations on the same viral genome
- Initially reduced viral fitness
- Compensatory changes restore fitness

Response to therapy – case 1



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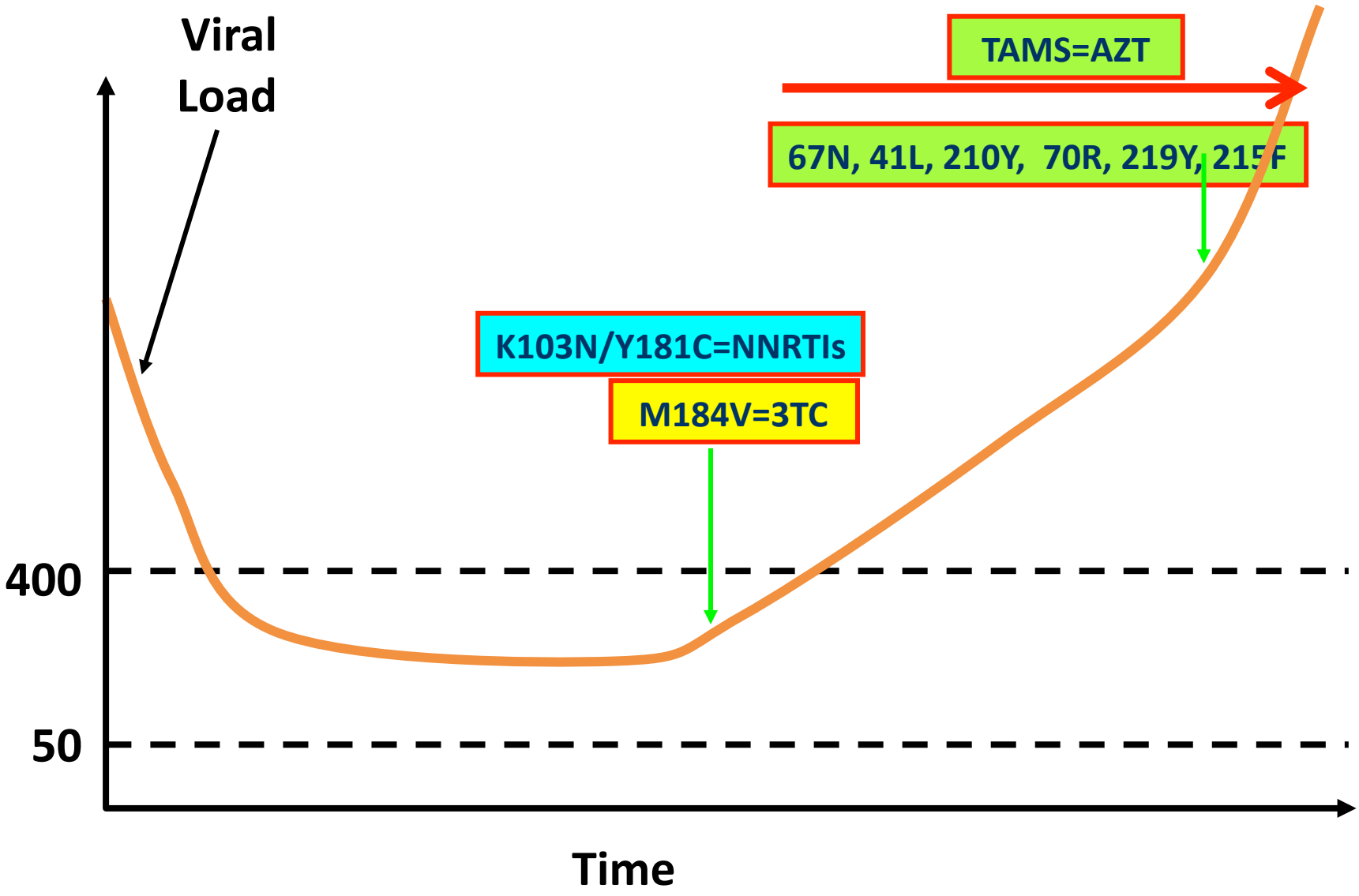


The more mutations the more resistance…

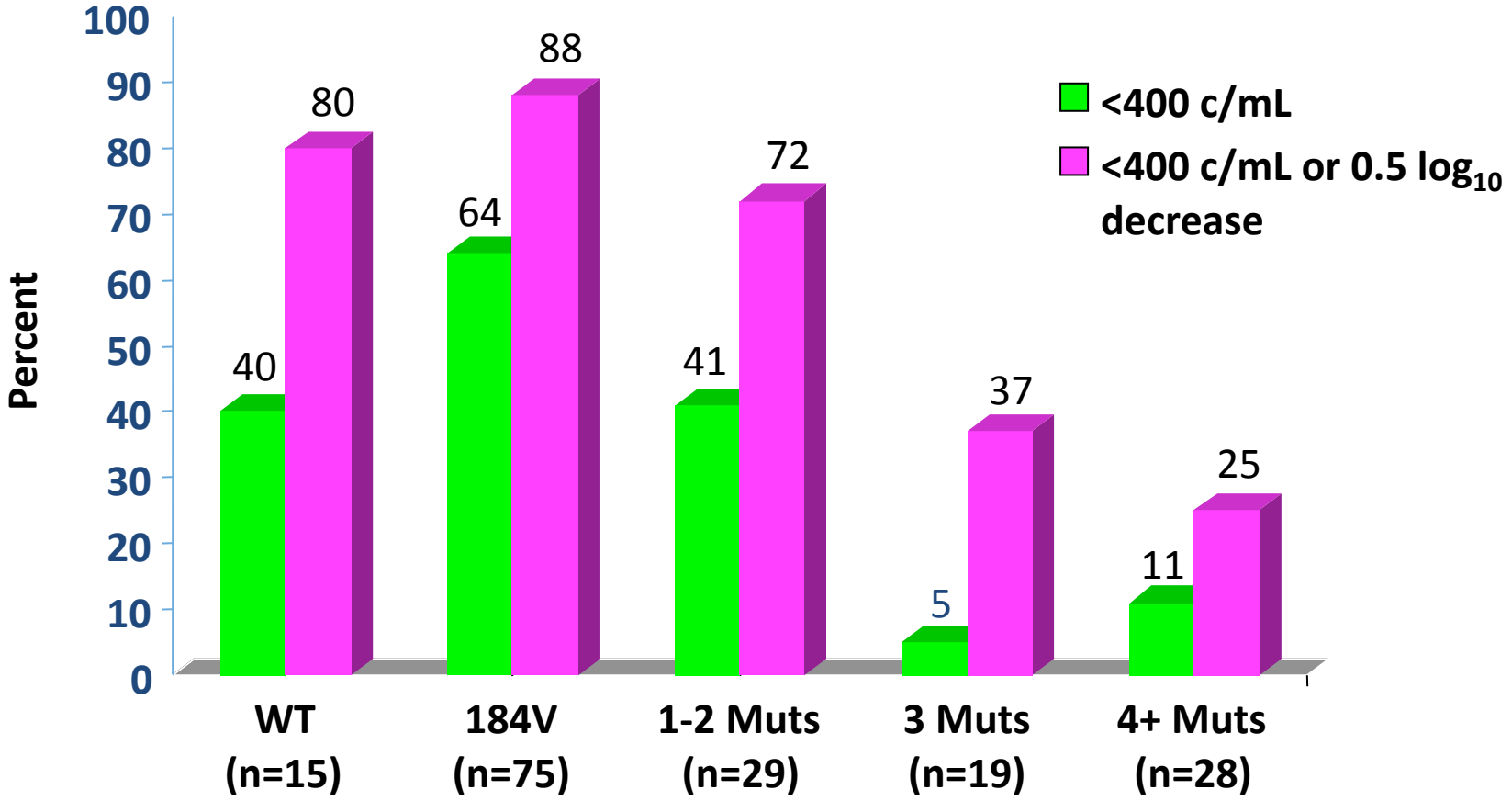
Accumulation of TAMs:

M41L, D67N, K70R, L210W, T215Y/F, K219Q/E

Susceptible Partial Resistance Resistance

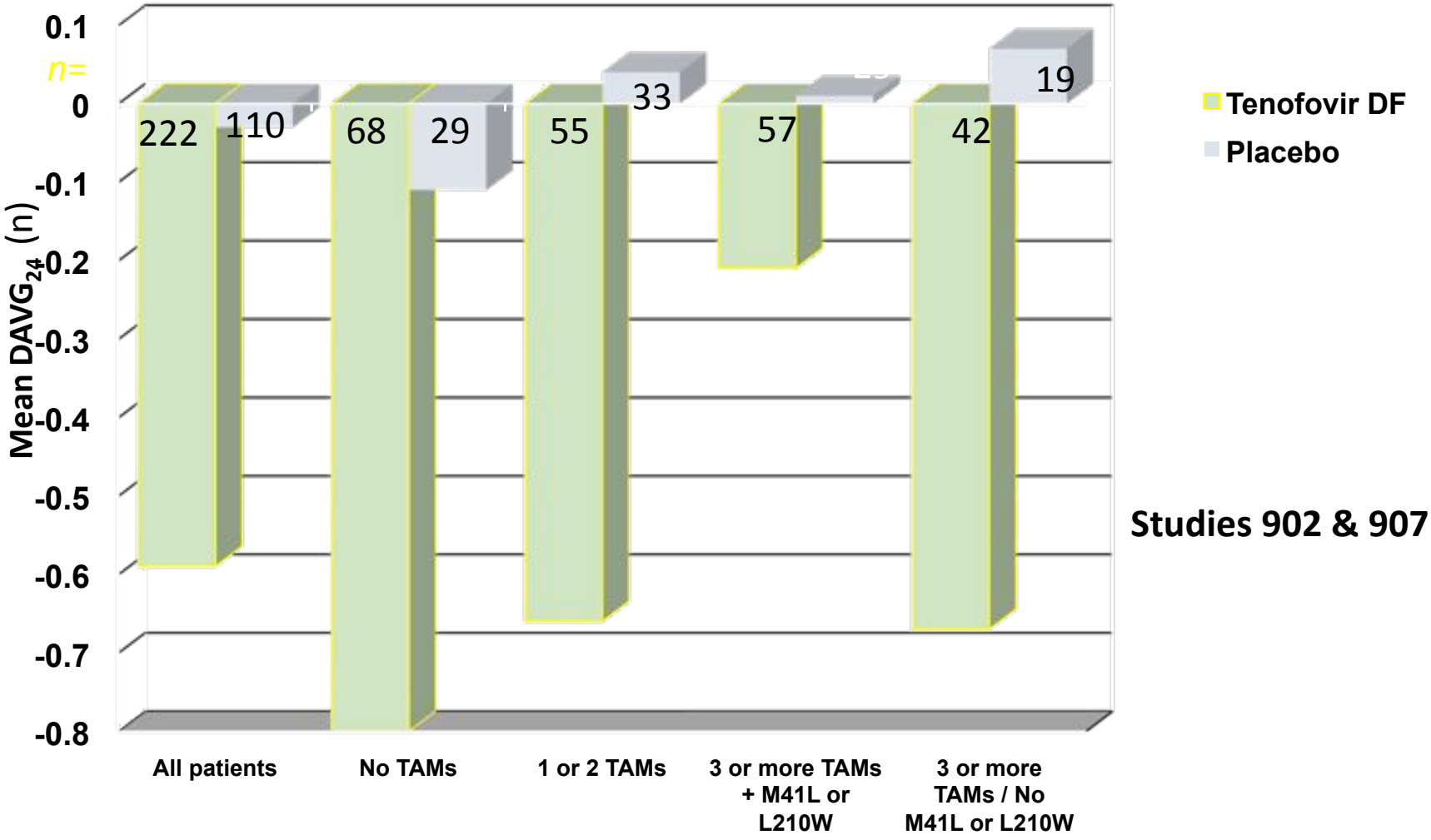
Number of TAMs present

The more TAMS the LESS abacavir effect..



Data on file, GlaxoSmithKline

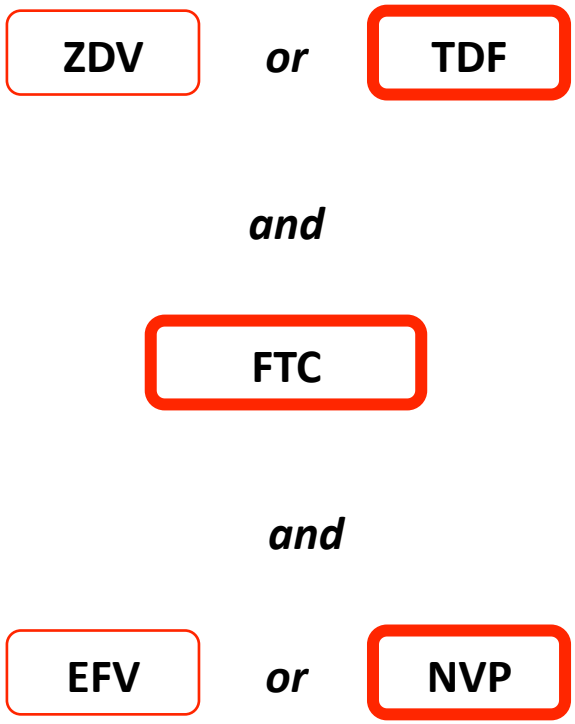
The more TAMs the LESS tenofovir effect…



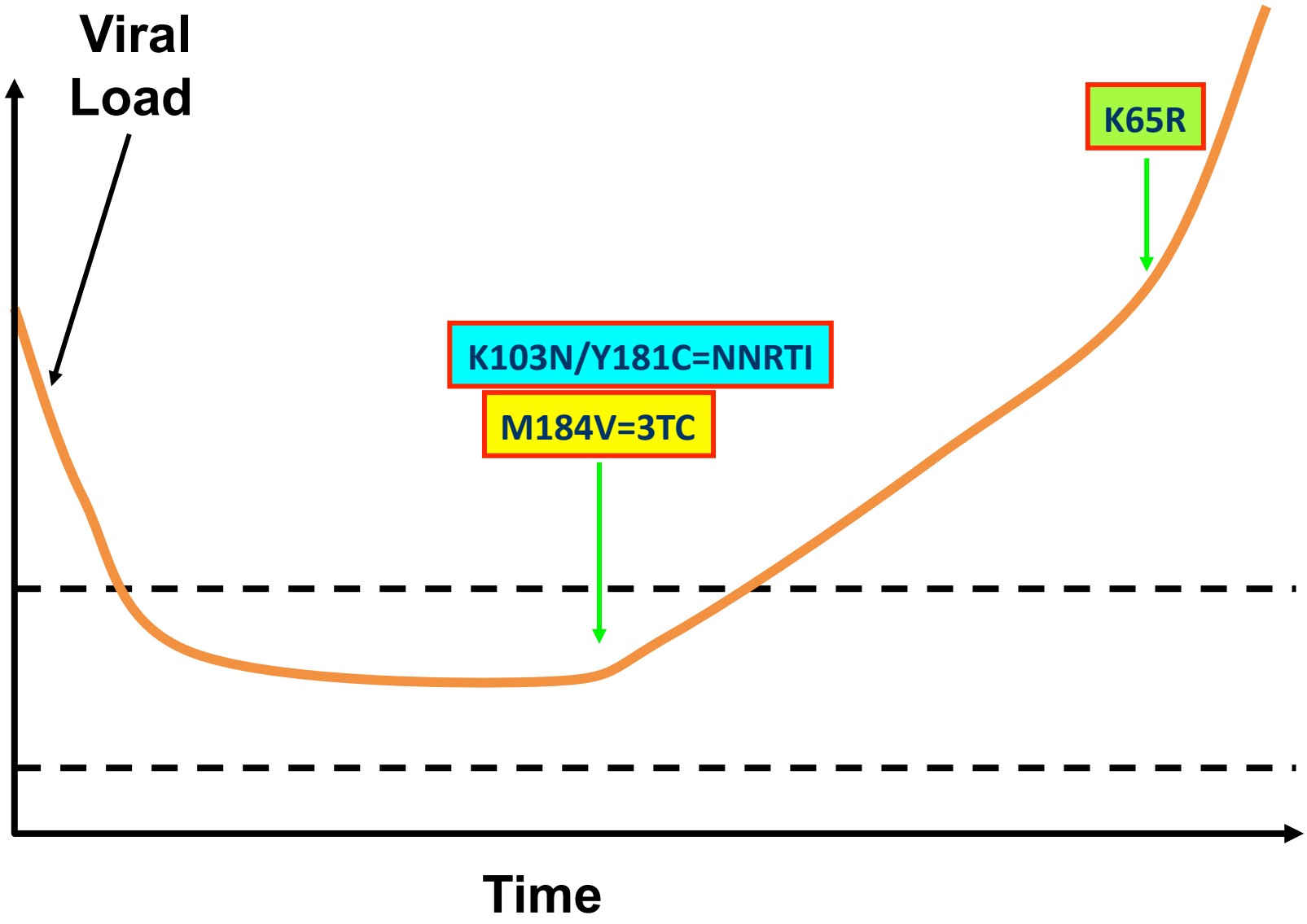
Studies 902 & 907

What if case 1 had been treated differently..

- 33 year old heterosexual male
- Presents with oropharyngeal and oesophageal candidiasis
- CD4 142 cells/mL
- Viral load 37,567 copies/ml
- Started on Septrin

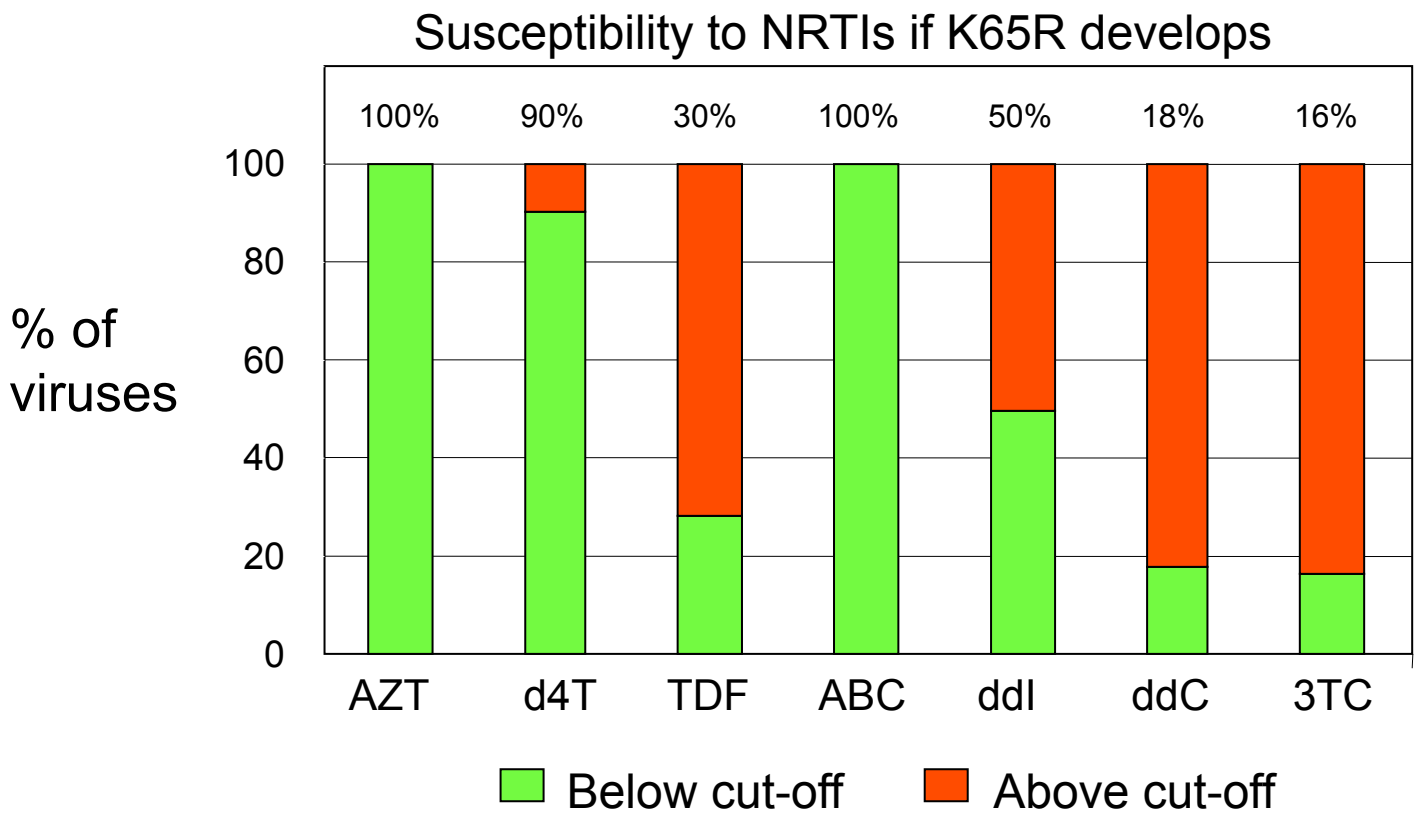


Case 1 with TDF/FTC…



Susceptibility to NRTIs if K65R develops

PhenoSense Results for K65R alone (n=50)

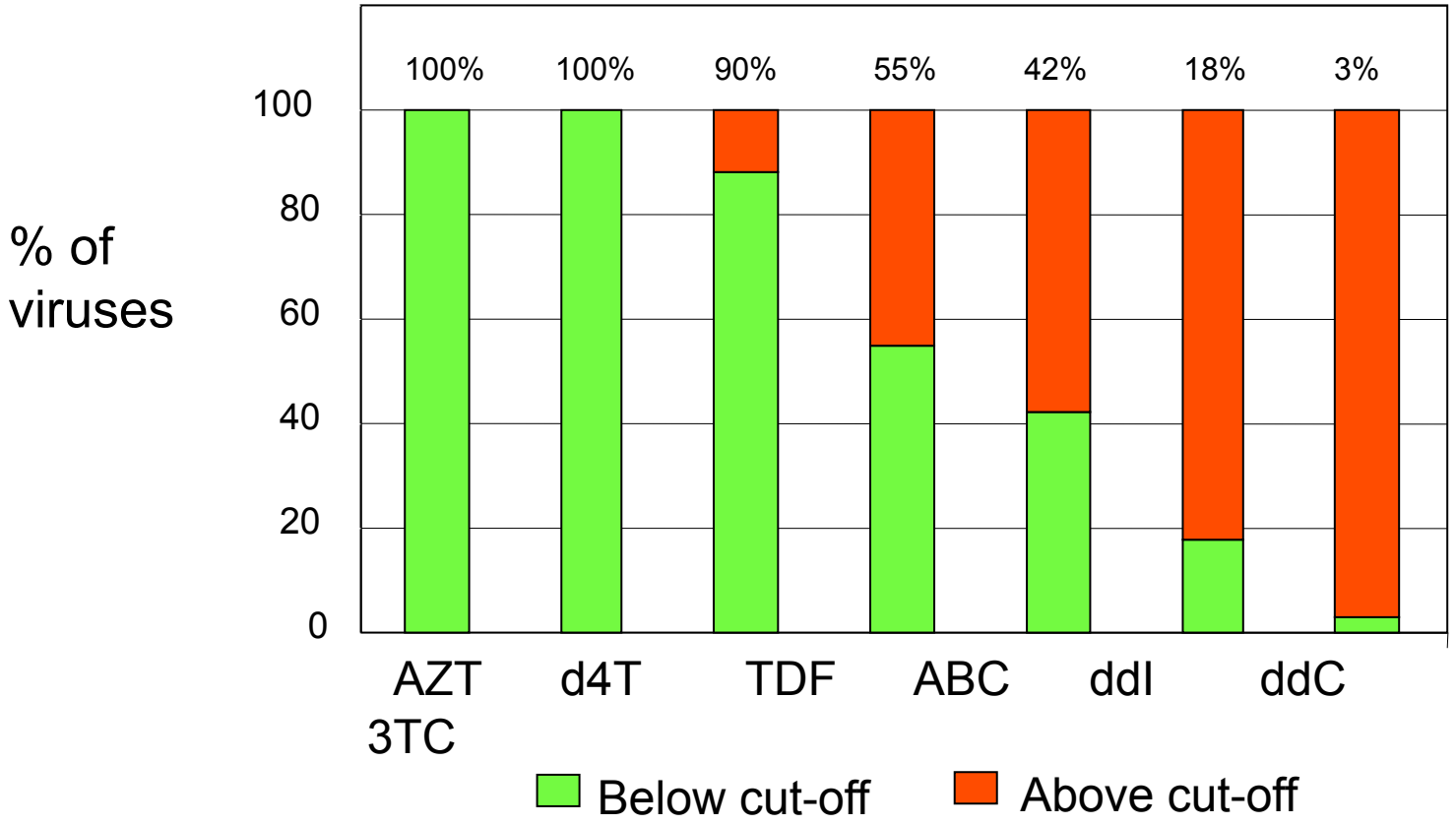


For tenofovir, all viruses were below the 4.0-fold cut off for no response.

