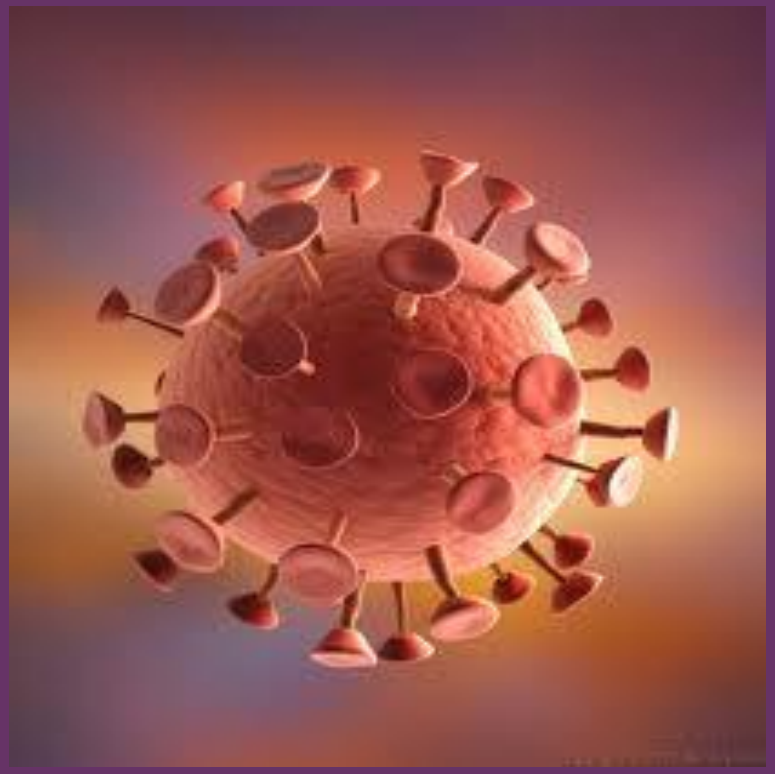
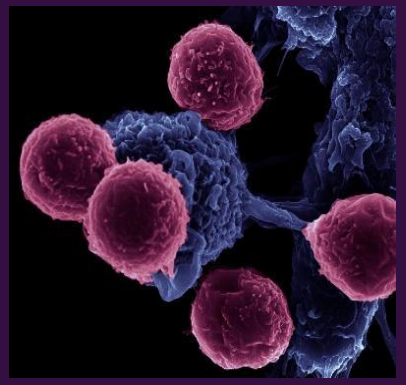