Miller et al (2003) 43rd ICAAC #H-904 and presentation
www.iasusa.org/resistance-mutations/mutations-figures.pdf. Vol 14 issue 3 Aug 06

Susceptibility to NRTIs if K65R ***and M184V*** develop

PhenoSense Results for K65R + M184V (n=58)



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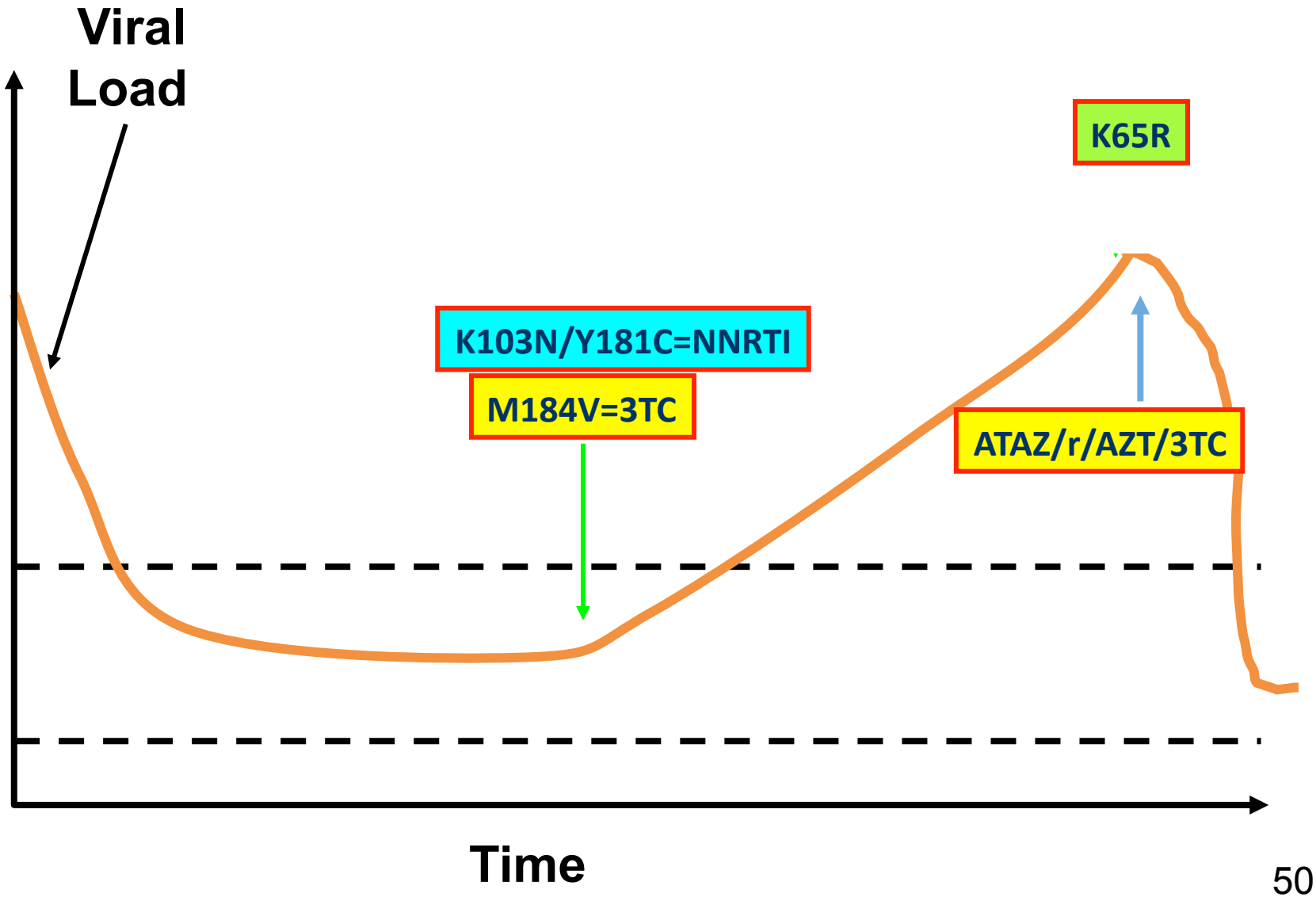
Case 1 with TDF/FTC…



Hence sequencing Options: PI AND

Hence sequencing Options: PI AND

AZT/d4T + 3TC/FTC	184V +/- TAMs	Resistance to 3TC/FTC Maybe Broader NRTI-class Resistance	Options?	TDF, ABC (if <3-4 TAMs) and depending on pattern
3TC/ FTC	184V	Resistance to 3TC/FTC	Options?	AZT (yes, ↑ activity) ABC, d4T, ddI (yes) TDF (yes, ↑ activity)

Hence sequencing Options: PI AND….

TDF + 3TC/FTC	K65R +184V	Resistance to TDF/3TC/FTC/ ddI and ABC	Options?	**Boosted PI +** AZT (yes, ↑ activity) TDF (maybe)
AZT/d4T + 3TC/FTC	184V +/- TAMs	Resistance to 3TC/FTC Maybe Broader NRTI-class Resistance	Options?	TDF, ABC (only if <3-4 TAMs) and depending on pattern
3TC/ FTC	184V	Resistance to 3TC/FTC	Options?	AZT (yes, ↑ activity) ABC, d4T, ddI (yes) TDF (yes, ↑ activity)

So hands up who will start with…

1. AZT and 3TC

2. TDF and either FTC or 3TC

Audience vote

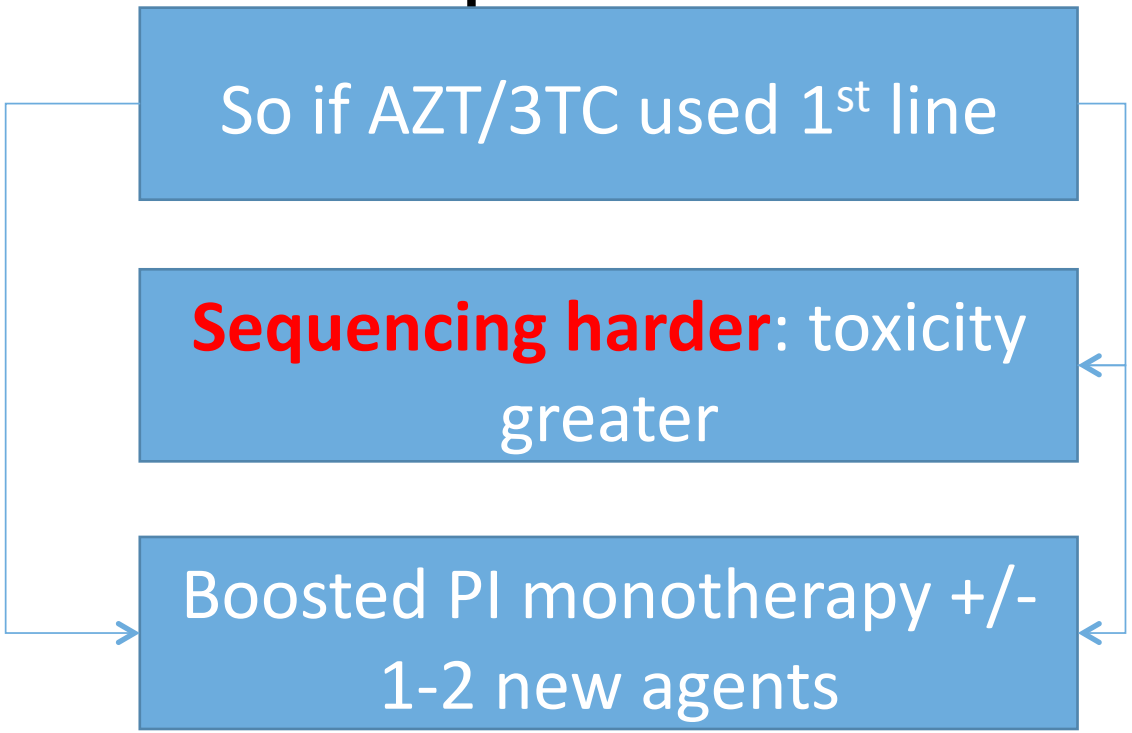
So hands up who will start with…

1. EFV or NVP

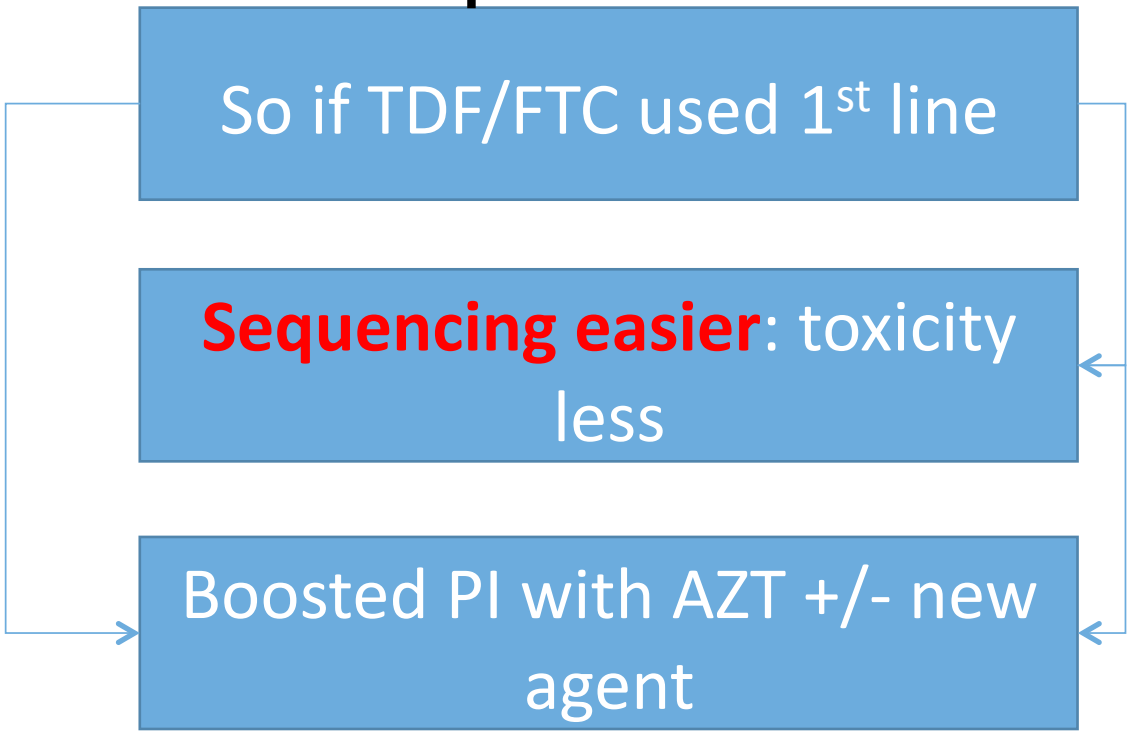
2. ATAZANAVIR boosted by ritonavir or KALETRA

Audience vote

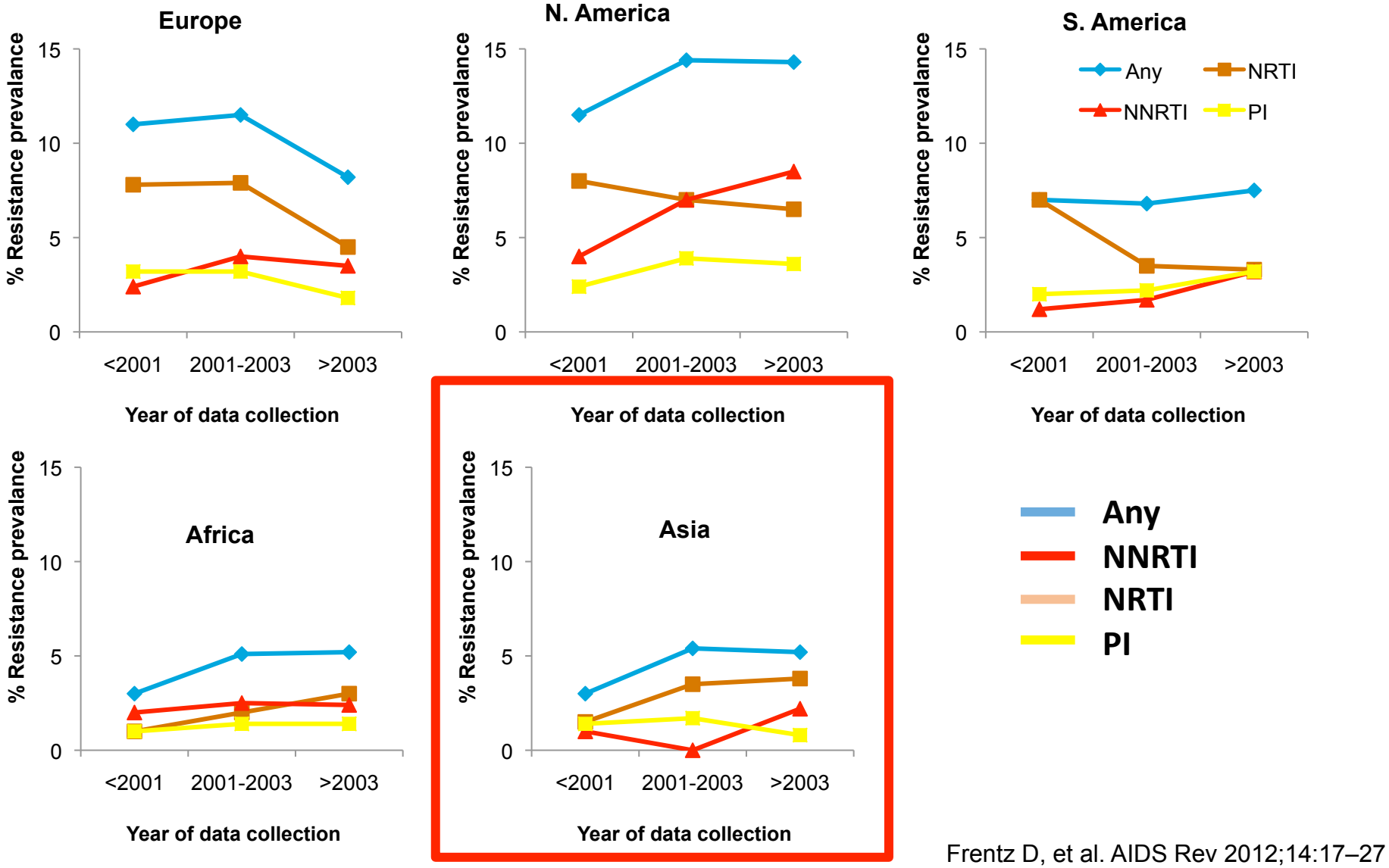
So choice of NRTI backbone is important when sequencing after resistance develops



So choice of NRTI backbone is important when sequencing after resistance develops

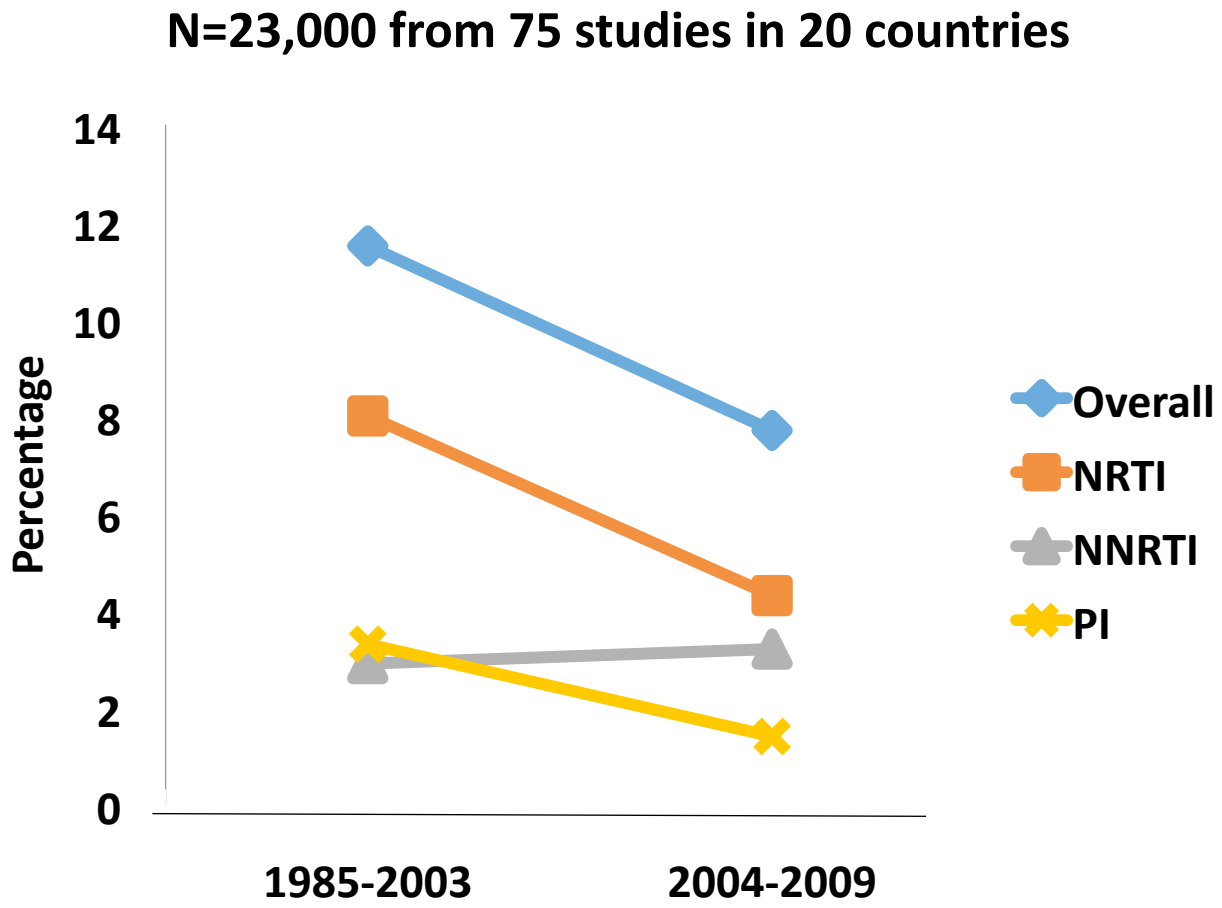


How common is drug resistance in Myanmar?



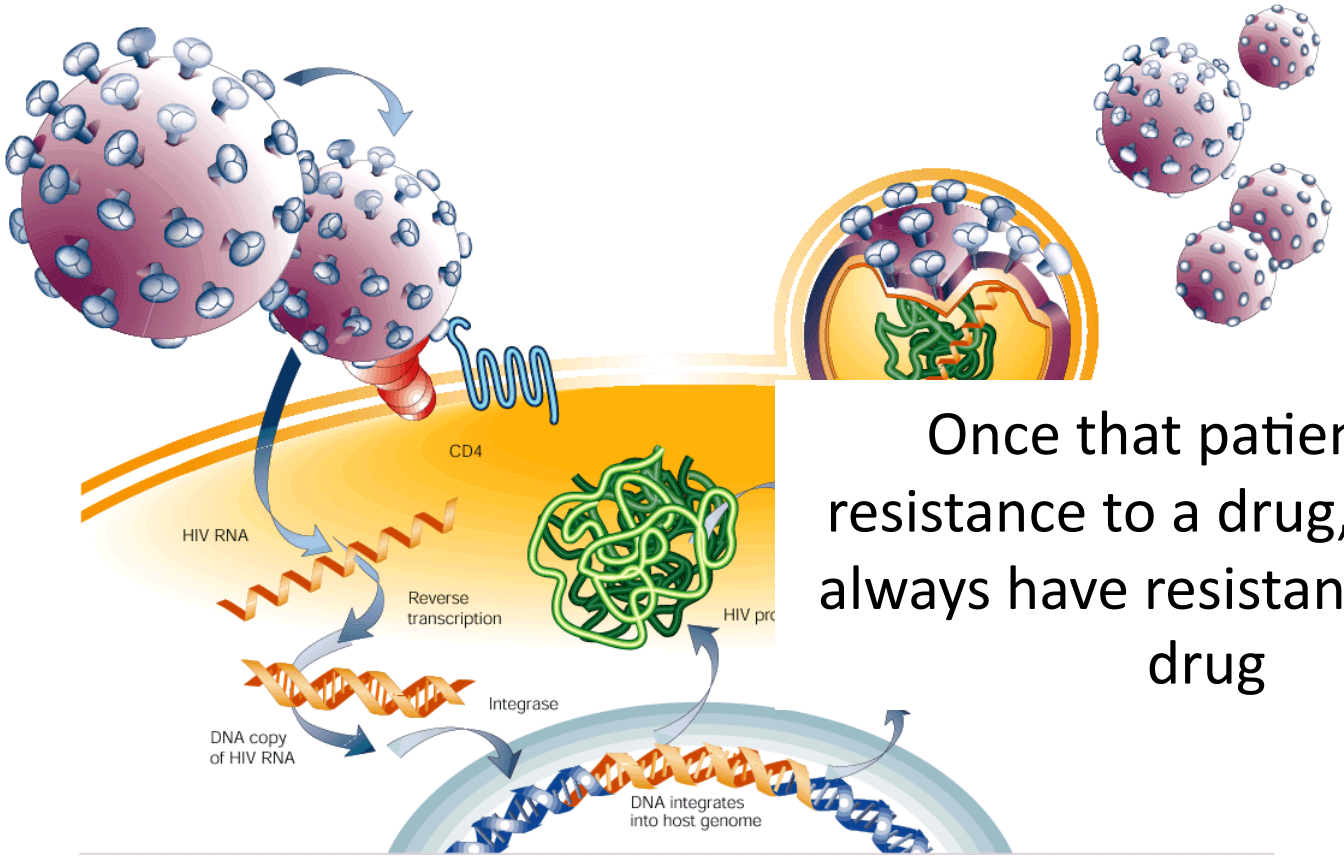
Frentz D, et al. AIDS Rev 2012;14:17–27

In Europe around 8%



Frentz 2012

Why are we so bothered?

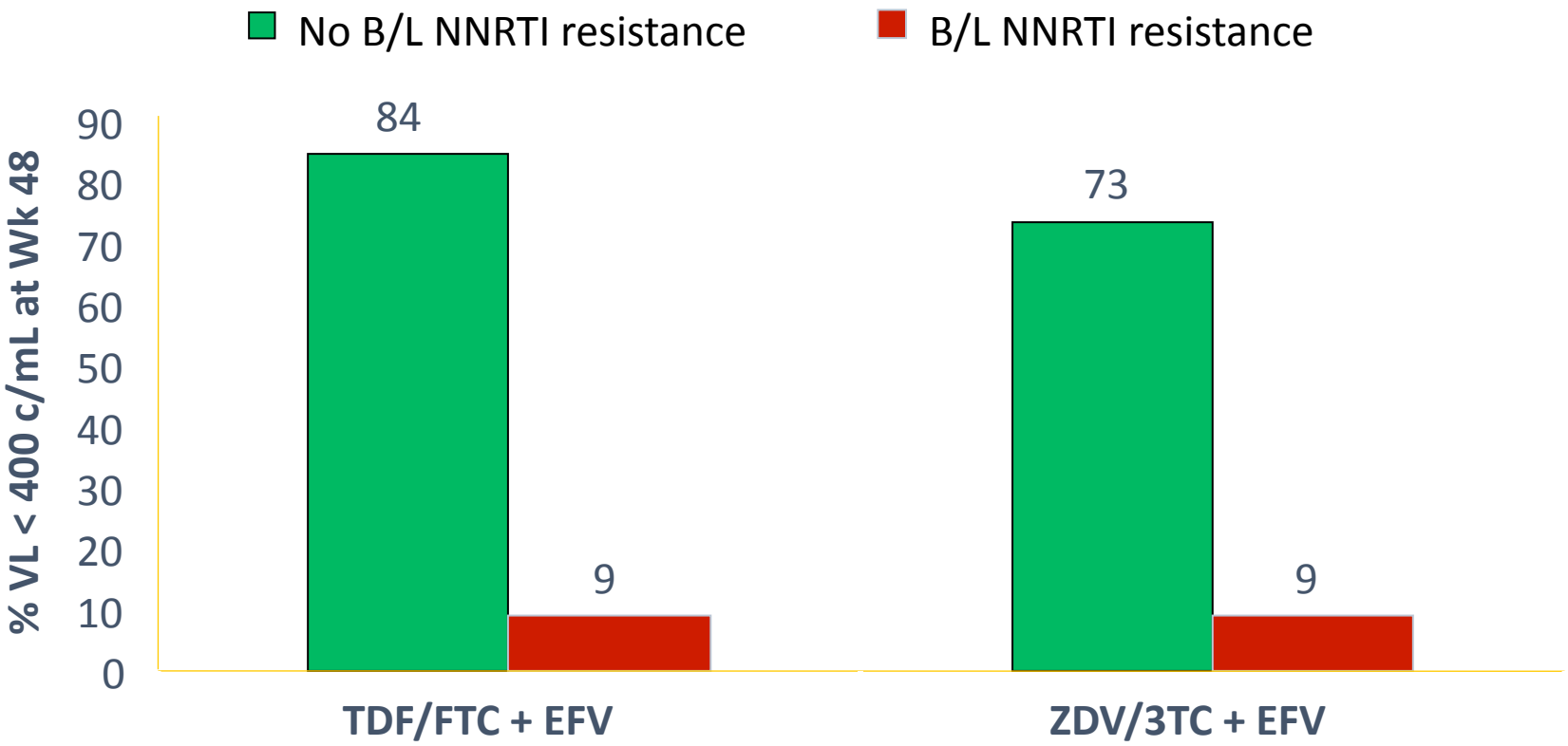


Once that patient has resistance to a drug, they will always have resistance to that drug

Limitations of resistance testing

- Archived resistance
  - May be so low they cannot be detected…. But they are still there…. and will rapidly re-emerge under drug pressure
  - So you need to look at all previous resistance test results too
  - And maybe make a guess on what might be there…..

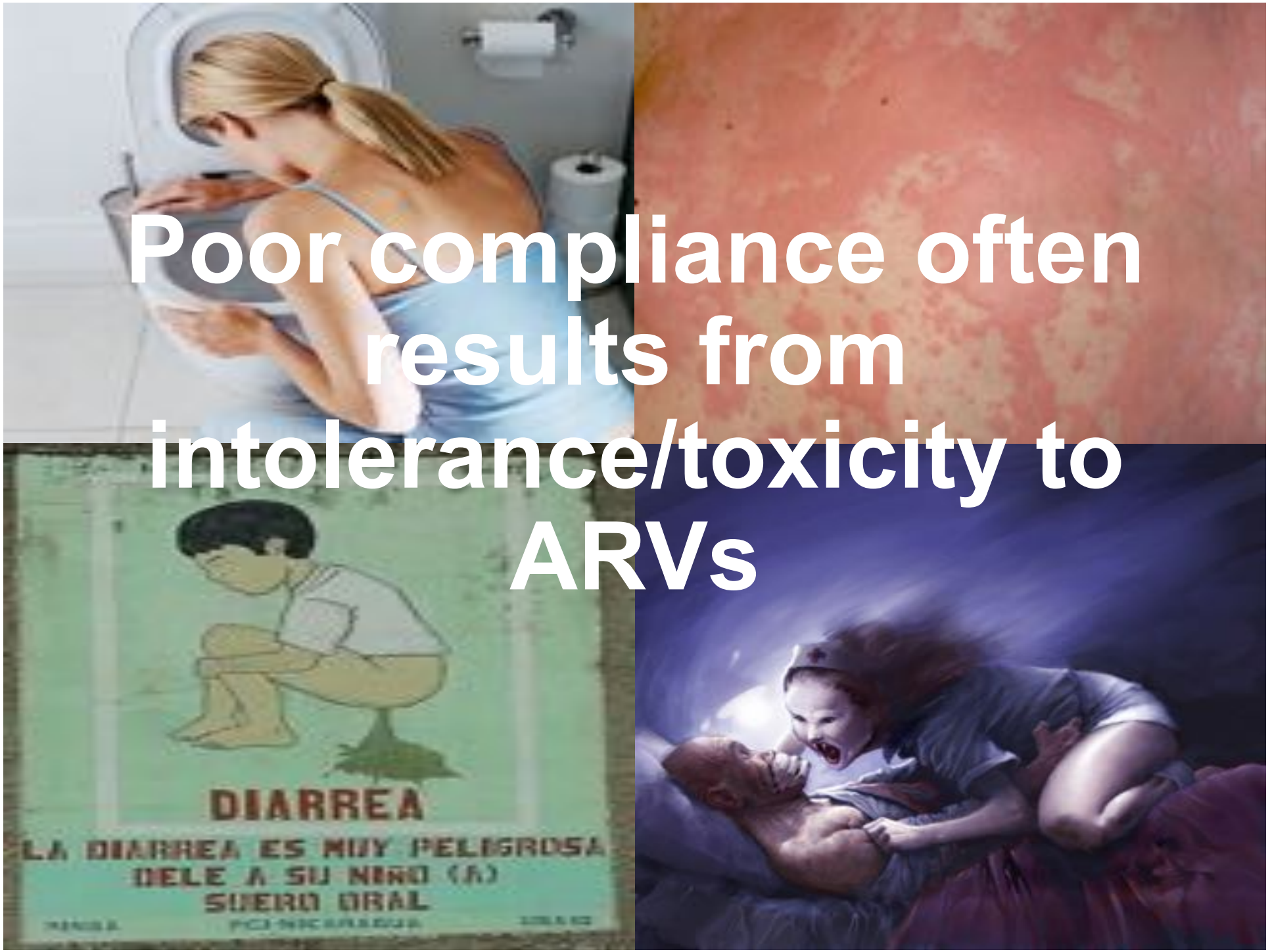
Archived NNRTI Resistance Markedly Reduces Treatment Response



Gallant JE, et al. N Engl J Med. 2006;354:251-260.

Why does it occur?

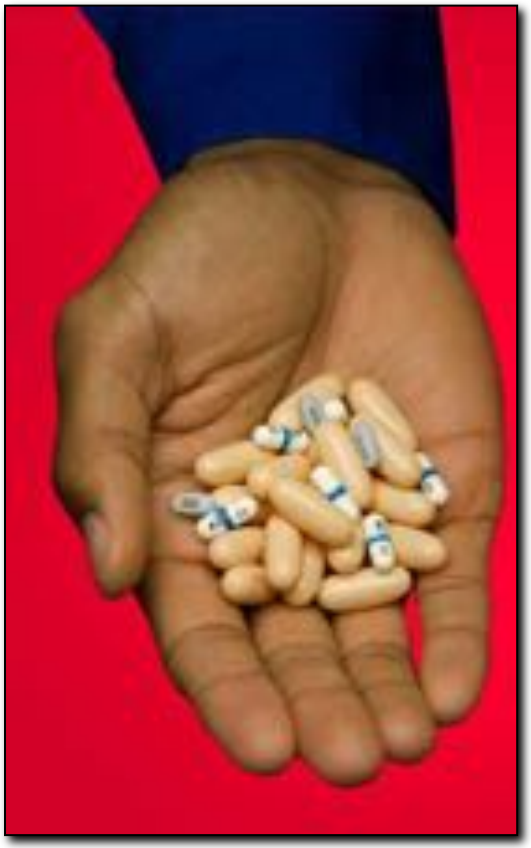
- Viral replication in presence of detectable drug(s)
  - Inadequate combination of drugs
    - Not potent enough
    - Pre-existing resistance
    - **Low levels**
      - **Compliance**
      - **Absorption/metabolism**
      - **Interactions**


Poor compliance often results from intolerance/toxicity to ARVs
DIARREA
LA DIARREA ES MUY PELIGROSA
DELE A SU NIÑO (A)
SUERO ORAL


……or too many tablets

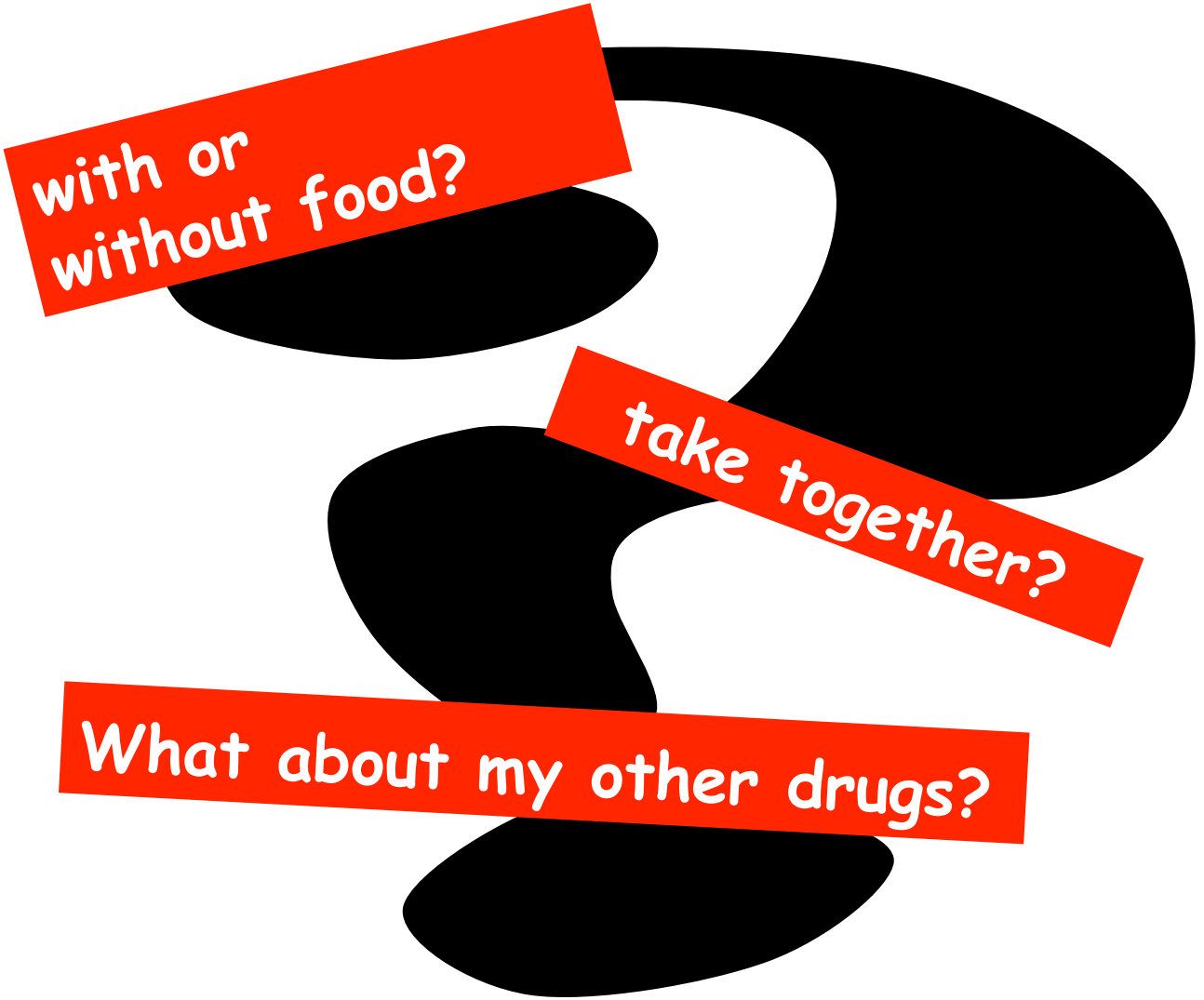
The advent of STRs

1 9 9 6
30+ Pills a Day

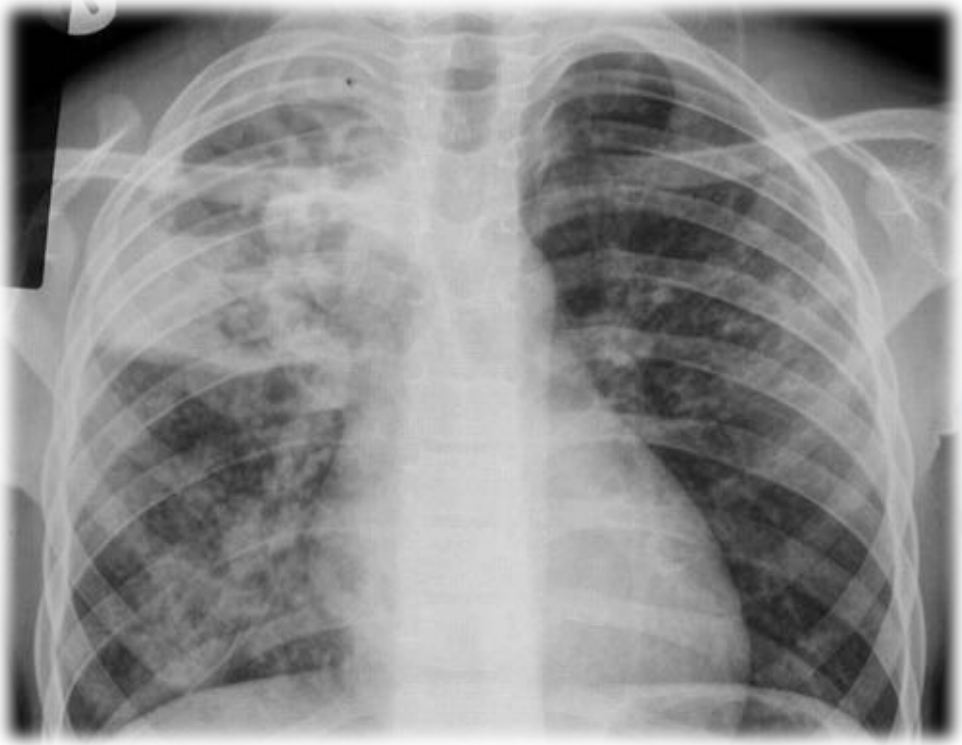


2 0 0 6
the first STR

Drug-drug Interactions



Drugs for HIV or non-HIV related issues



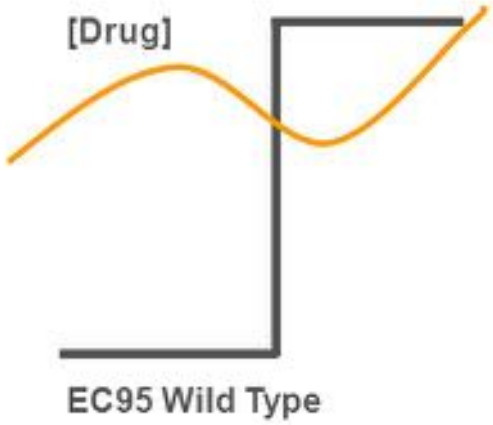
Age and illnesses of getting old

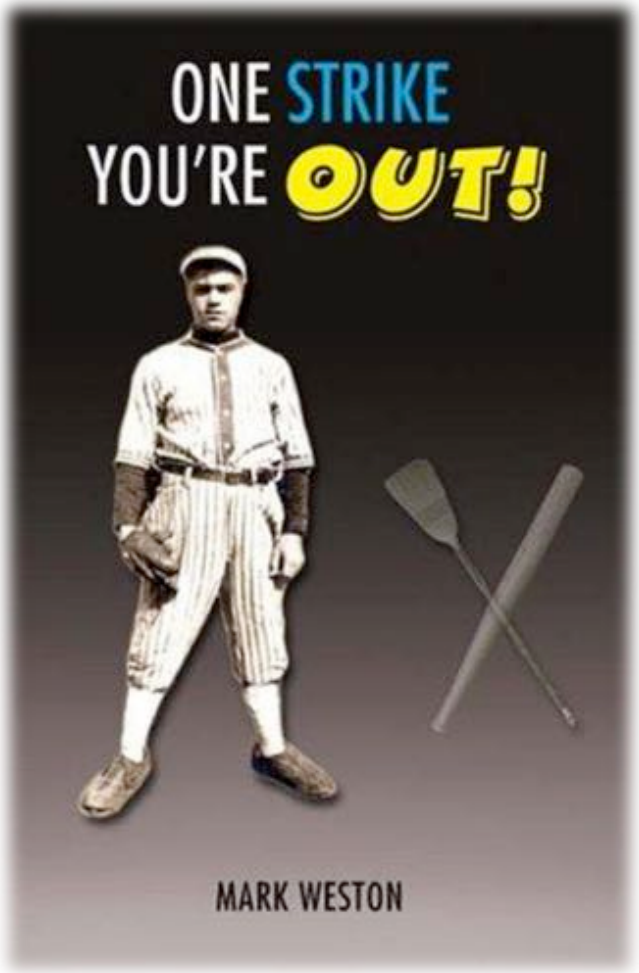
Why does it occur?

- Viral replication in presence of detectable drug(s)
  - Inadequate combination of drugs
    - Not potent enough
    - Pre-existing resistance
    - Low levels
      - Compliance
      - Absorption/metabolism
      - Interactions
  - Treatment interruption
    - Patient
    - Healthcare system/professional

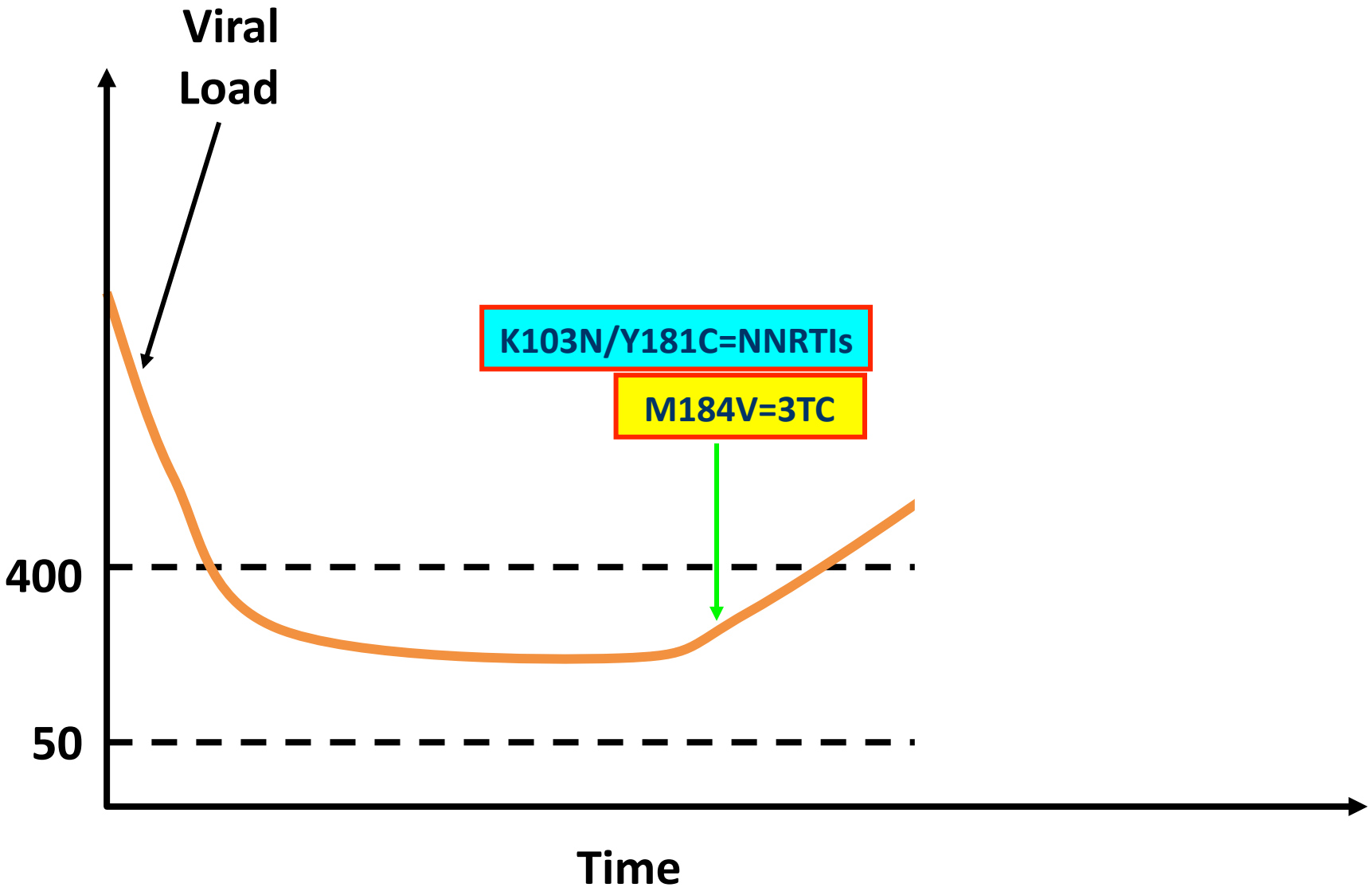
Resistance - simple

- A single mutation may wipe out activity…..
  - M184V - lamivudine or emtricitabine
  - K103N – efavirenz or nevirapine



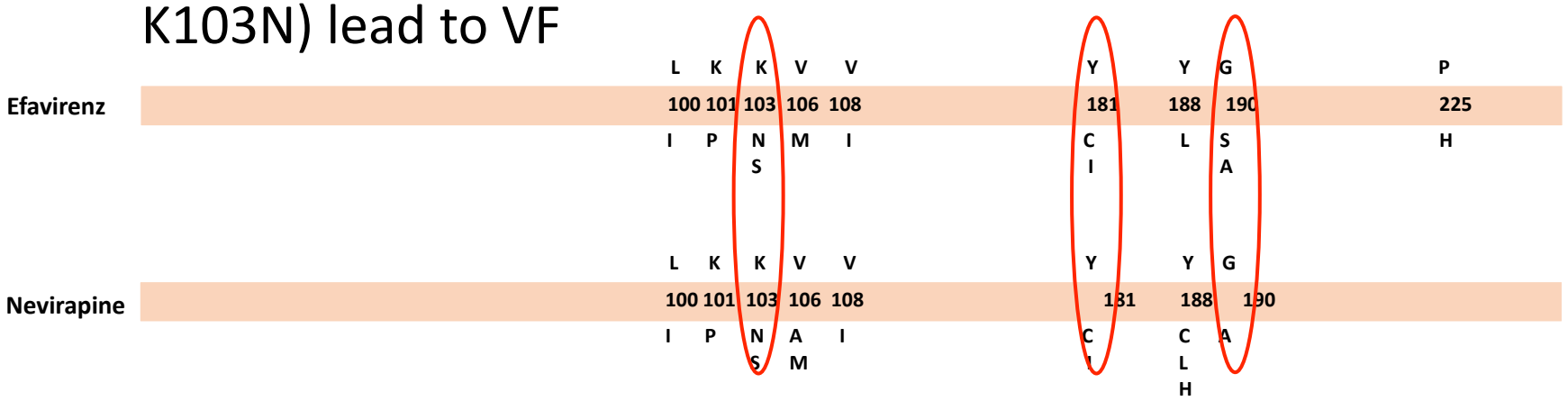


Response to therapy – case 1



In these situations class cross-resistance is usual

Single point mutations in the NNRTI binding pocket (e.g. K103N) lead to VF



- As EFV and NVP share similar binding sites, mutations often lead to cross resistance to the other agent[2]
- NNRTI resistance accumulation can compromise the efficacy of second-generation NNRTIs[3]

1. Johnson VA, et al. Top Antivir Med 2011;19:156–54
2. Delaugerre C, et al. J Med Virol 2001;65:445–48
3. Ghosn J, et al. AIDS Rev 2009;11:165–73

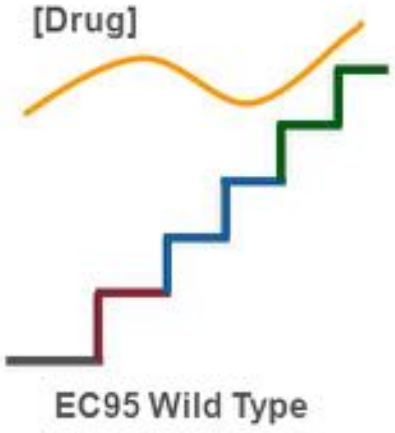
Resistance not always so simple - NRTIs

All or nothing;

- Nevirapine and 3TC

The more mutations the more resistance:

- AZT
- Mutations (TAMS): M41L, D67N, K70R, L210W, T215Y/F, K219Q/E/N



Resistance: not always so simple – 2nd generation NNRTIs (etravirine).

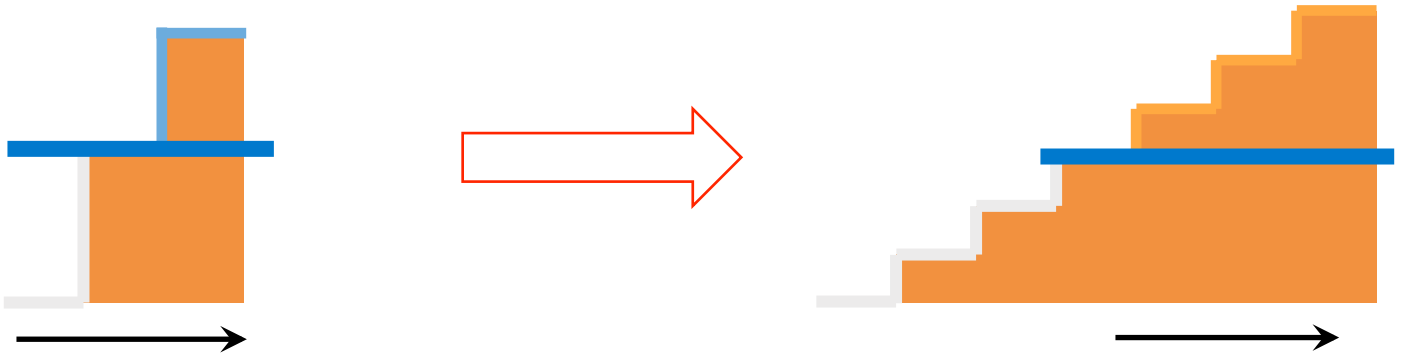
The number of mutations required to substantially decrease the efficacy of an antiviral drug

First-generation NNRTI

One mutation correlates with reduced virological response

Next-generation NNRTI (ETR)

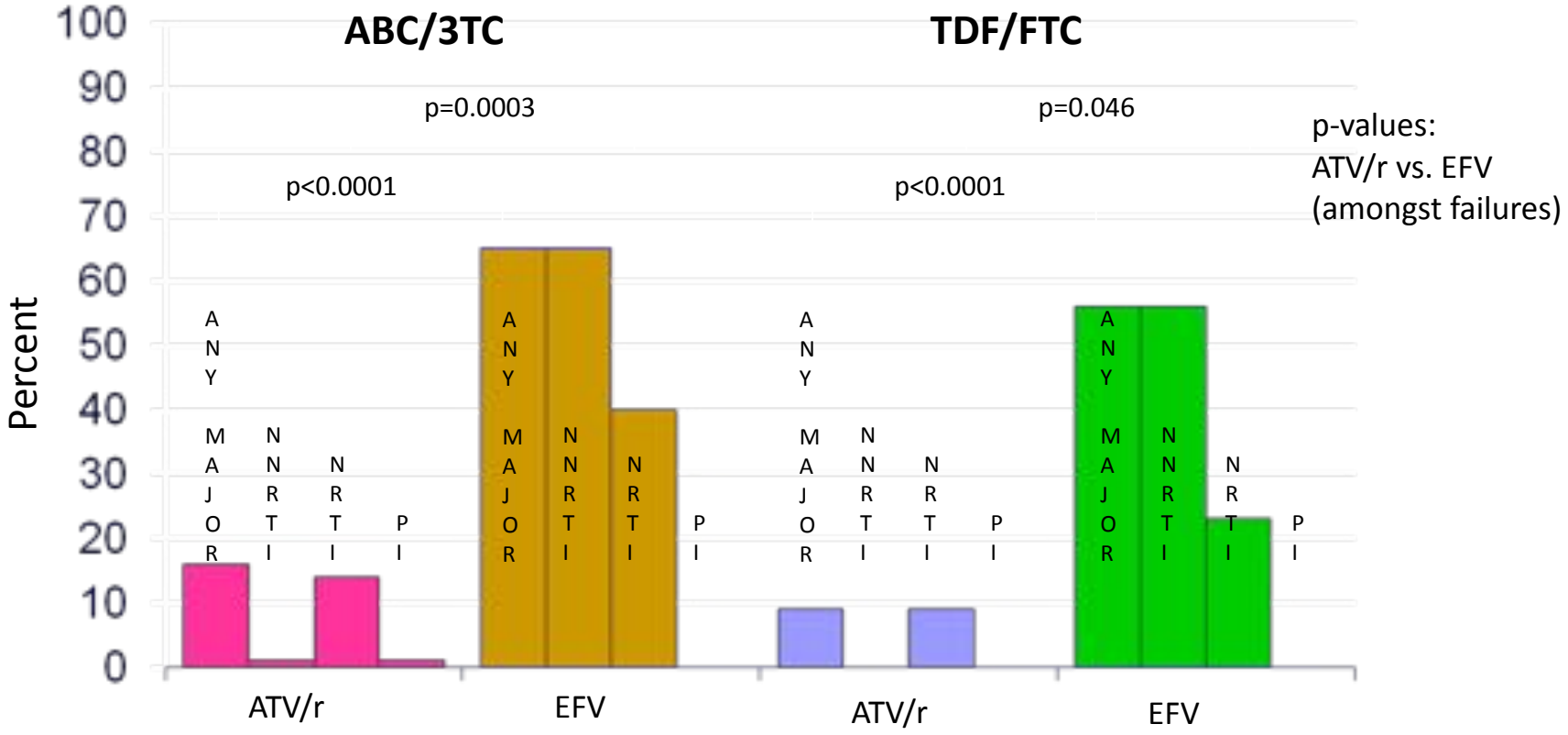
The presence of multiple NNRTI mutations at baseline is usually required to confer a reduced response



Increasing number of mutations at baseline

1. Antinori A, et al. AIDS Res Hum Retroviruses. 2002;18:835–8.
2. Lecossier D, et al. J Acquir Immune Defic Syndr. 2005;38:37–42.
3. Vingerhoets J, et al. 17th IDHRW 2008 [Poster 32].
4. De Béthune MP, et al. 4th EHDRW 2006 [Poster 51].
5. de Mendoza C, et al. HIV Clin Trials. 2006;7:163–71.

Resistant to resistance: boosted PI's



Viral failures

No baseline resistance N=	76	63	54	48

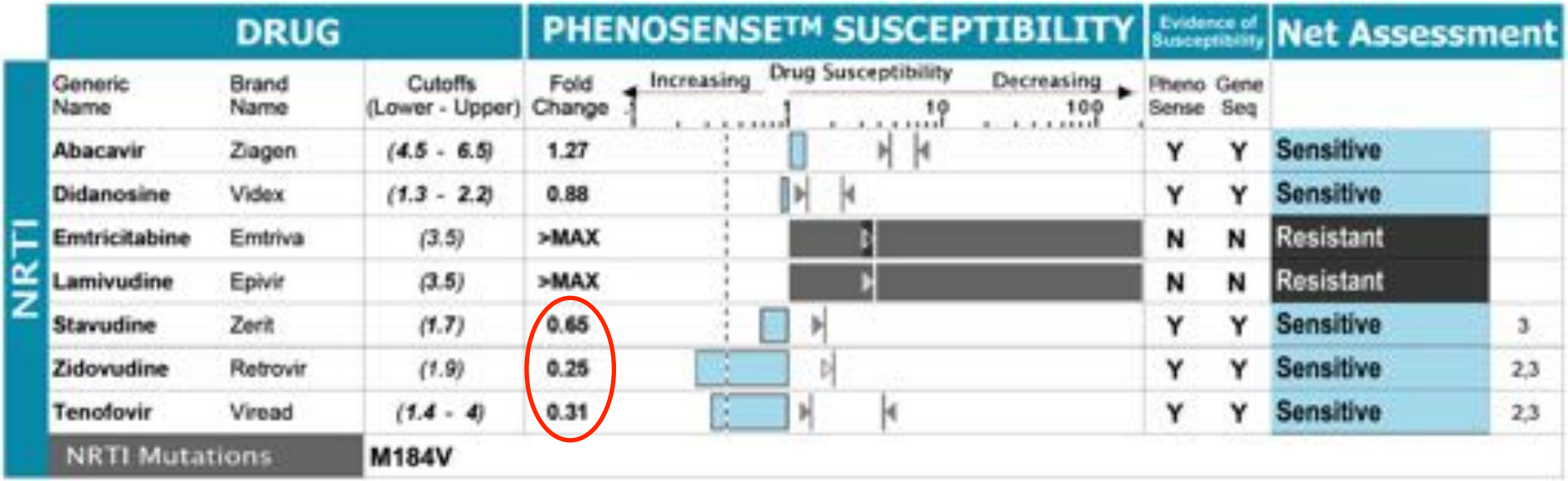
*Major mutations defined by IAS-USA (2008) list plus T69D, L74I, G190C/E/Q/T/V for RT and L24I, F53L, I54V/A/T/S and G73C/S/T/A for PR

Using resistance to your advantage

- Hypersusceptibility
  - A resistance to one ARV makes the virus even more susceptible to another…..

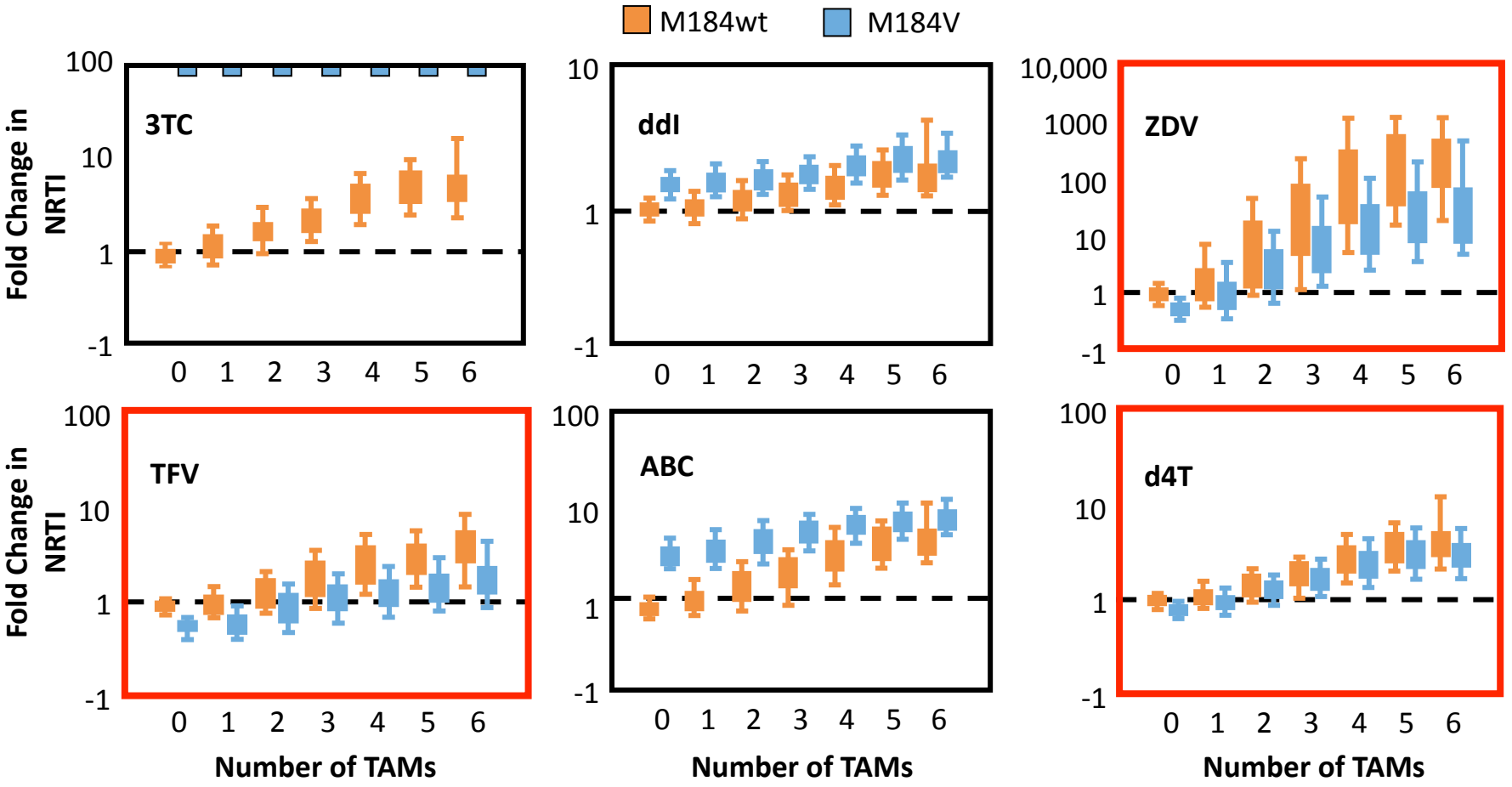
- Viral fitness
  - The resistance required to resist a drug interferes with other vital processes in the virus and it is not so ‘replication-competent’….

M184V Increases Susceptibility to d4T, ZDV, and TDF



	DRUG			PHENOSENSE™ SUSCEPTIBILITY		Evidence of Susceptibility		Net Assessment	
	Generic Name	Brand Name	Cutoffs (Lower - Upper)	Fold Change	Increasing ← Drug Susceptibility → Decreasing (1, 10, 100)	Pheno Sense	Gene Seq		
NRTI	Abacavir	Ziagen	(4.5 - 6.5)	1.27		Y	Y	Sensitive	
	Didanosine	Videx	(1.3 - 2.2)	0.88		Y	Y	Sensitive	
	Emtricitabine	Emtriva	(3.5)	>MAX		N	N	Resistant	
	Lamivudine	Epivir	(3.5)	>MAX		N	N	Resistant	
	Stavudine	Zerit	(1.7)	0.65		Y	Y	Sensitive	3
	Zidovudine	Retrovir	(1.9)	0.25		Y	Y	Sensitive	2,3
	Tenofovir	Viread	(1.4 - 4)	0.31		Y	Y	Sensitive	2,3
	NRTI Mutations		M184V						

Change in NRTI Susceptibility and Number of TAMs, ± M184V



Whitcombe JM, et al. J Infect Dis. 2003;188:992-1000.

Doing it without access to a resistance test

The principle aim of the RDI is to provide a treatment decision-making aid free of charge over the Internet such that physicians entering the genotype and other baseline data for a patient will receive a report containing predictions of virological responses to a range of alternative antiretroviral combinations.

No resistance test…

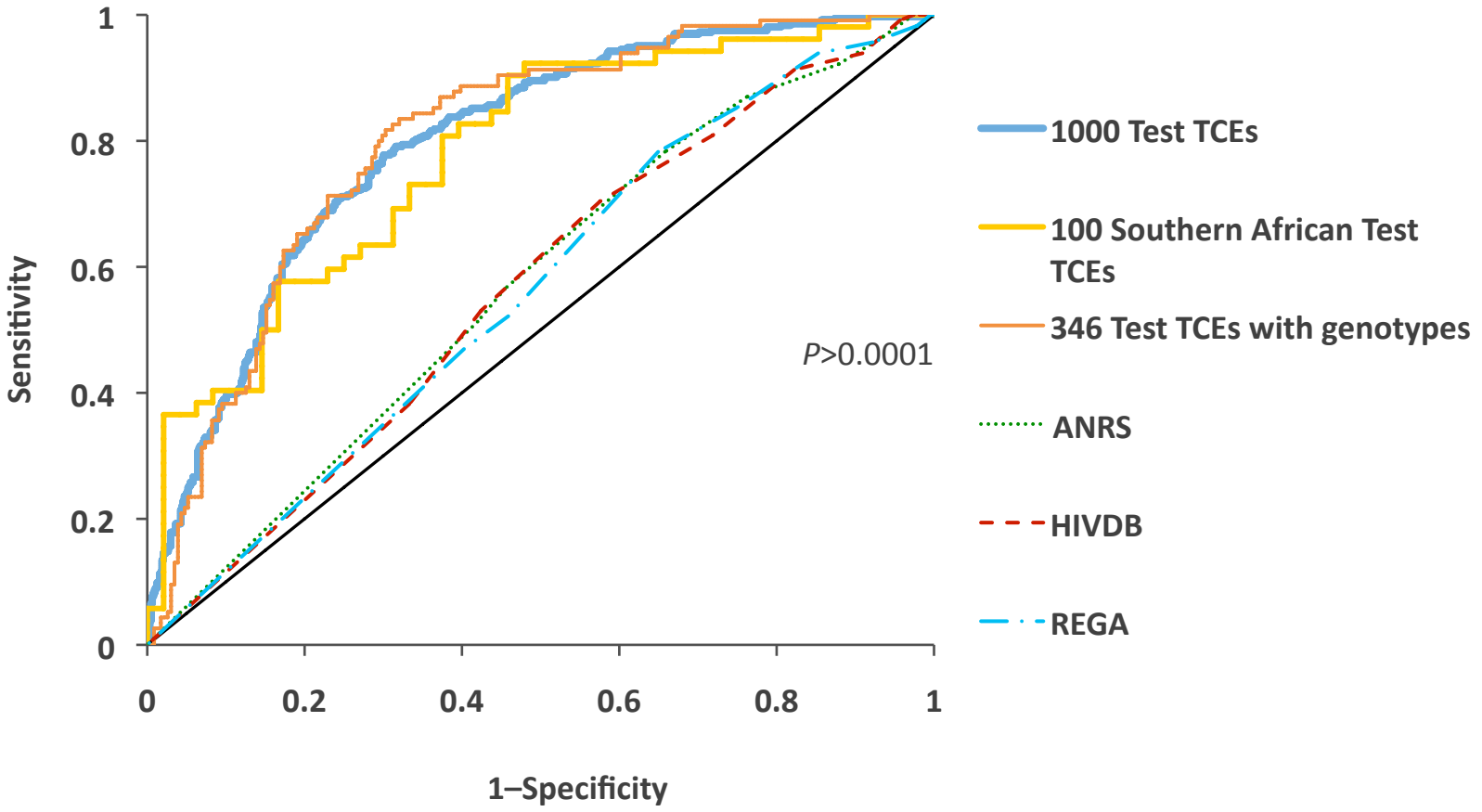
After failing NNRTI/2NRTIs

- Baseline viral load
- Treatment history
- Baseline CD4 count
- Time to follow-up

Resistance	Time	Accuracy (%)
Genotype	12w	66
No genotype	**12w**	**68**
Genotype	24w	65
No genotype	**24w**	**64**

- With or without genotype

RDI models: Predicting treatment response without a genotype versus genotyping with interpretation



ANRS, Agence Nationale de Recherches sur le SIDA; RDI, Response Database Initiative; TCE, treatment change episode

Revell AD *et al*. *J Antimicrob Chemother* 2013; [Epub ahead of print]

Managing without a resistance test

- Predict virological response to salvage ART accurately (approximately 80%) **without** the use of a genotype[1]
- Significantly more accurate predictors of response then genotyping with rules-based interpretation *(P*<0.001)[1]
- As accurate for cases from southern Africa as for other regions[1]
- Identify alternative regimens that are predicted to be effective for the majority of cases where the new regimen in the clinic failed[1,2]
- Identified cost-saving alternatives for most cases of failure in a study of second-line therapy in India[2]

1. Revell AD *et al*. *J Antimicrob Chemother* 2013; [Epub ahead of print]; 2. Revell AD *et al. 11th International Congress on Drug Therapy in HIV Infection* 2012;oral late breaker O234.

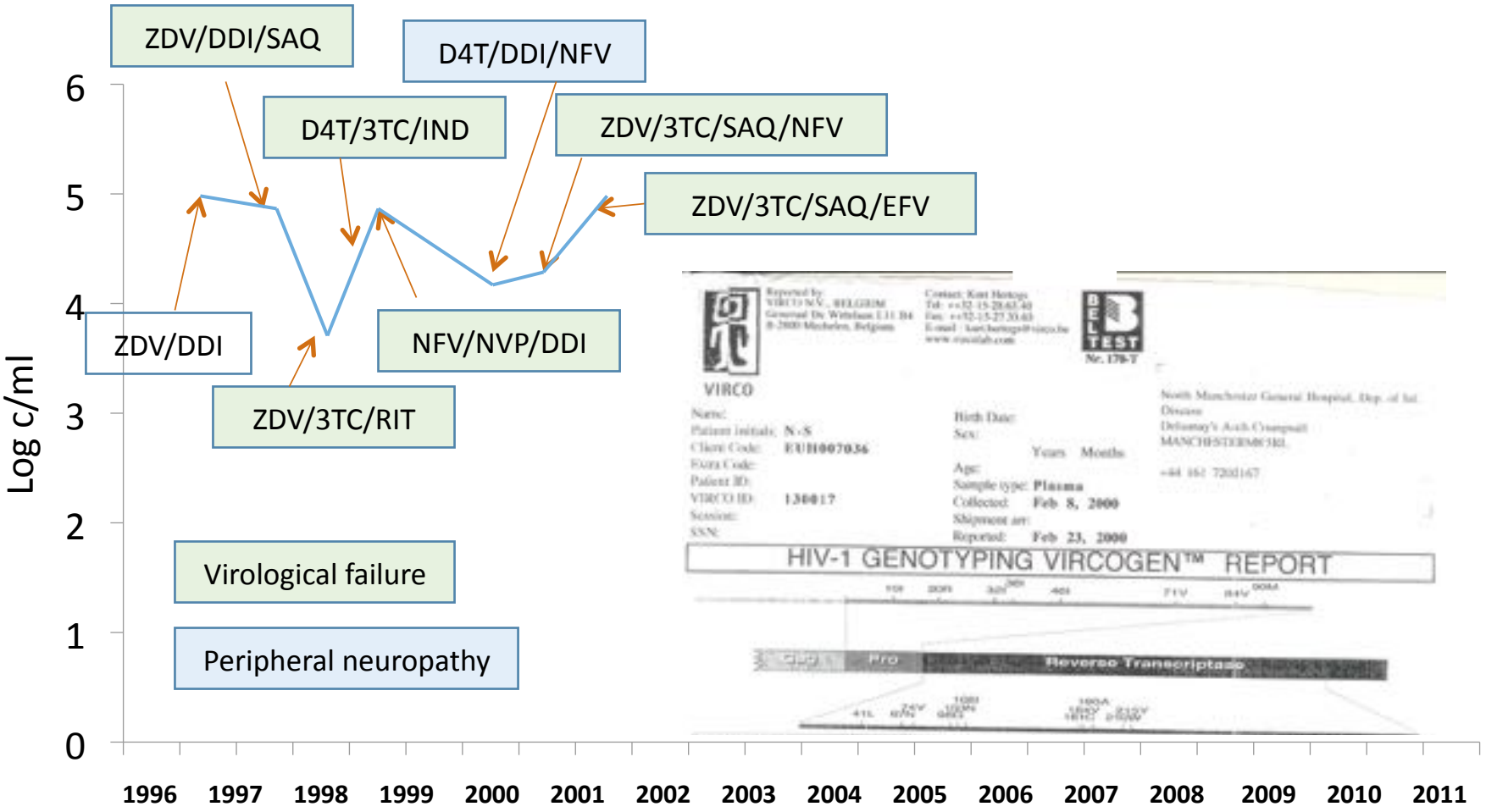
Preventing resistance

1. Choose a good combination
   - (= 3 active drugs)
2. Ensure good levels
   - Compliance
   - Absorption
   - Interactions
3. Monitor for viral control & react quickly to failure
4. Build a robust new regimen on virological failure
   - Known resistance now
   - All previous resistance
   - *Guesstimate* other resistance
5. Go back to 2….

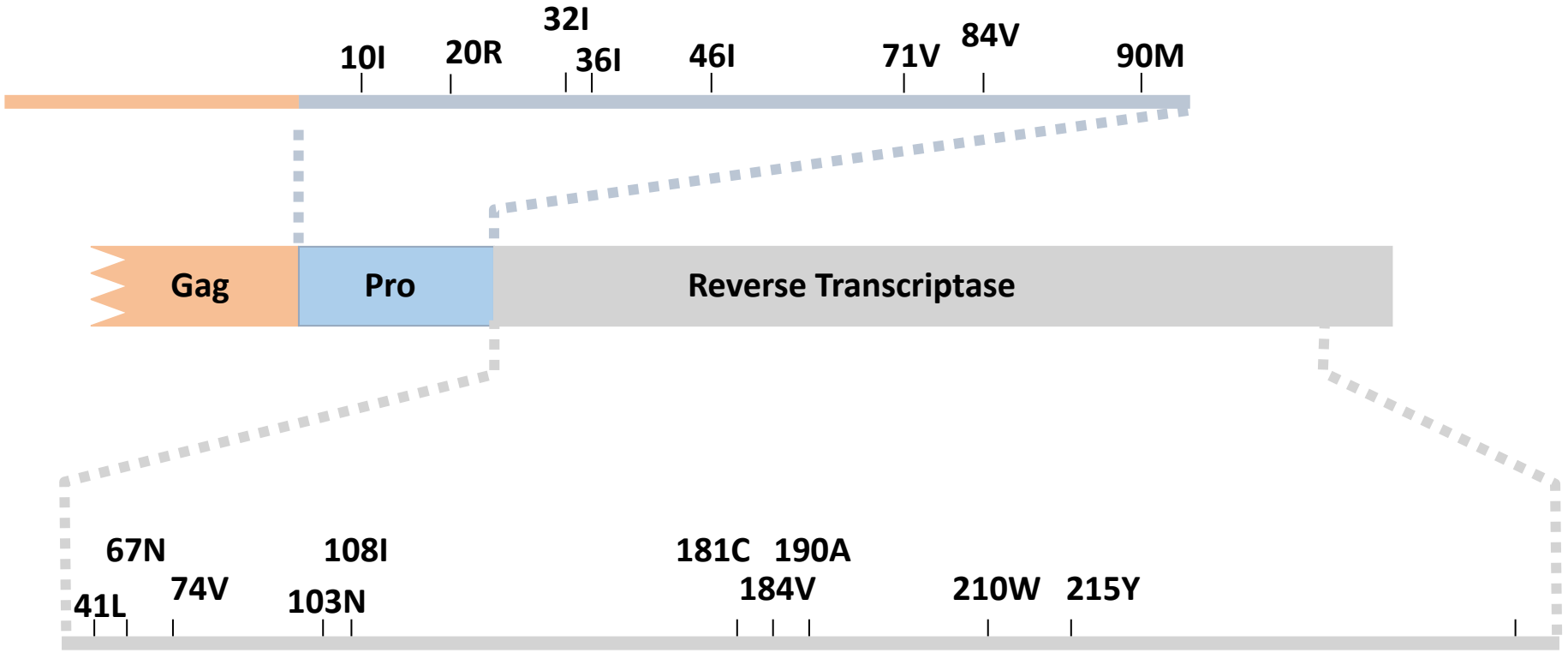
Case 1

- 49yr old woman diagnosed 1995 (then 32)
  - PCP, CD4 50
  - Weight loss, OPC
- HBV/HCV –ve
- No significant co-morbidity
- CVD risk factors:
  - Non-smoker, No FHx, BMI 19
  - BP 120-5/80
  - TC 4.2, HDL-C 0.9
- Started ZDV/DDI

Case 1


ZDV/DDI/SAQ
D4T/DDI/NFV
D4T/3TC/IND
ZDV/3TC/SAQ/NFV
ZDV/3TC/SAQ/EFV
ZDV/DDI
NFV/NVP/DDI
ZDV/3TC/RIT
Virological failure
Peripheral neuropathy
Log c/ml
6
5
4
3
2
1
0
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
VIRCO
HIV-1 GENOTYPING VIRCOGEN™ REPORT
Protease
Reverse Transcriptase

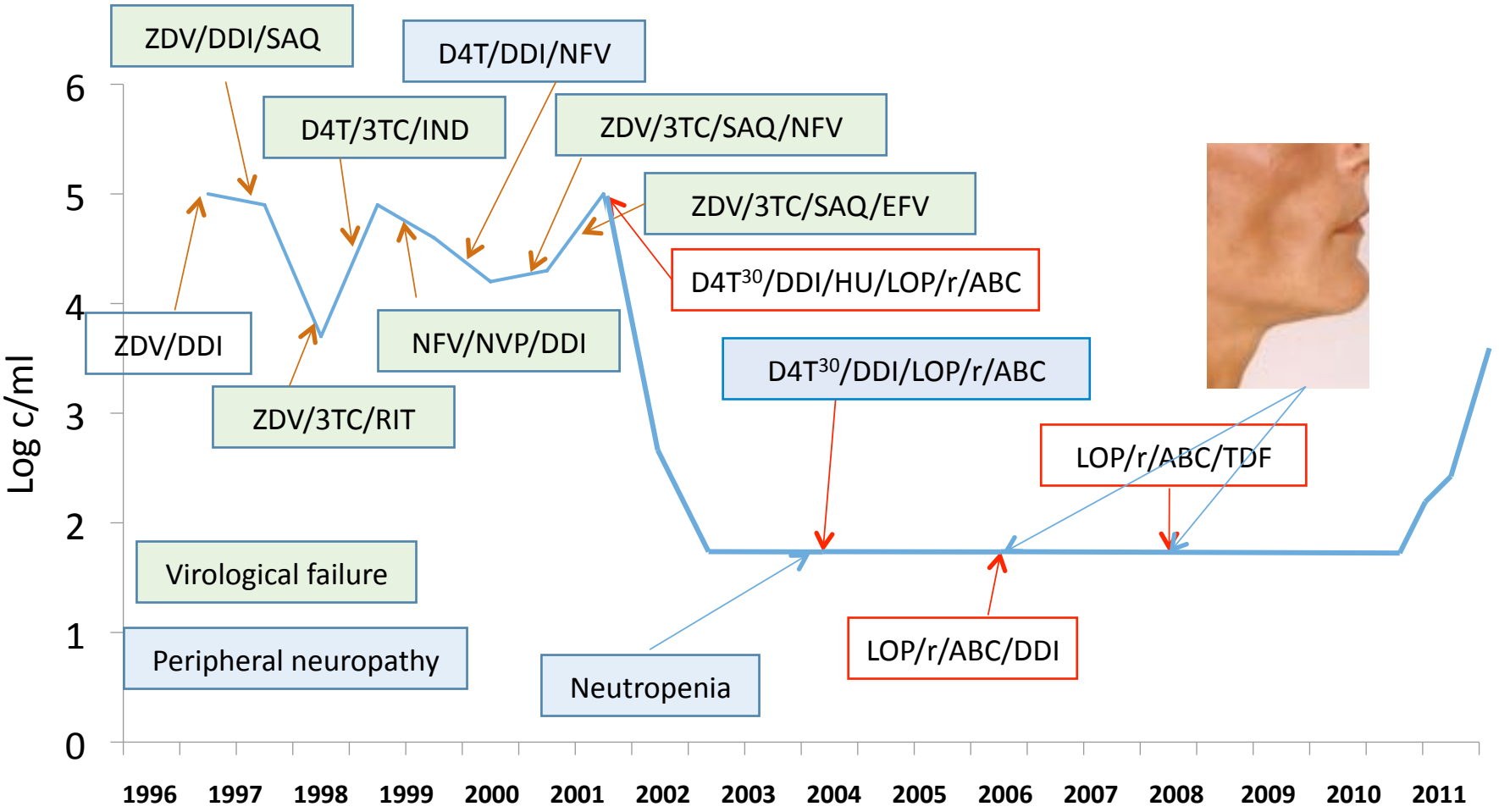
Genotypic resistance test



Case 1


ZDV/DDI/SAQ
D4T/DDI/
P/r
Log c/ml
6
5
4
3
2
0
Pro
Reverse Transcriptase
41L
67N
184V
210W
215Y
Trade Name
Generic Name
Muta-tions
Interpretation
Additional Information
Retrovir®
Zidovudine
AZT resistance may be reversed
Epivir®
Lamivudine
184: characteristic mutation
Videx®
Didanosine
Hivid®
Zalcitabine
Zerit®
Stavudine
Ziagen®
Abacavir
Adefovir
Viramune®
Nevirapine
Rescriptor®
Delavirdine
Sustiva®
Efavirenz
Crixivan®
Indinavir
Norvir®
Ritonavir
Viracept®
Nelfinavir
Invirase®/Fortovase®
Saquinavir
Agenerase®
Amprenavir
No Evidence of Resistance
2009

Viral loads

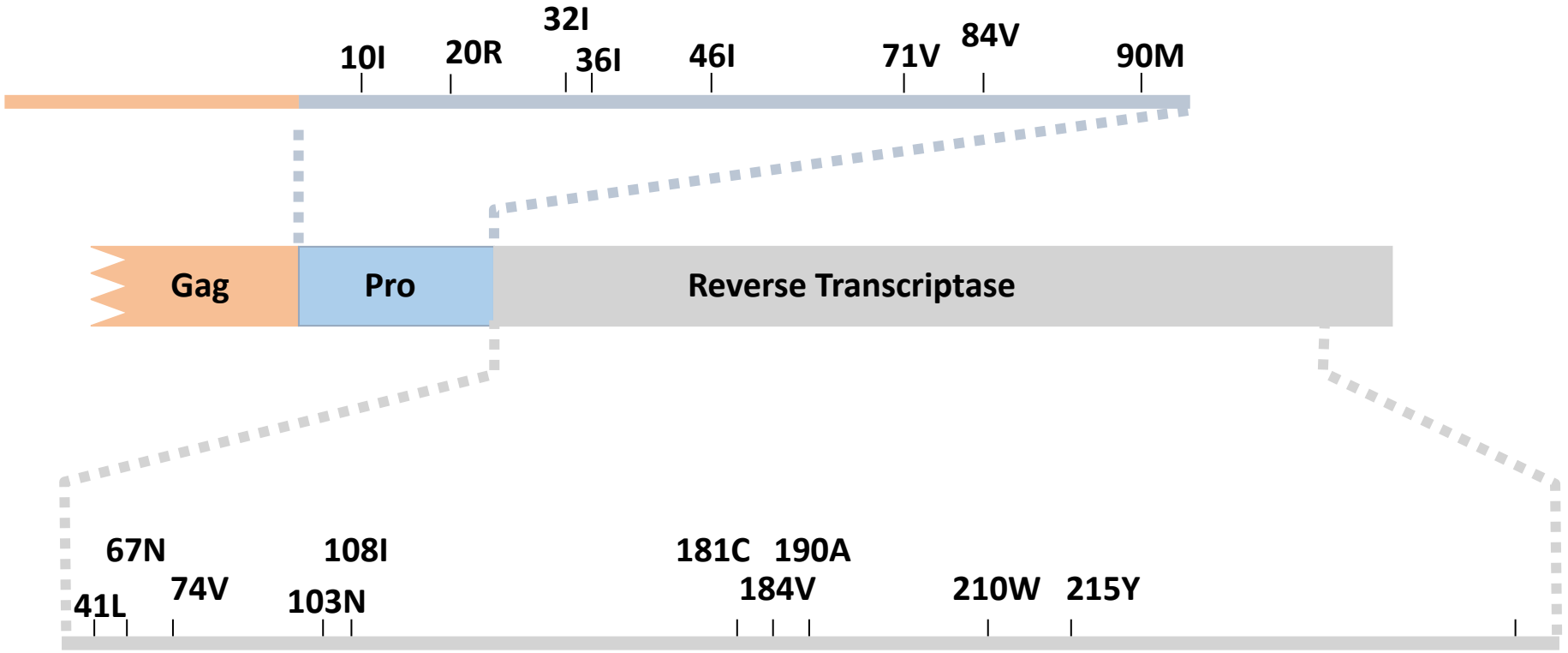

ZDV/DDI/SAQ
D4T/DDI/NFV
D4T/3TC/IND
ZDV/3TC/SAQ/NFV
ZDV/3TC/SAQ/EFV
D4T30/DDI/HU/LOP/r/ABC
ZDV/DDI
NFV/NVP/DDI
D4T30/DDI/LOP/r/ABC
ZDV/3TC/RIT
LOP/r/ABC/TDF
Virological failure
Peripheral neuropathy
Neutropenia
LOP/r/ABC/DDI
Log c/ml
0
1
2
3
4
5
6
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011

Most likely cause?

Taking only 25% tablets

- Depressed
  - Life in a mess
- Diarrhoea
  - I’ve had enough!!!
- Aware of new agents
  - Wants to take fewer tablets
- Fed up with current combination
  - CD4 224, viral load 60,000
  - Tropism R5

Going back to resistance test



So what's available?

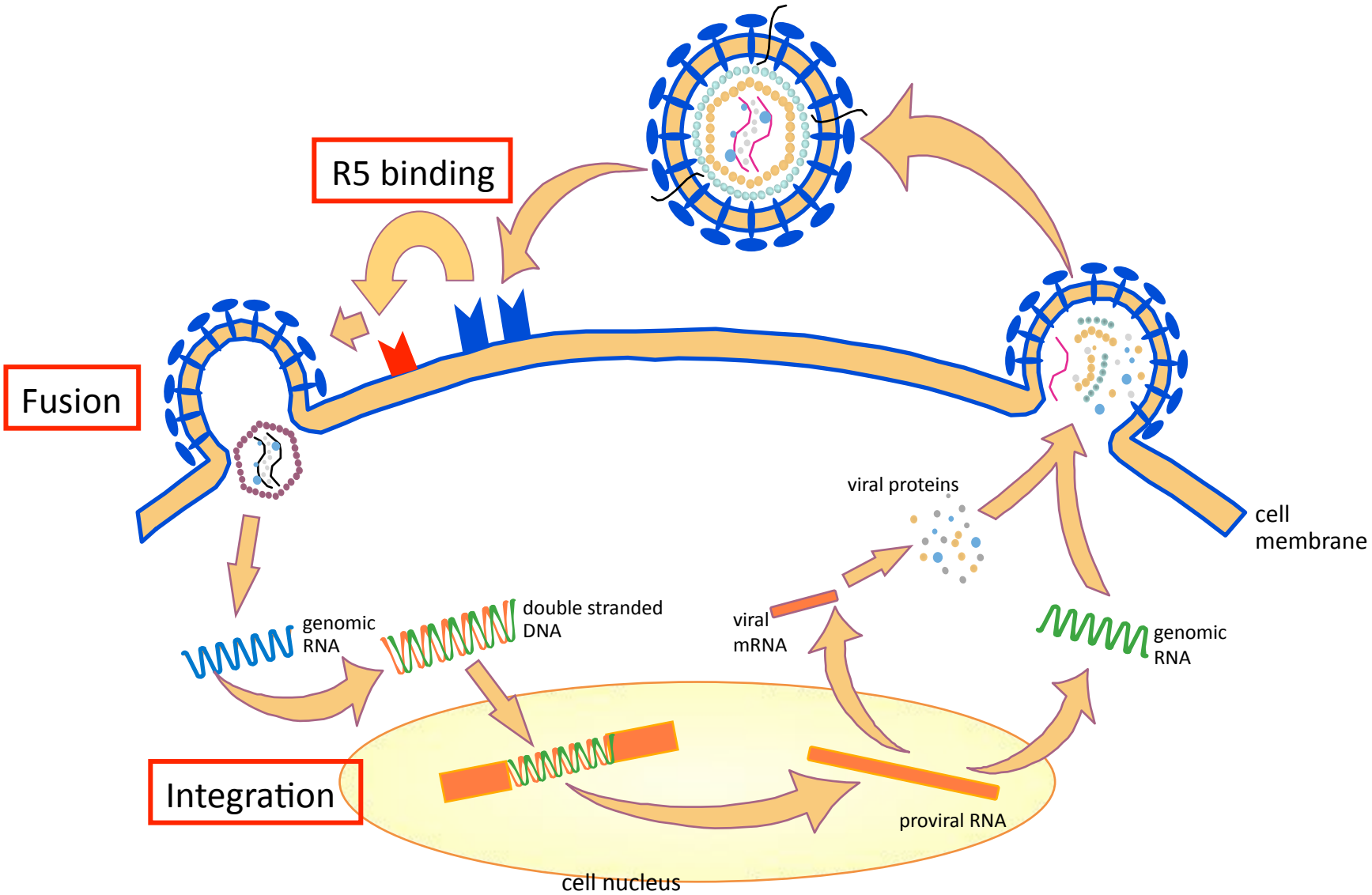
- Definitely active:
  - RAL
  - T-20
  - MRV

BENCHMMRK

TORO

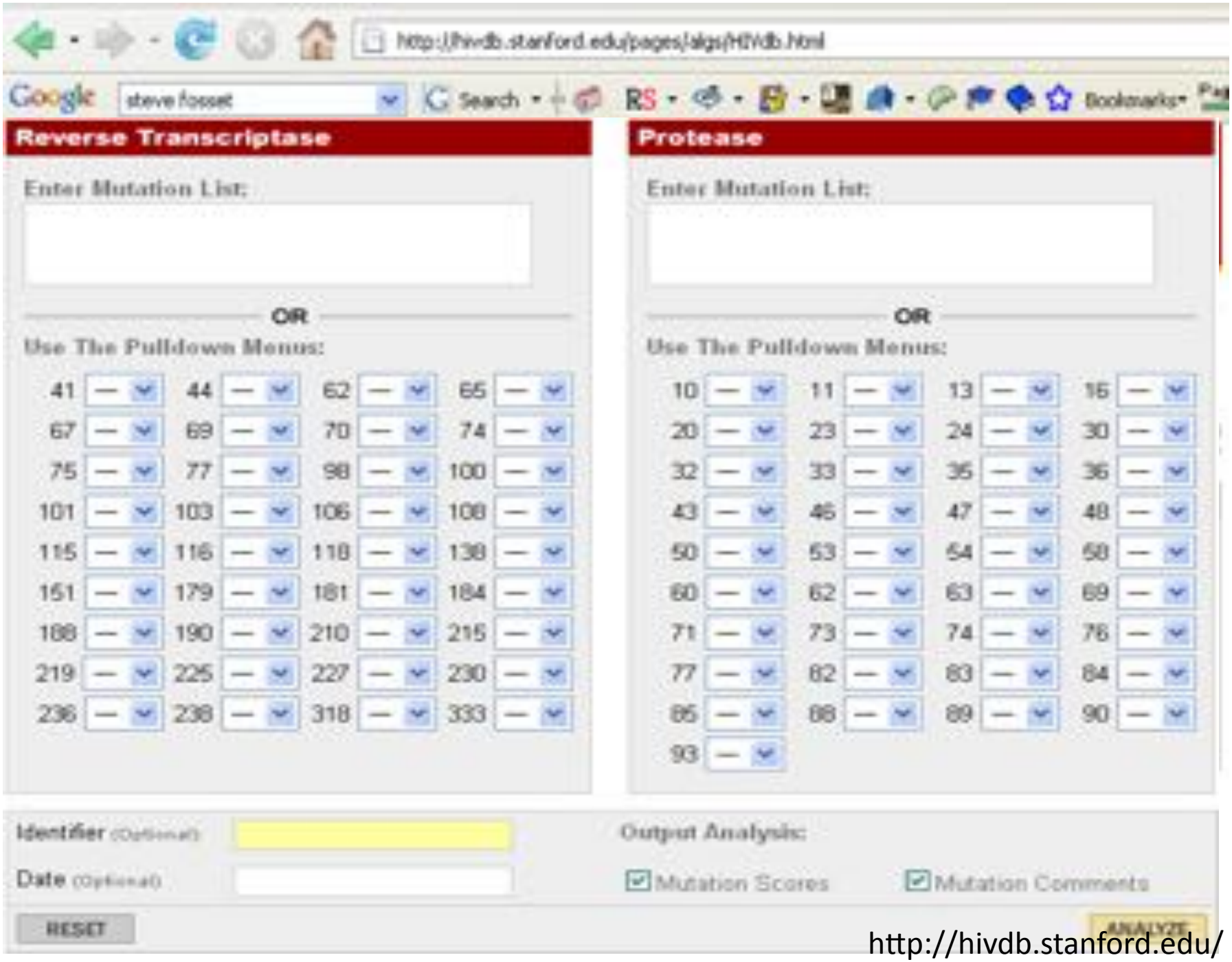
MOTIVATE

Where do these act - life cycle of HIV



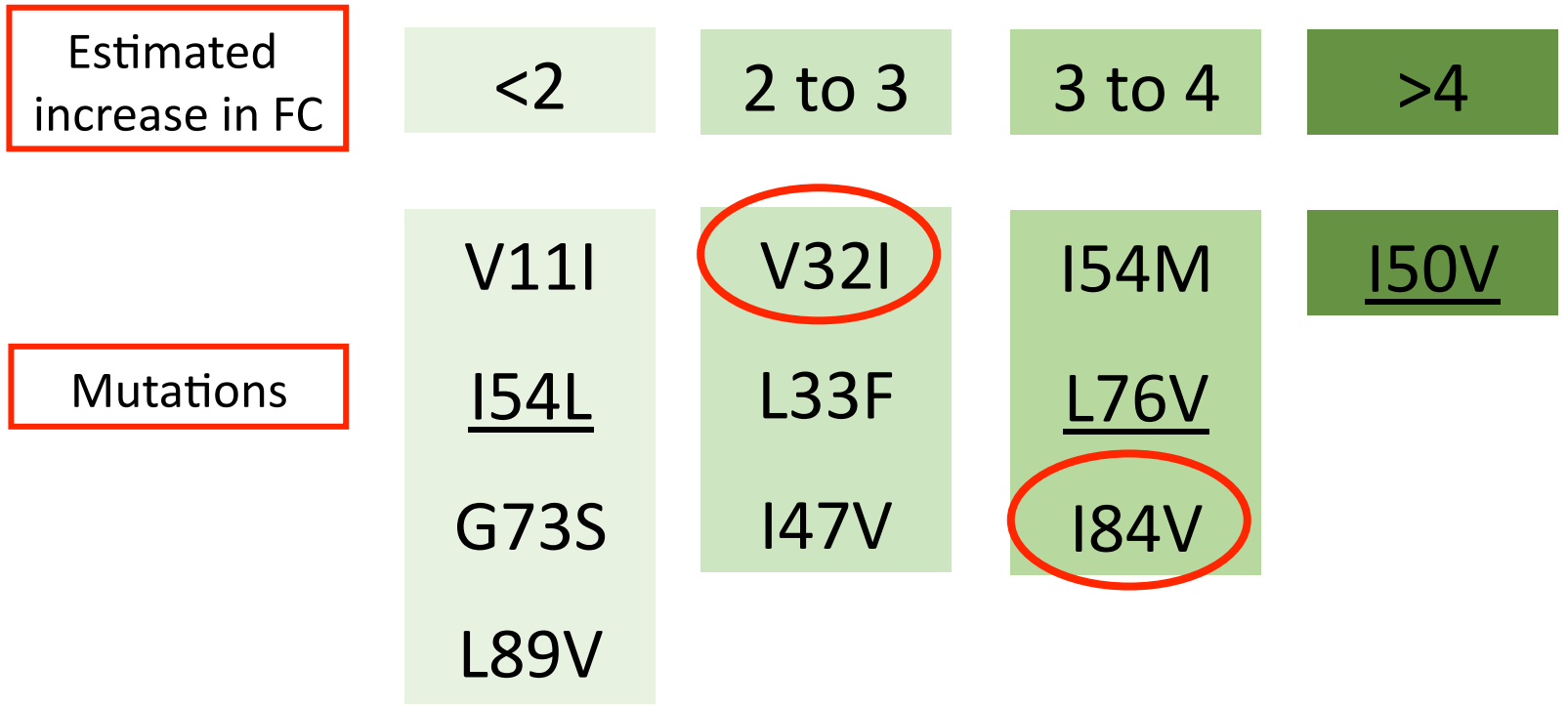
So what's available?

- Reduced activity:



http://hivdb.stanford.edu/

Increasing predictive accuracy to DRV score by weighting mutations



Add mutations up for fold-change

Example: = ~ 5–7 fold-change = **Intermediate activity**

De Meyer S, *et al*. IHDRW 2006;Abstr. 73.
Data on file. Tibotec Therapeutics. 2006.

Increasing predictive accuracy to TPV score by weighting mutations

- 1	0.5	1	2
L24I	L10V/I	V11L	I47V
D30N	I13V	V32I	I54A
I50L/V	K20R	A71L	V82T
154L	M46L	G73T	I84V
L76V	L90M	L89V	
V82I			

Add mutations up for fold-change

Example: = ~ 4 fold-change = **Intermediate activity**

De Meyer S, *et al*. IHDRW 2006;Abstr. 73.
Data on file. Tibotec Therapeutics. 2006.

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

HIVdb: Genotypic Resistance Interpretation Algorithm

SeqID: Date Feb 2011

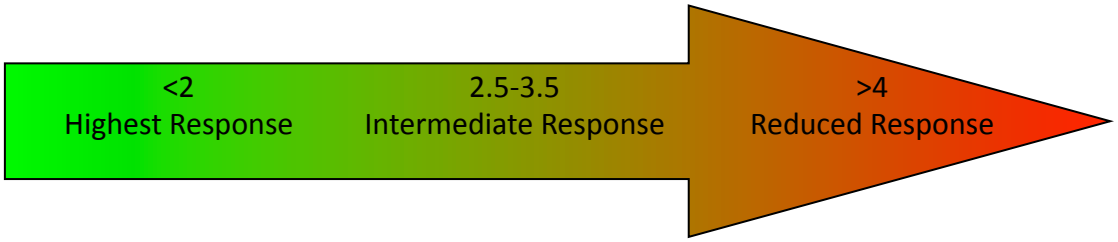
Drug Resistance Interpretation

PI Major Resistance Mutations:	V32I, M46I, I84V, L90M
PI Minor Resistance Mutations:	L10I, A71V
Other Mutations:	K20R, M36I

	Protease Inhibitors
atazanavir/r (ATV/r)	High-level resistance
darunavir/r (DRV/r)	Intermediate resistance
fosamprenavir/r (FPV/r)	High-level resistance
indinavir/r (IDV/r)	High-level resistance
lopinavir/r (LPV/r)	Intermediate resistance
nelfinavir (NFV)	High-level resistance
saquinavir/r (SQV/r)	High-level resistance
tipranavir/r (TPV/r)	Intermediate resistance

Increasing predictive accuracy to ETR score by weighting mutations

0	1	1.5	2.5	3
K103N	V90I	V106I	L100I	Y181I
	A98G	E138A	K101P	Y181V
	K101E	V179F	Y181C	
	K101H	G190S	M230L	
	V179D			
	V179T			
	G190A			



Adapted from Vingerhoets J et al. Oral Presentation IHDRW 2008

STANFORD UNIVERSITY
HIV DRUG RESISTANCE DATABASE

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

HIVdb: Genotypic Resistance Interpretation Algorithm

SeqID: Date Feb 2011

Drug Resistance Interpretation

NRTI Resistance Mutations:	M41L, D67N, L74V, L210W, T215Y
NNRTI Resistance Mutations:	A98G, K103N, V108I, Y181C, G190A
Other Mutations:	None

Nucleoside RTI	
lamivudine (3TC)	Potential low-level resistance
abacavir (ABC)	High-level resistance
zidovudine (AZT)	High-level resistance
stavudine (D4T)	High-level resistance
didanosine (DDI)	High-level resistance
emtricitabine (FTC)	Potential low-level resistance
tenofovir (TDF)	Intermediate resistance

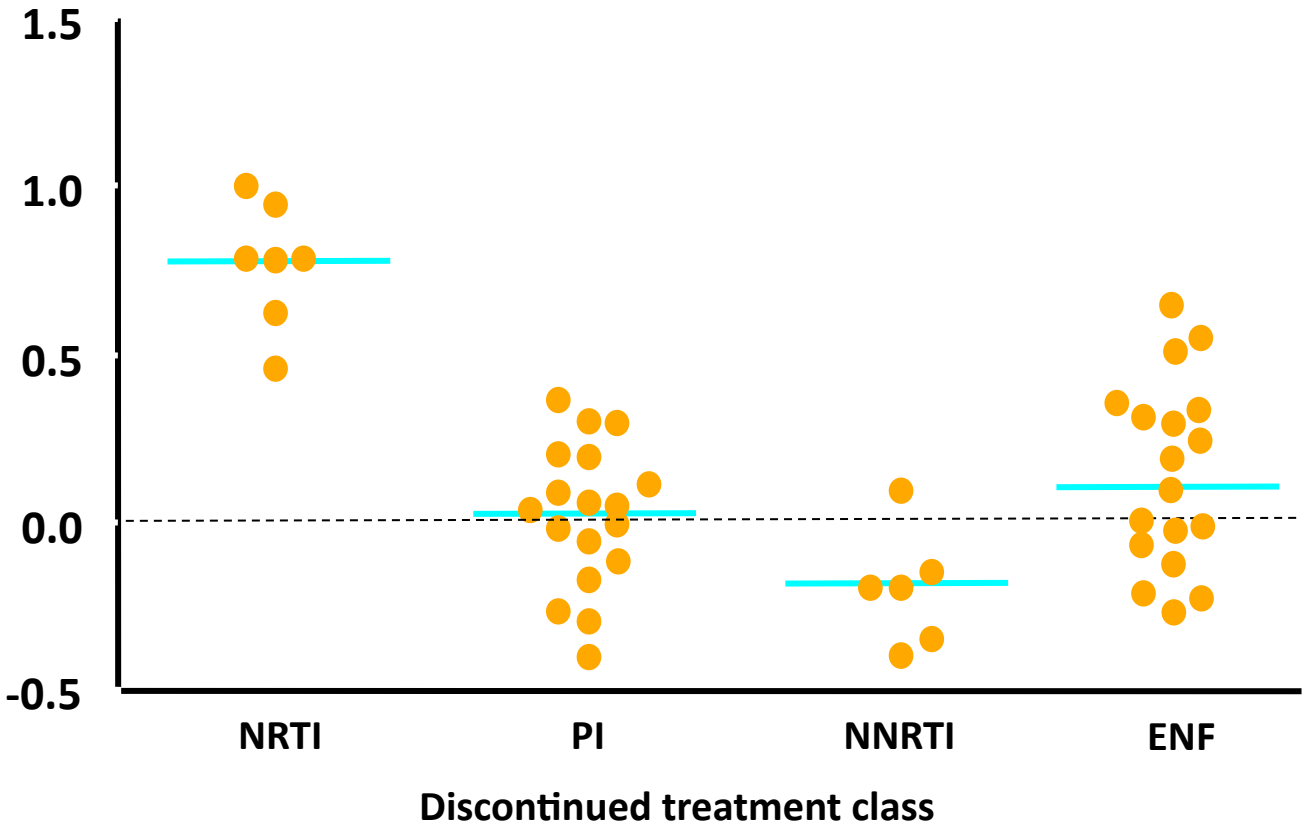
Non-Nucleoside RTI	
delavirdine (DLV)	High-level resistance
efavirenz (EFV)	High-level resistance
etravirine (ETR)	High-level resistance
nevirapine (NVP)	High-level resistance

So what's available?

- Definitely active:
  - RAL, MRV, T-20
- Reduced activity:
  - DAR/r & TIP/r
- Some benefit or not?
  - NRTI's, 3TC/FTC

Partial treatment interruption studies Maintain NRTIs

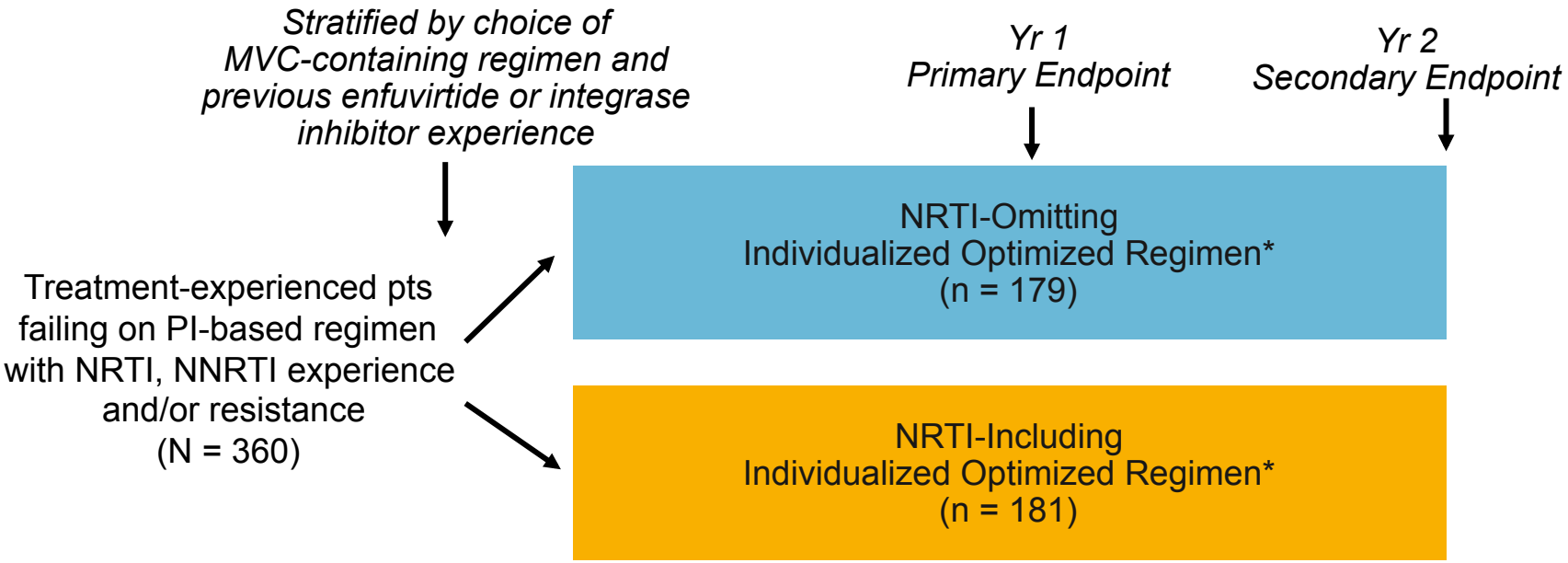
Week 2 viral load increase after drugs in one class interrupted; other ARVs maintained



Deeks *et al. 12th CROI* 2005; Poster 680.

OPTIONS: NRTIs vs No NRTIs in Regimens for Highly ART-Experienced

- Randomized, noninferiority, multicenter trial (ACTG A5241)
  - Primary endpoint: regimen failure (VF or divergence from NRTI assignment, whichever occurred first)

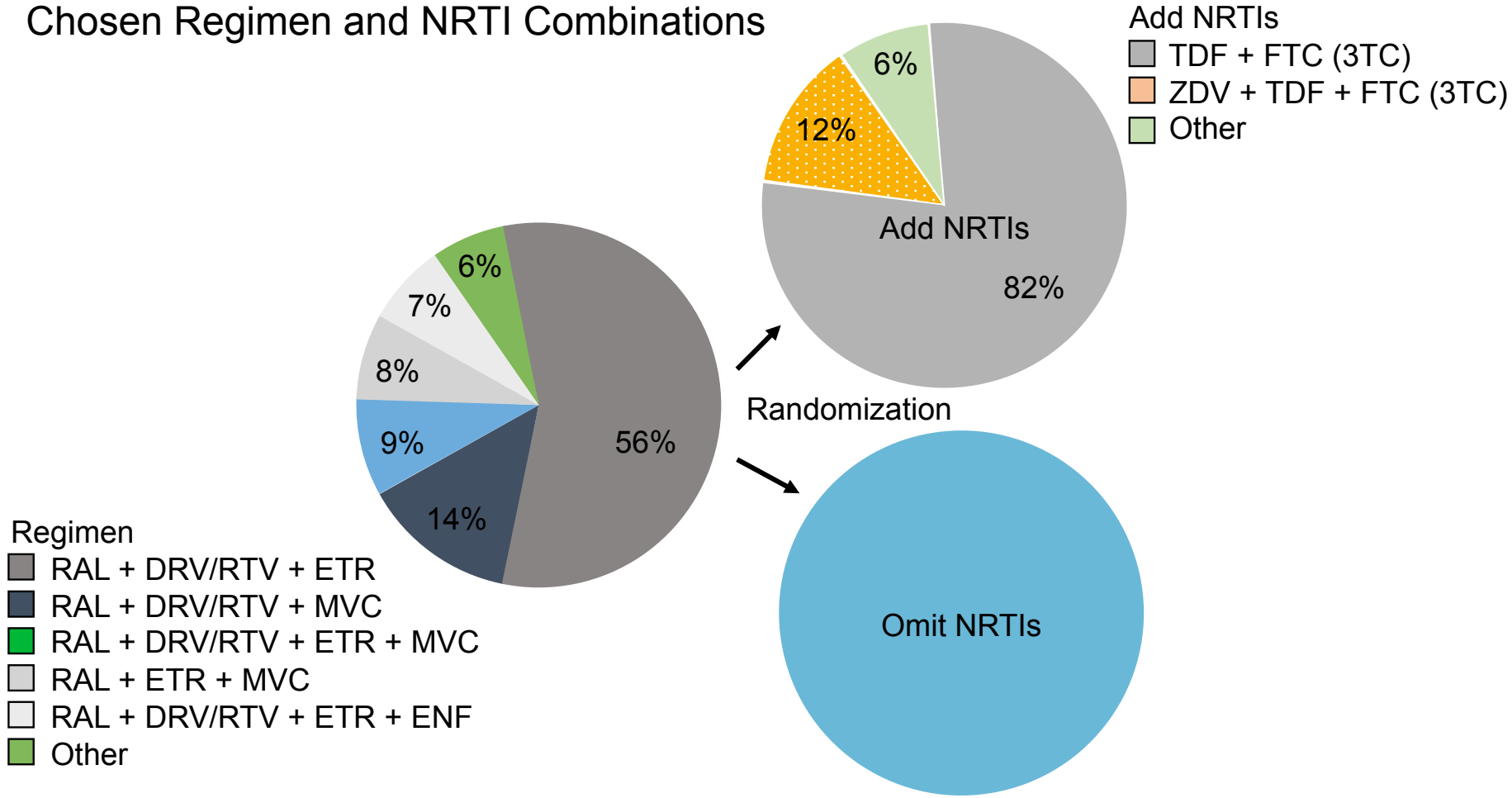


*20 potential 3- to 4-drug combinations including DRV/RTV, ENF, ETR, MVC, RAL, TPV/RTV. Individualized selection of regimens with PSS > 2.

Tashima K, et al. CROI 2013. Abstract 153LB.

OPTIONS: Pt-Specific Regimen Selected Then Randomized to ± NRTI

Chosen Regimen and NRTI Combinations

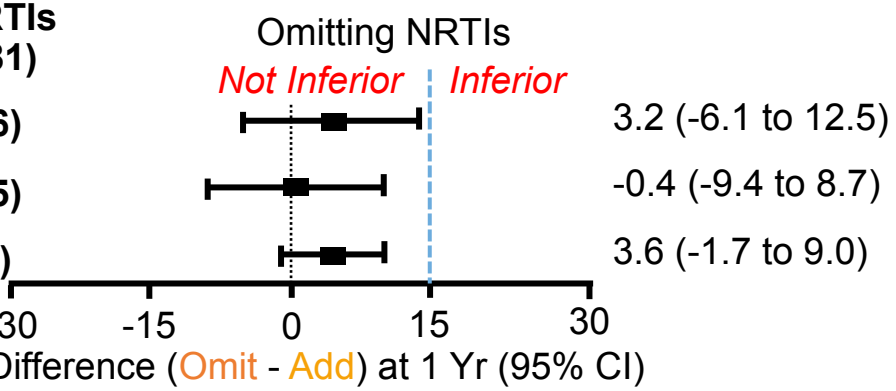


Tashima K, et al. CROI 2013. Abstract 153LB. Graphic used with permission.

OPTIONS: Omitting NRTIs Non-inferior to Adding NRTIs to Optimized Regimen

Primary Efficacy Outcome Comparisons

Outcome, n (%)	Omit NRTIs (n = 179)	Add NRTIs (n = 181)
Regimen failure	53 (30)	48 (26)
Virologic failure	44 (25)	45 (25)
Stop NRTI assignment	19 (8)	10 (6)

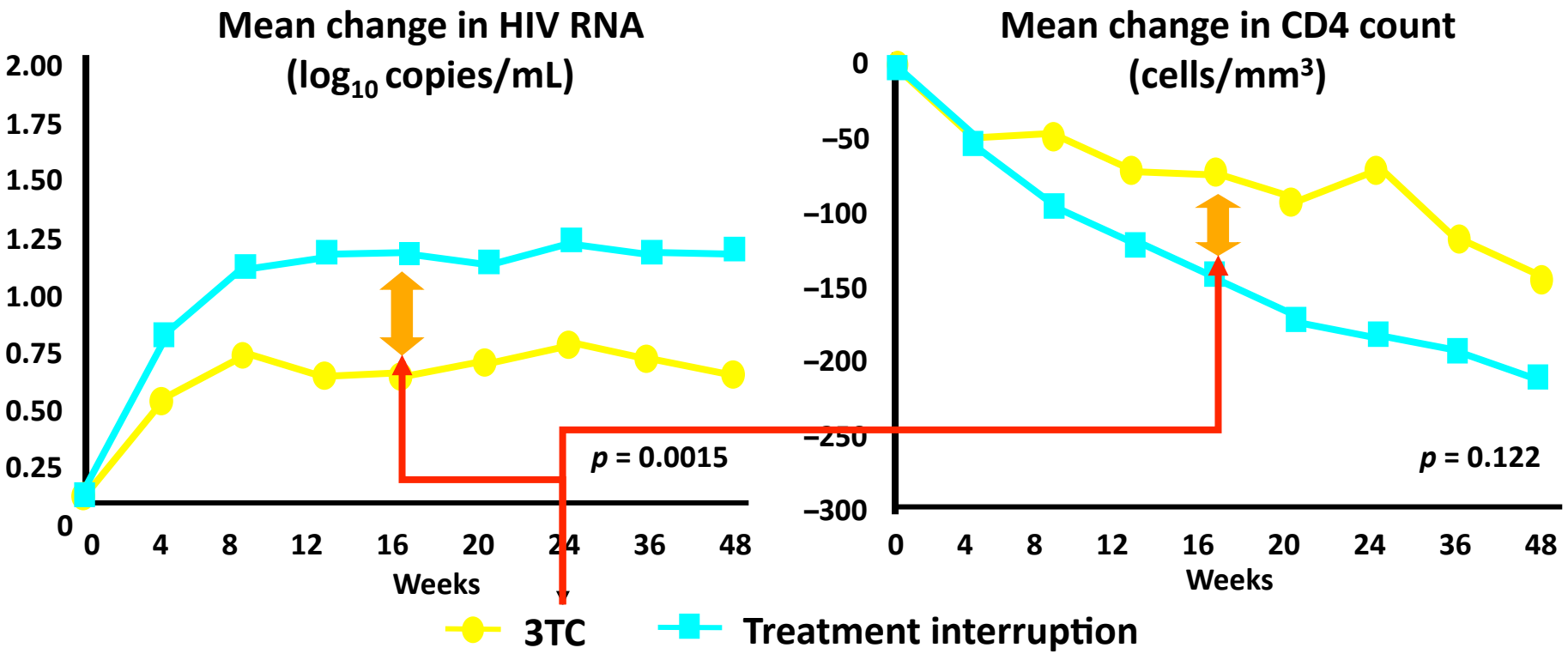


- Similar virologic suppression (HIV-1 RNA < 50 c/mL) in each arm (~ 65%)
- Similar CD4+ cell count increases in each arm (90-106 cells/mm^3)
- No significant difference in any safety outcome when globally evaluating symptoms and laboratory abnormalities
  - However, mortality significantly higher in NRTI-added arm ($P < .001$)
  - 6 deaths in NRTI arm, 2 possibly due to ART drug

Tashima KT, et al. CROI 2013. Abstract 153LB. Graphic used with permission.

Partial treatment interruption:
3TC monotherapy benefits over STI

- HIV RNA > 1000 copies/mL
- CD4 > 500 cells/mm^3
- Have M184V mutation



Castagna *et al*. *AIDS* 2006 20(6):795-803

What are you going to do?

She is currently on LOP/r/TDF/ABC

She wants to change her ART

Choices?

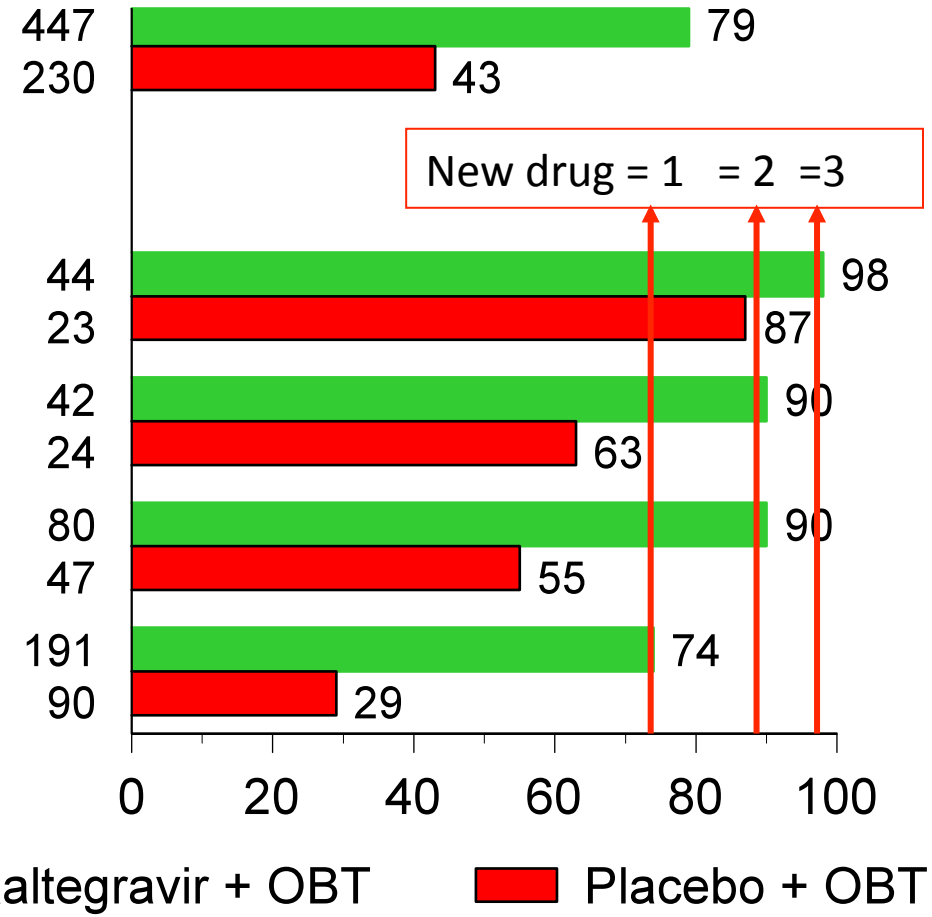
Fully active	Partially active	Some benefit
RAL	DAR/r	
MRV	TIP/r	3/FTC
T-20		

Data for >1 active drug + OBR in triple-class failure

Overall Efficacy Data

Efficacy by ARTs in OBT

Enfuvirtide	Darunavir
+	+
+	-
-	+
-	-



+ : First Use in OBT
- : No Use in OBT

*** Virological failures carried forward**

Cooper D et al., 14th CROI, Los Angeles 2007, #105aLB, Steigbigel R et al., 14th CROI, Los Angeles 2007, #105bLB

Patient

- Received adherence support

- DAR/r
- RAL/MAR
- TDF/FTC

- Has been undetectable since

Summary

- Antiretroviral resistance can seem confusing and complex
- A lot of it is actually quite simple
- People might bluff you with lots of numbers
  - You don't really need to know them as there are programmes to help

- It is important to understand:
  - How resistance develops
  - That it is archived forever
  - That you may not detect resistance even if it is there (look at previous regimens and if failed)

If time for discussion

Case 1

- 49 yr old MSM
- HIV diagnosed 2006
  - CD4 = 95
- Commenced on Nevirapine and Truvada (Tenofovir/ FTC)
  - Poor compliance → virologic failure
- Resistance testing:
  - K103N – NNRTI resistance
  - M184V – 3TC/FTC resistance

Case 1 cont.

- Intensive counselling
  - Compliance issues addressed
- Commenced on Atazanavir/ritonavir & Truvada
  - Remains undetectable since, good CD4
- Wants a single tablet regimen….
  - We have:
    - Atripla = Efavirenz, Tenofovir, FTC
    - Eviplera = Rilpivirine, Tenfovir, FTC
    - QUAD in the future (Elvitegravir, Cobicistat, Tenofovir, FTC)
- Can he have any of these?
- What are the issues?

Case 2

- 37 year old woman
- HIV positive, CD4 157
  - Referred from elsewhere
  - Diagnosed 6 weeks before, all other tests and baselines ‘normal’
- Commenced on Atripla (Efavirenz, Tenofovir, FTC)
- Viral load decreased from 780,000 to 12,000 over 6 weeks but then rebounded…
- Why?

Case 2 cont.

- Possibilities:
  - Poor compliance
  - Poor absorption / PK interactions
  - Virus was resistant already….
  - Something else

- In fact baseline resistance test was abnormal
  - Primary K103N resistance…
    - Which knocked out Efavirenz

Case 3

- 47 yr MSM
- HIV positive since 1991
  - Regimens:
    - AZT 1992 for two years
    - D4T, 3TC and Indinavir Oct ’97 to Nov ‘97
    - D4T, 3TC and Saquinavir Nov ’97 to March ‘98
    - DDI, Nevirapine, AZT and Indinavir Oct ’98 to Feb ‘99
    - DDI, Nevirapine, AZT, Nelfinavir and Ritonavir Feb ’99 to Apr ‘99
    - DDI, Nevirapine, AZT and Nelfinavir Apr ’99 to Dec 2000
    - AZT, 3TC and Abacavir Feb ’01 to Aug ’02
    - Lopinavir/ritonavir, 3TC and Abacavir till 1 month ago, when stopped treatment
- Resistance test now wild-type
- What more do I need to know and what can I use?

Case 3 cont.

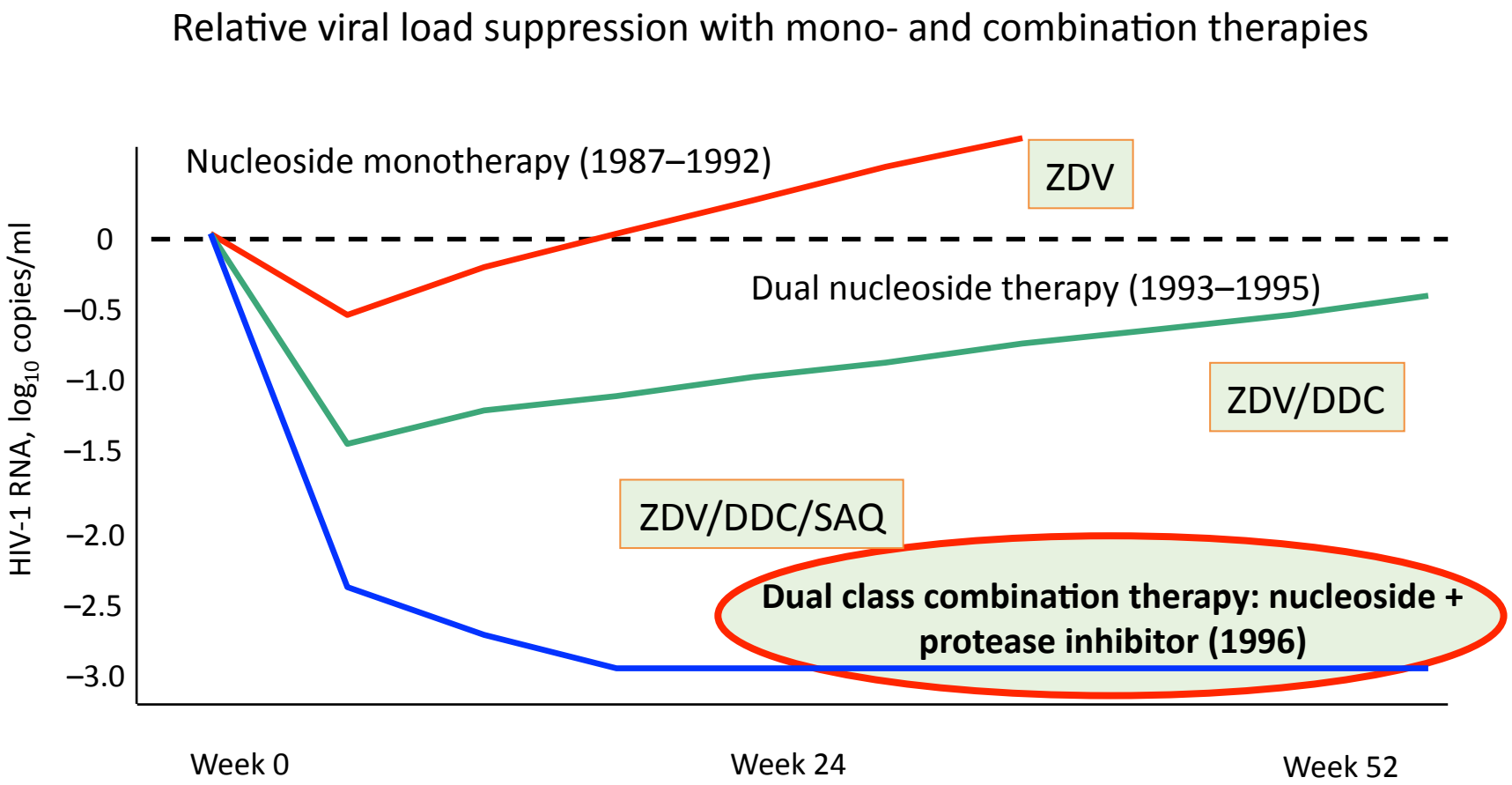
- Any previous resistance tests?
  - No
- Why did they switch previously - ?intolerance ? AEs
  - Generally from failure
- Therefore have to guesstimate resistance…
  - Multiple NRTI resistance
  - First-line NNRTI resistance
  - (Possible some PI resistance)

Case 4

- 27 yr woman
  - HIV positive 2009
- Commenced Efavirenz, AZT, 3TC
  - Complied and was undetectable for 2 years
- Then lost job, got fed up etc. and stopped therapy
  - Now off therapy for 1 year
  - Resistance test wild-type
- Do I have to be wary of any resistance?
- May have had a ‘functional monotherapy’ for a while…

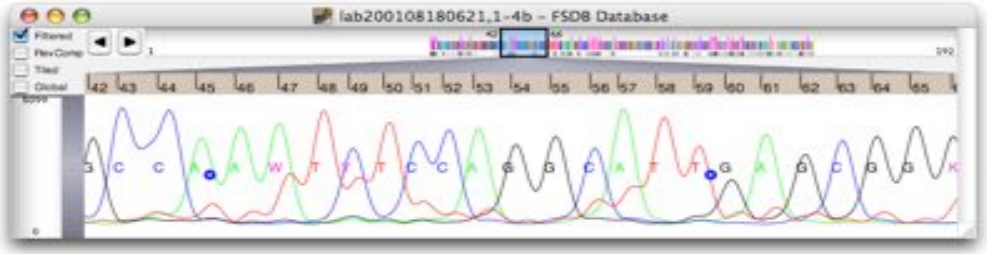
Data was limited

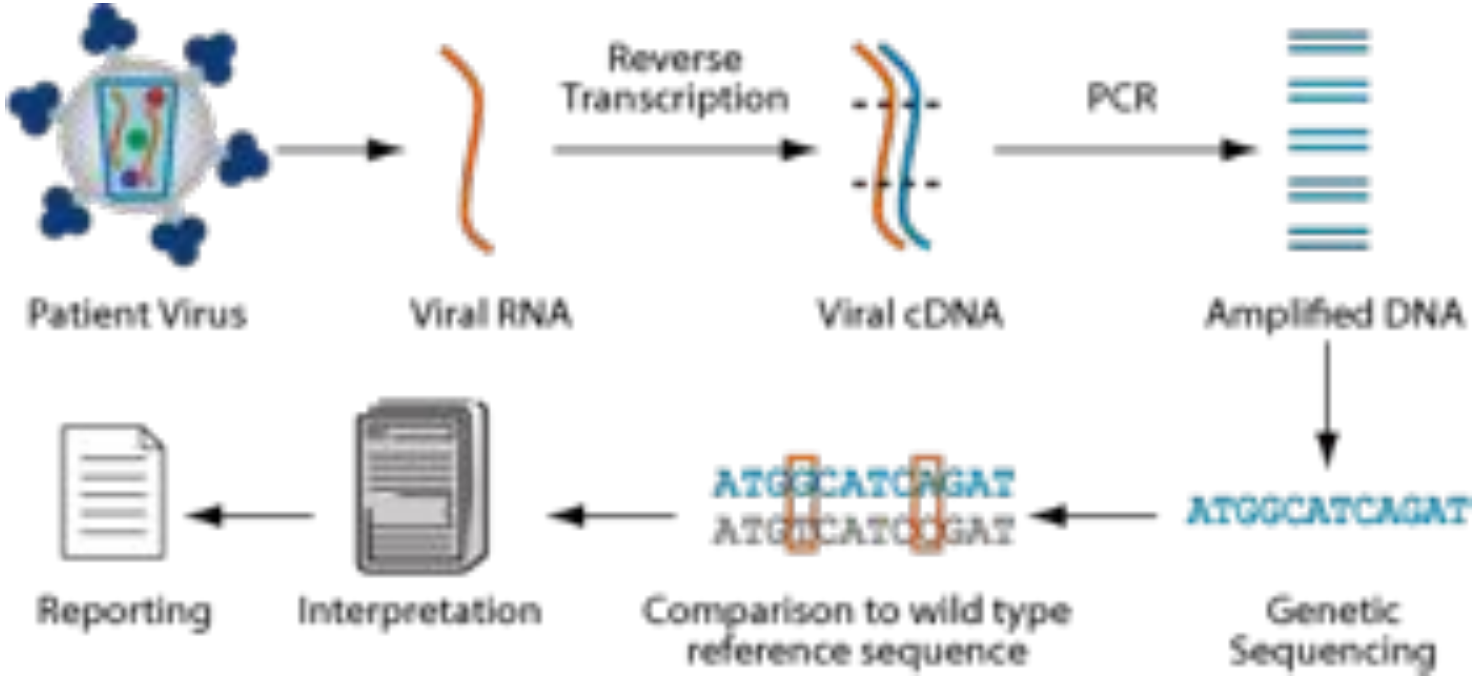
And ART was still a pipedream



Adapted from Facui, AS. Nat. Med 2003. 6: 839–843

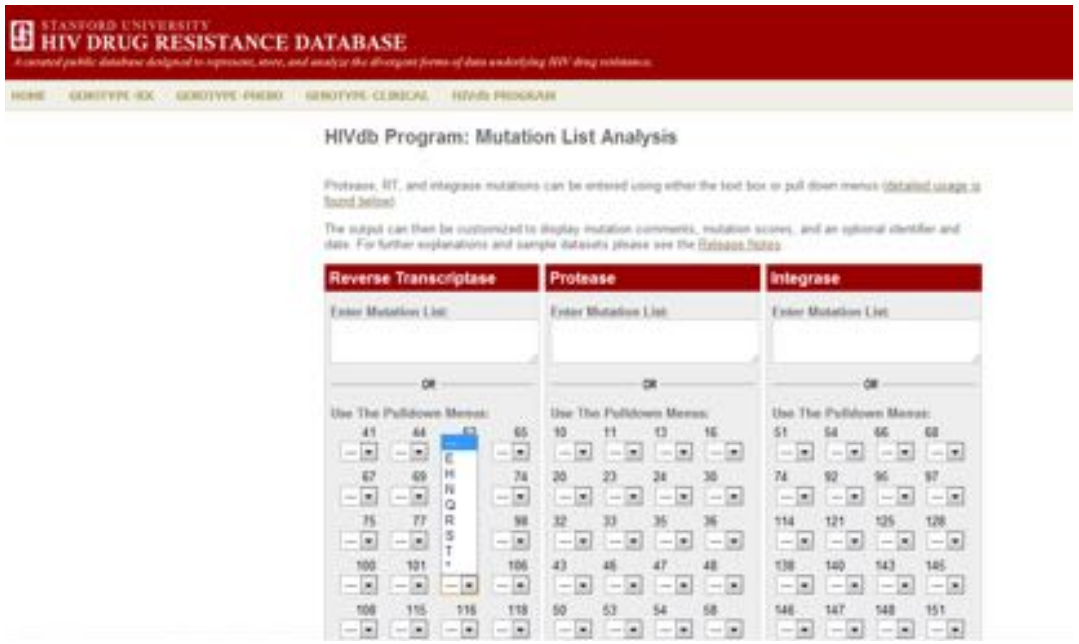
You request a resistance test - how does it work?

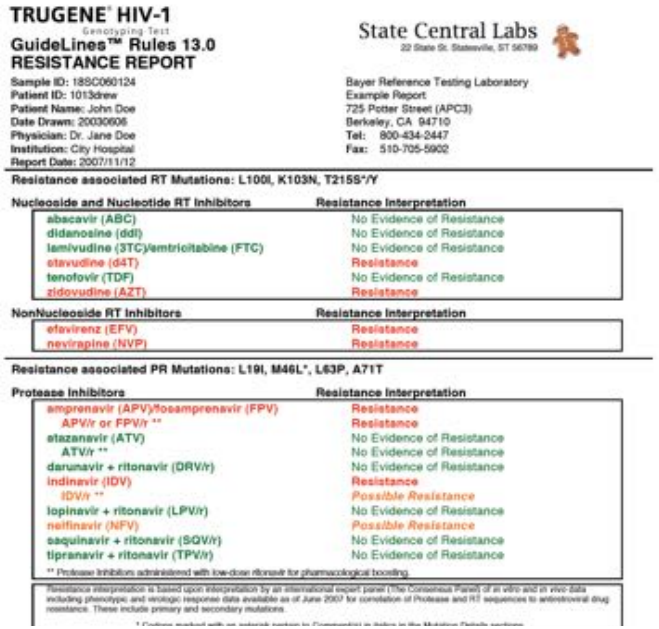




And how do you interpret?

- **Genotypic** Testing: Prediction of phenotype based on sequence

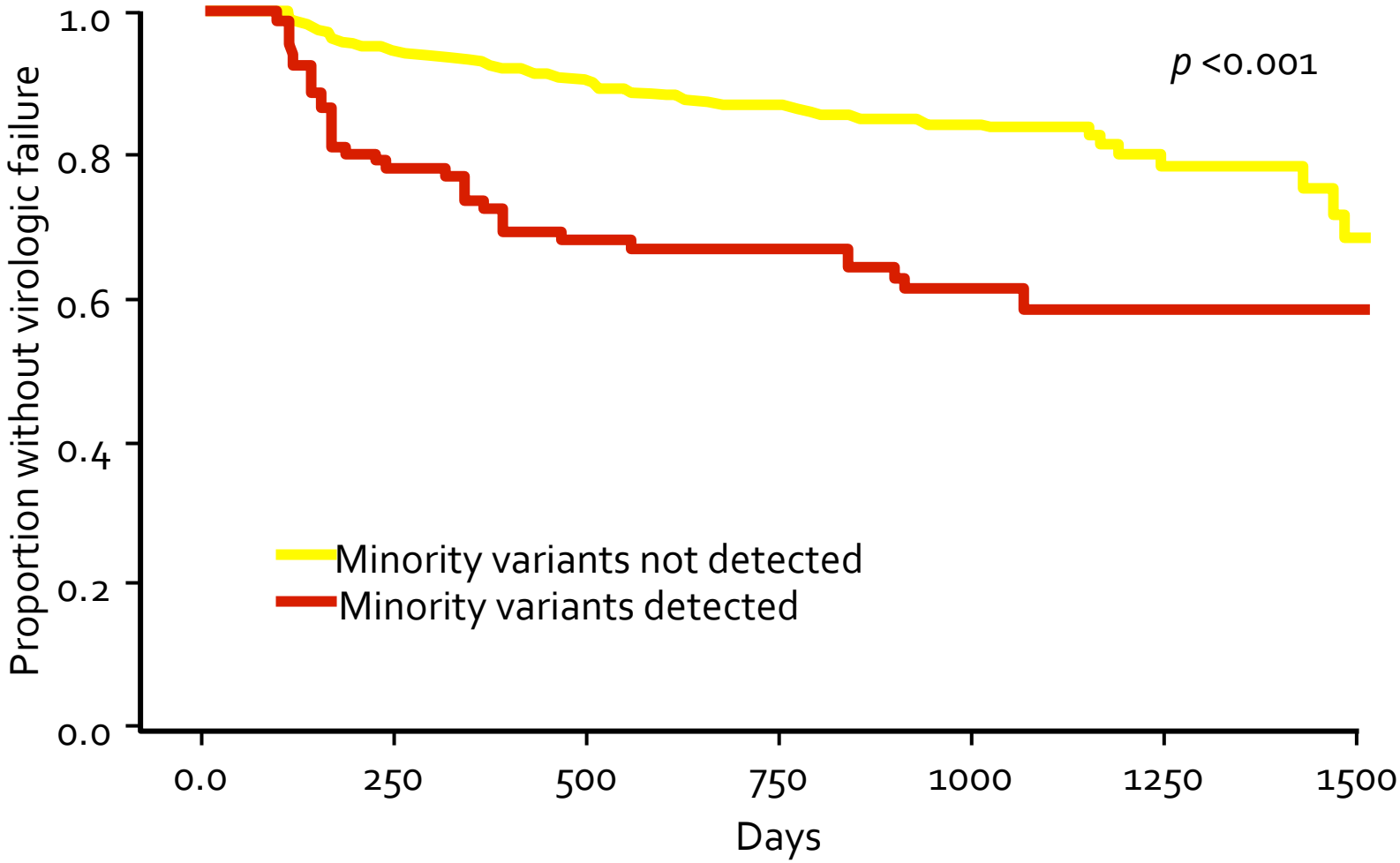




Limitations of resistance testing

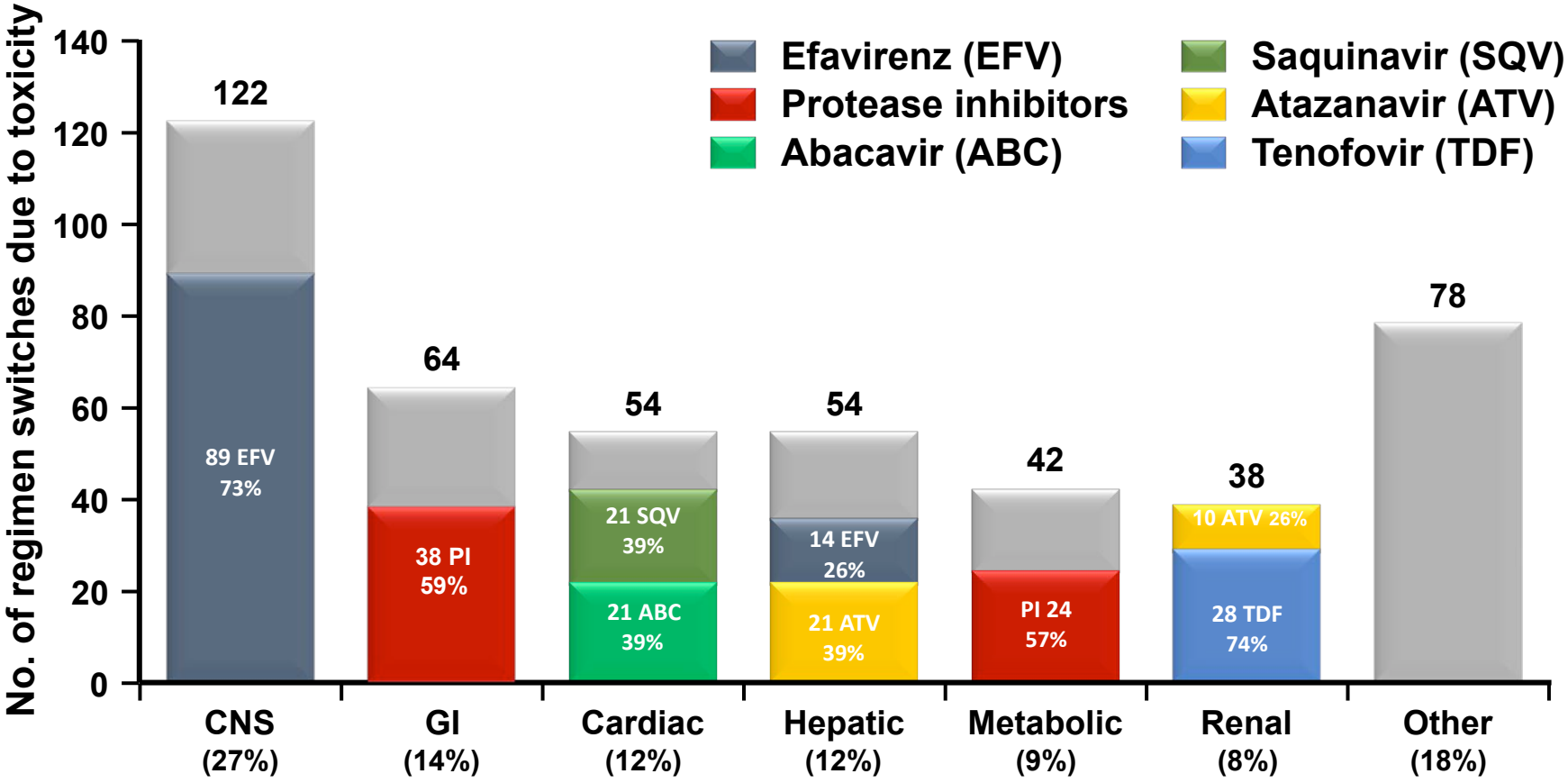
- Population sequencing
  - Standard resistance testing will only detect mutations that are in >20% of the circulating virus

Kaplan-Meier curves for the proportion of patients without virologic failure



Drugs still main reason to switch…

- 452 switches due to toxicity/perceived toxicity

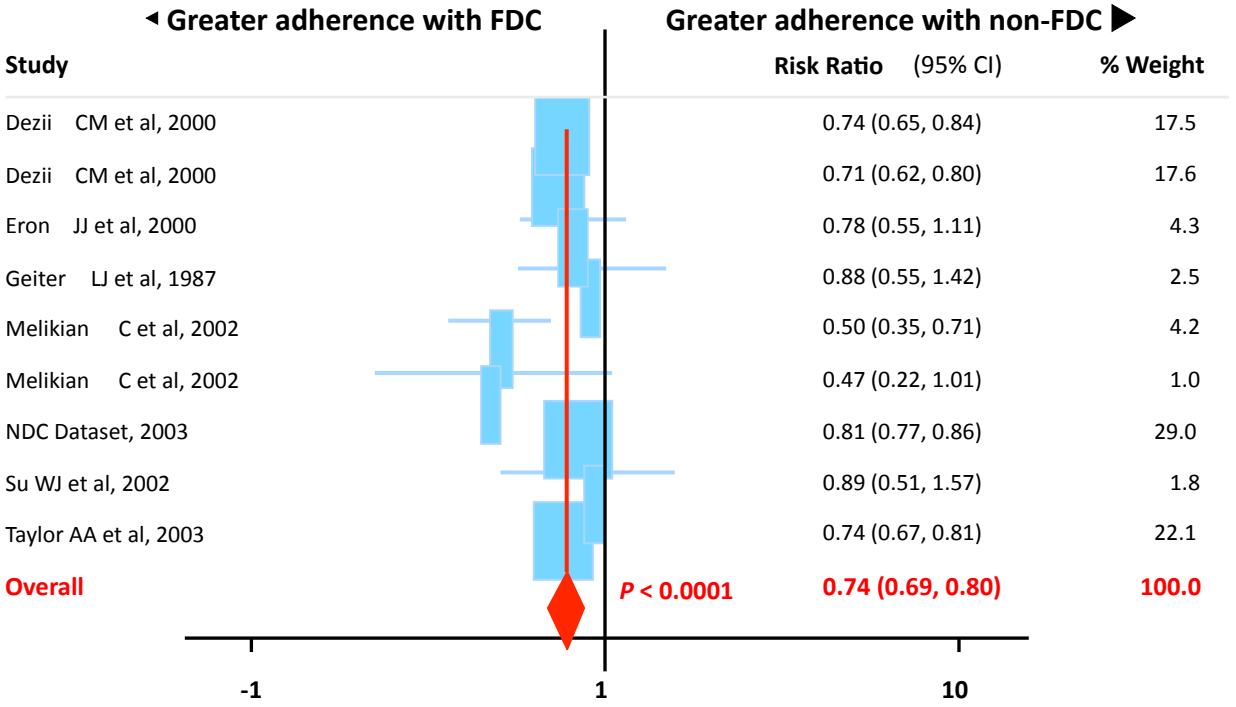


Boyle A *et al.* HIV11 Glasgow 2012, UK - abstract O312

Adherence benefits of STR/ FDC

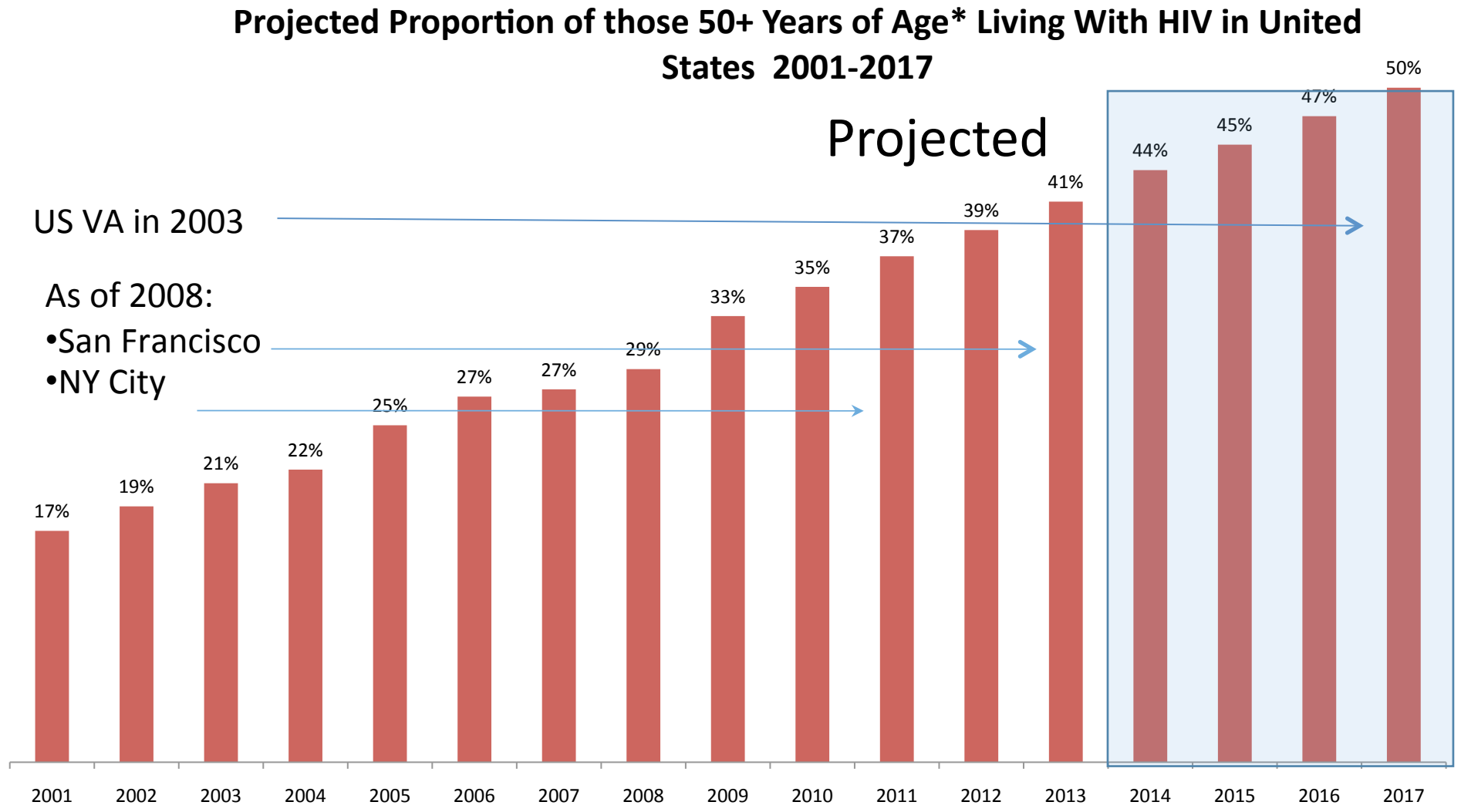
Meta-analysis of 9 clinical trials in 4 therapeutic areas (TB, HTN, HIV, DM)
11,925 FDC patients and 8317 non-FDC patients

Effect of FDCs versus non-FDC on risk of non-adherence



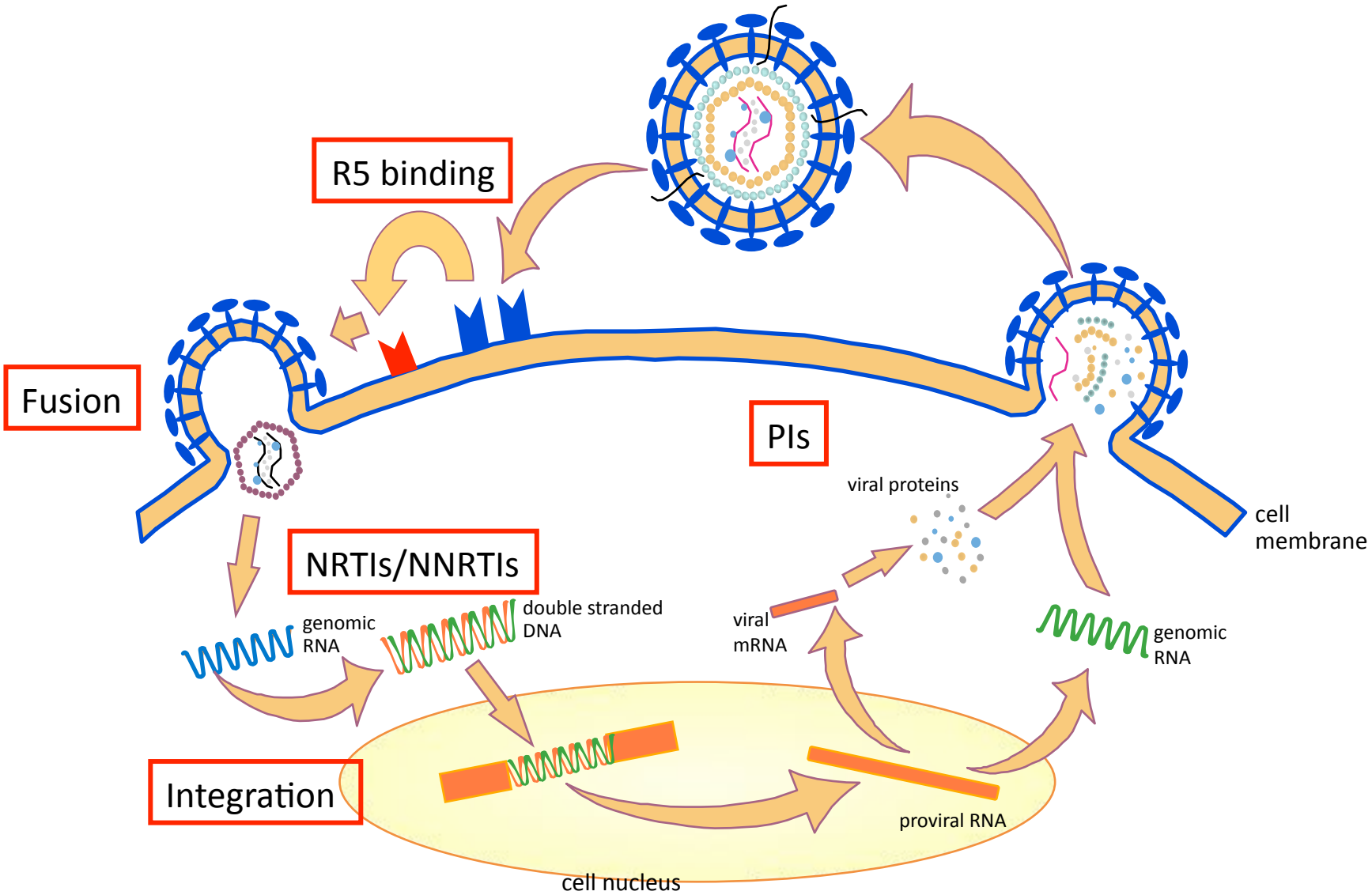
FDC regimens reduce risk of non-adherence by ~25% (compared to dosing with individual pills)

Drugs associated with ageing



*Data from 2008, onward projected based on 2001-2007 trends (calculated by author), 2001-2007 data from CDC Surveillance Reports 2007. New York and San Francisco data from their Departments of Public Health.

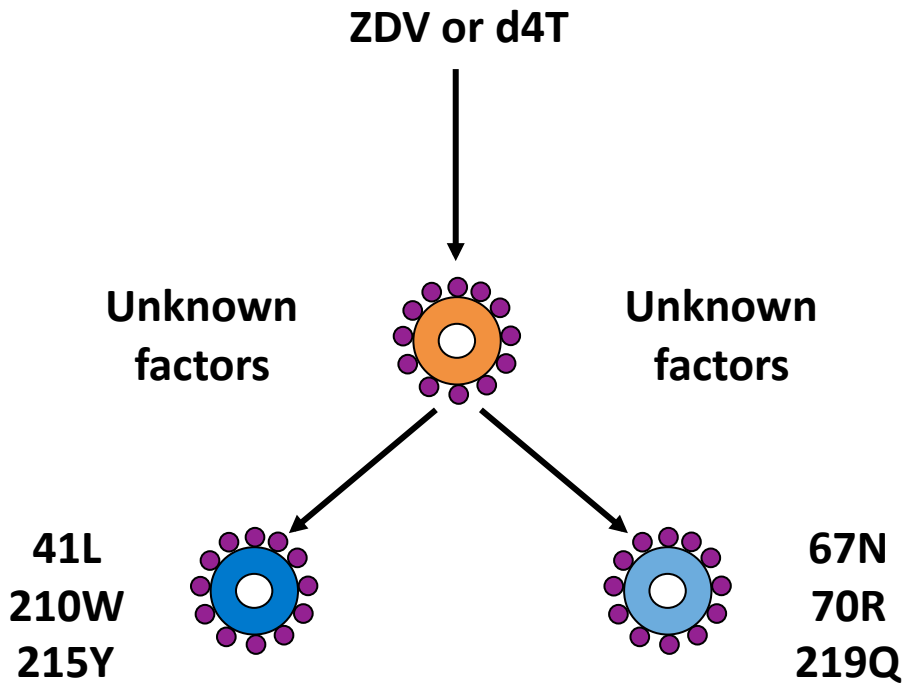
HIV lifecycle and where ARVs act….



Resistance: not always so simple – NRTIs. Dichotomous Pathways to Resistance

TAMs emerge sequentially with ZDV- and d4T-containing regimens after M184V

6 identified:
M41L, D67N, K70R, L210W, T215Y/F, K219Q/E/N/R



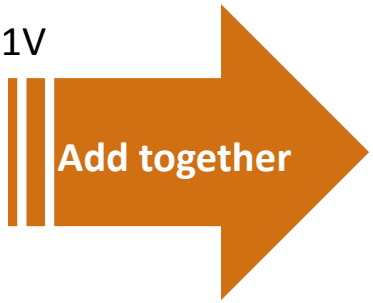
Higher-level ZDV resistance
More NRTI cross-resistance
Less effect of M184V

Lower-level ZDV resistance
Less NRTI cross-resistance
Greater effect of M184V

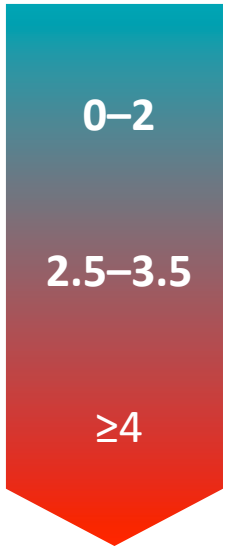
Resistance not always so simple – NNRTIs Weighting mutation system helps predict response

Relative weight* for individual ETR RAMs

1	1.5	2.5	3
V901	V106I	L100I	Y181I
A98G	E138A	K101P	Y181V
K101E	V179F	Y181C	
K101H	G190S	M230L	
V179D			
V179T			
G190A			



Total weighted genotypic score



Highest response

Intermediate response

Reduced response

Example: K101H + G190A = Weighted score of 2 = Highest response

*When the genotype report shows a mixture of two or more different substitutions at the same position, only the highest of the individual weight factors for these substitutions is counted when calculating the weighted genotypic score.

Vingerhoets J, et al. 17th IHDRW 2008 [Poster 24].

Resistant to resistance: boosted PI's

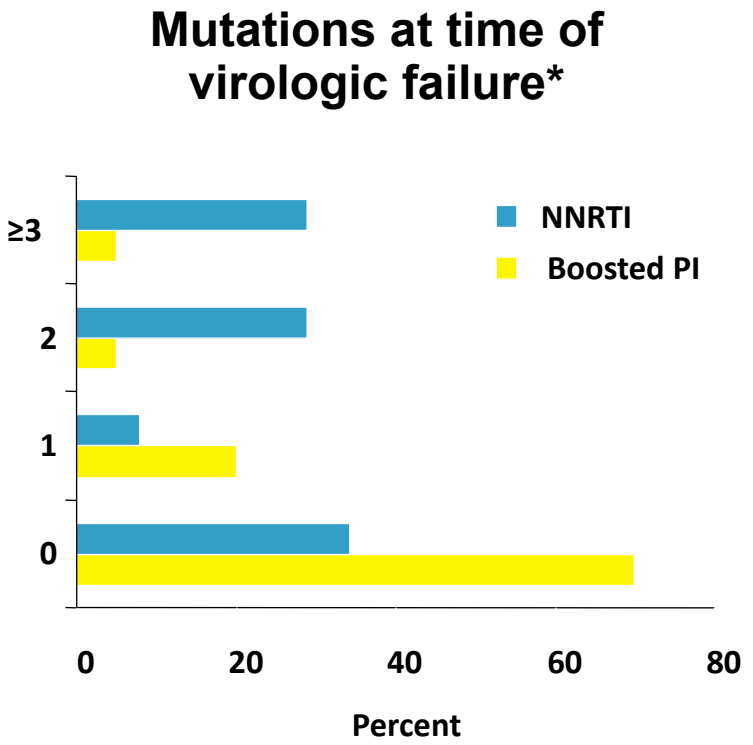
	Quad (n=353)	ATV/r + FTC/TDF (n=355)
Subjects Analyzed for Resistance[a], n (%)	12 (3)	8 (2)
Subjects with Resistance to ARV Regimen, n (%)	5 (1)	0
Any Primary Integrase-R, n	4	-
E92Q	1	-
T66I	1	-
Q148R	2	-
N155H	2	-
Any Primary PI-R, n	-	0
Any Primary NRTI-R, n	4	0
M184V/I	4	
K65R	1	

DeJesus E, et al., CROI 2012; Seattle. Poster 627.

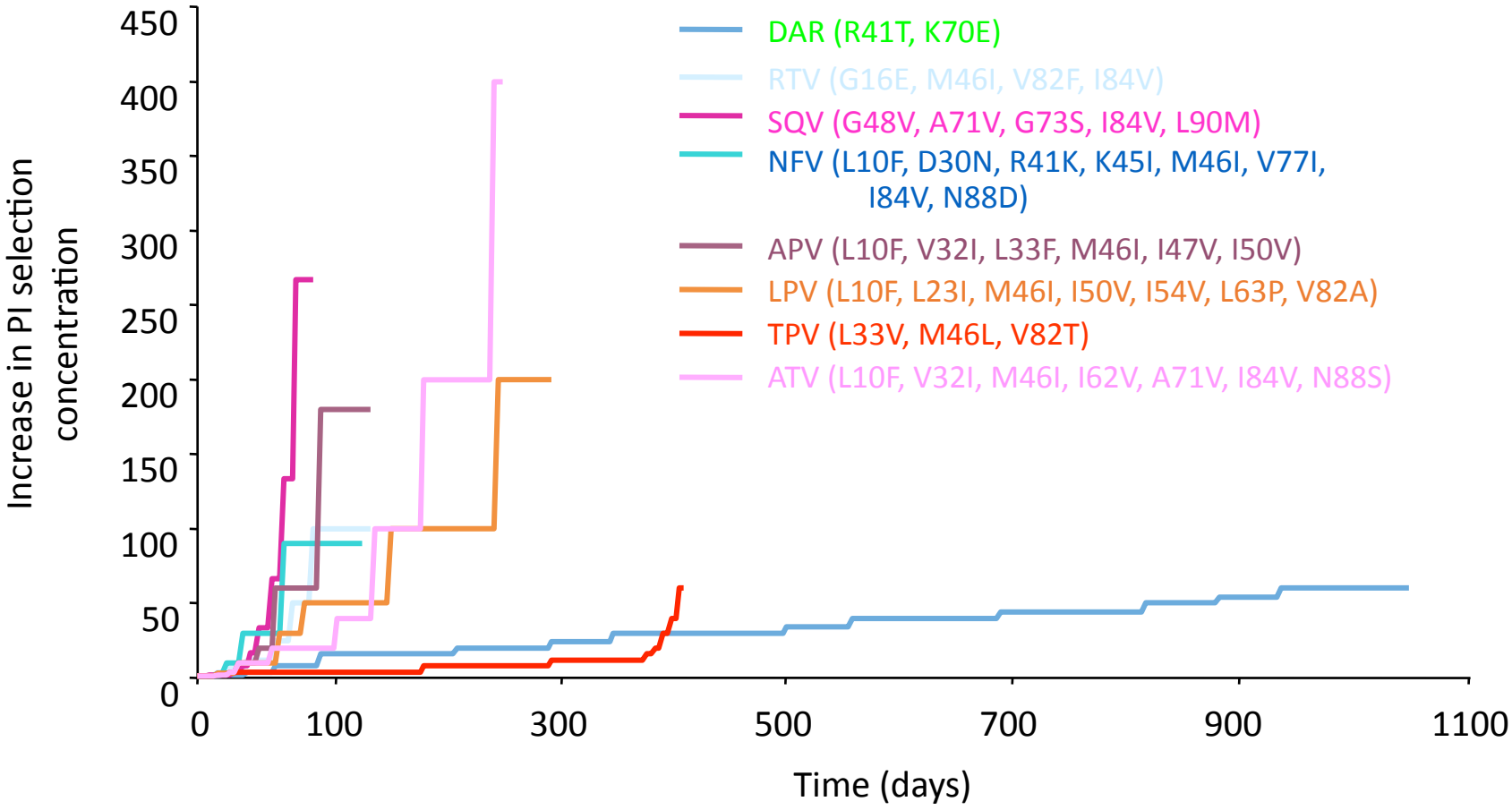
Boosted PIs protect against emergence of drug resistance after 1st line ART

Swiss Cohort Study

- Combination ARV therapy started Jan 1999 – Dec 2005 (n=1323)
  - Boosted PI (n=518)
  - NNRTI (n=805)
- Viral failure (defined as HIV RNA >500 c/mL after more than 180 days of treatment) by third agent
  - Boosted PI (n=4.6%); NNRTI (n=5.6%)
  - No difference by regimen but more resistance emerged with NNRTI-based regimens



But also differences…



De Meyer S, *et al. Antimicrob Agents Chemother.* 2005;49: 2314-21.
De Meyer S, *et al. XV IHDRW,* 2006, Poster 19.

Resistance not always so simple – PIs

DRV Weighting mutation system helps predict response

Estimated increase in FC	<2	2 to 3	3 to 4	>4
Mutations	V11I	V32I	I54M	I50V
	I54L	L33F	L76V	
	G73S	I47V	I84V	
	L89V			

Add mutations up for fold-change

Example: = ~ 5–7 fold-change = **Intermediate activity**

De Meyer S, *et al*. IHDRW 2006;Abstr. 73.
Data on file. Tibotec Therapeutics. 2006.

And for tipranavir….

- 1	0.5	1	2
L24I	L10V/I	V11L	I47V
D30N	I13V	V32I	I54A
I50L/V	K20R	A71L	V82T
154L	M46L	G73T	I84V
L76V	L90M	L89V	
V82I			

Add mutations up for fold-change

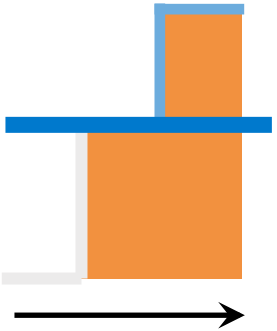
Example: = ~ 4 fold-change = **Intermediate activity**

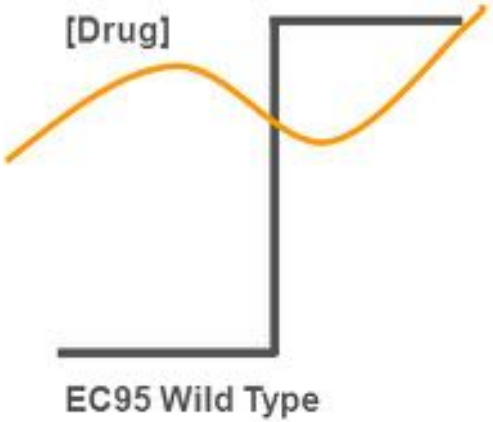
De Meyer S, *et al*. IHDRW 2006;Abstr. 73.
Data on file. Tibotec Therapeutics. 2006.

Single mutation leading to resistance – all or nothing

First-generation NNRTI

One mutation correlates with reduced virological response





Increasing number of mutations at baseline

1. Antinori A, et al. AIDS Res Hum Retroviruses. 2002;18:835–8.
2. Lecossier D, et al. J Acquir Immune Defic Syndr. 2005;38:37–42.
3. Vingerhoets J, et al. 17th IDHRW 2008 [Poster 32].
4. De Béthune MP, et al. 4th EHDRW 2006 [Poster 51].
5. de Mendoza C, et al. HIV Clin Trials. 2006;7:163–71.

Thank you

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