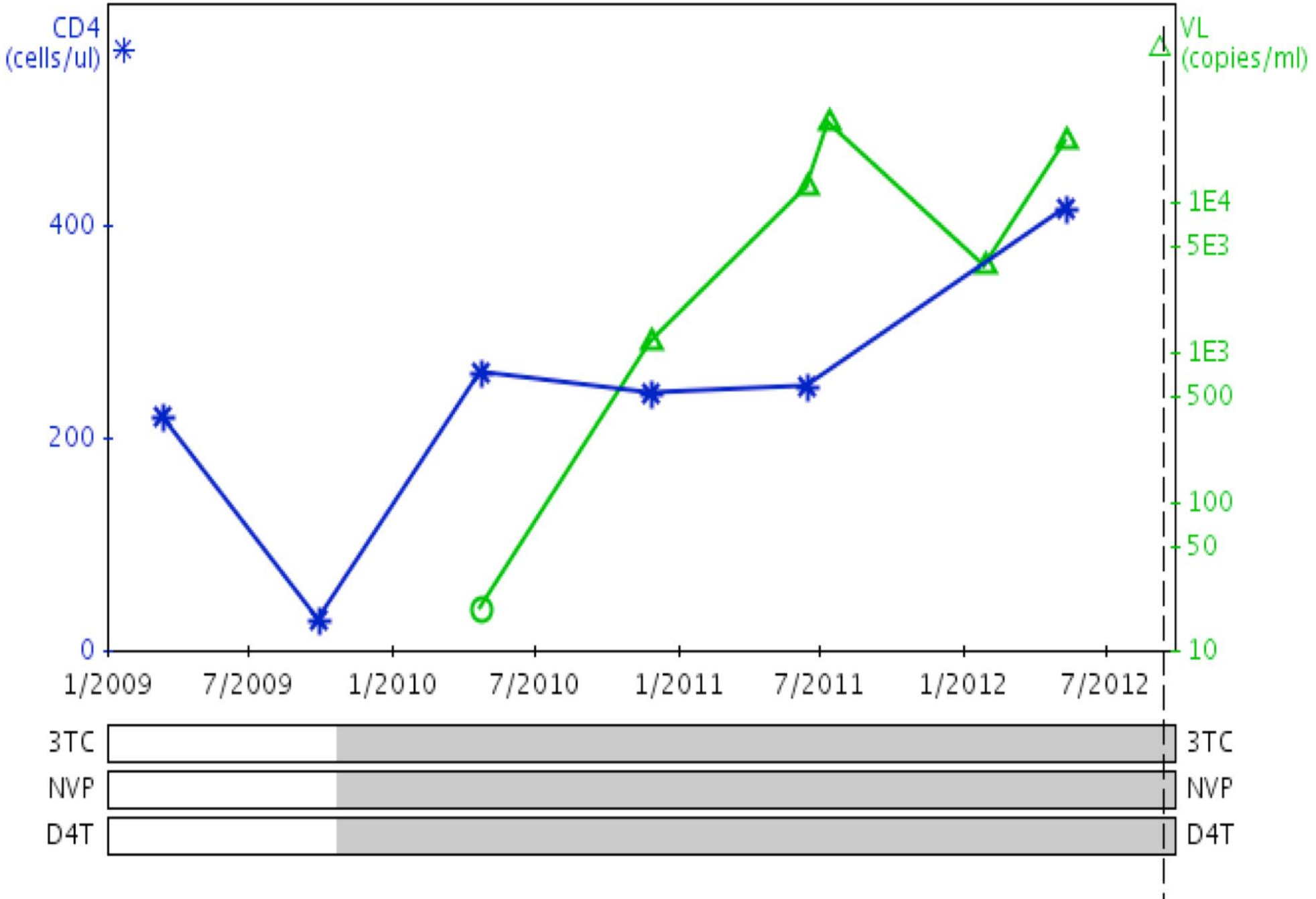


Viral Fitness – A Clinical Look

Dr Theresa Rossouw

University of Pretoria

+ Patient 1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3TC
NVP
D4T
3TC
NVP
D4T

Question 1: Do you think this patient has resistance?

A. Yes

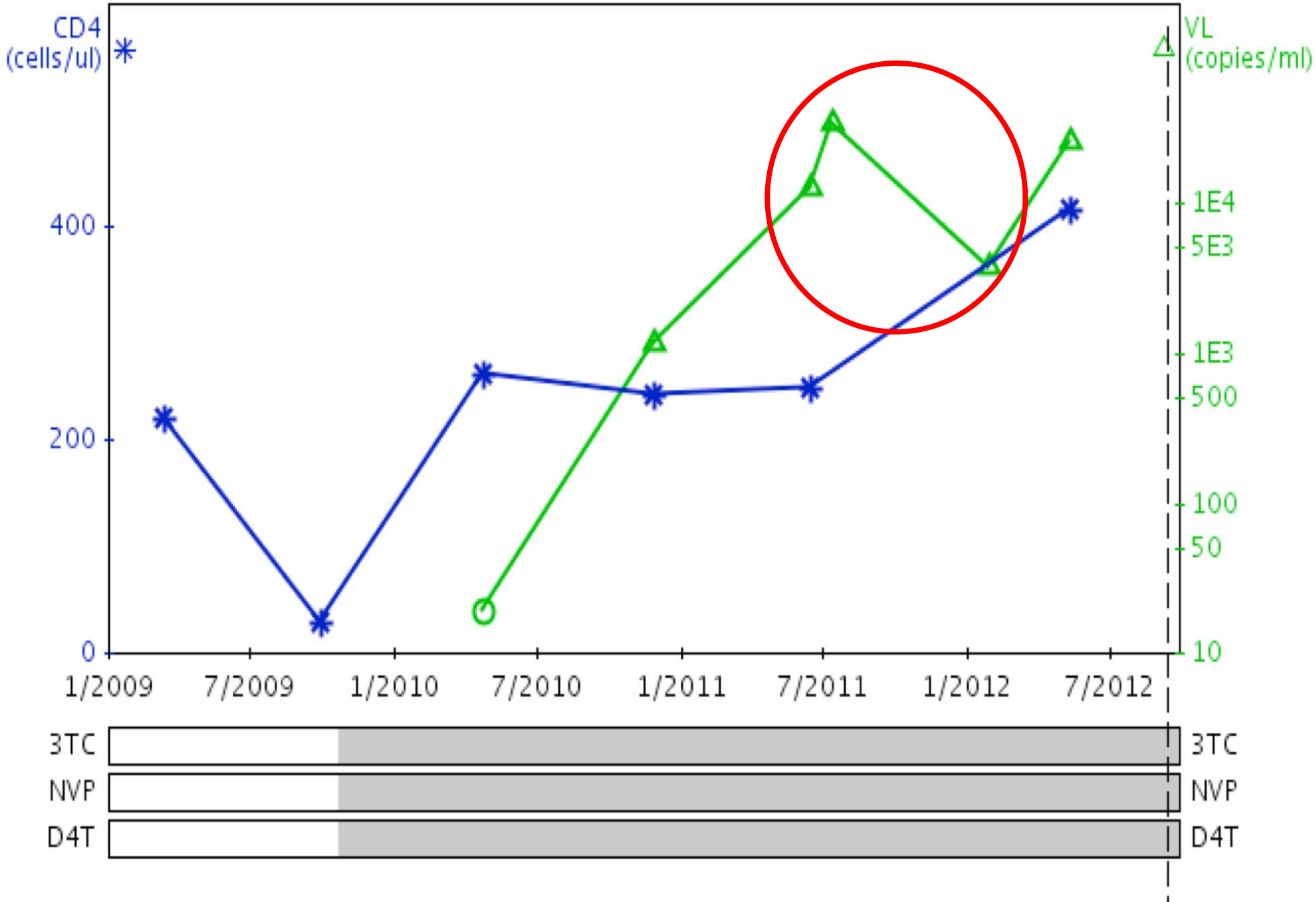
B. No

C. I don't know

Question 2: How many mutations do you think this patient has?

A. None
B. One
C. Two
D. Three
E. More than three

+ Patient 1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3TC
NVP
D4T
3TC
NVP
D4T

Question 3: Why did the VL drop?

A. Patient had stopped ART and has now restarted it

B. Patient had been on treatment all-along but now the adherence has improved

C. Patient has developed resistance to one or more of the drugs

D. I don't know

+ Resistance Profile

Drug	Mutations	Description	Level	GSS
zidovudine	181C 184V	Susceptible	1	1.0
zalcitabine	N/A	N/A	N/A	N/A
didanosine	184V	Susceptible	1	1.0
lamivudine	184V	High-level resistance	5	0.0
stavudine	184V	Susceptible	1	1.0
abacavir	184V	Potential low-level resistance	2	1.0
emtricitabine	184V	High-level resistance	5	0.0
tenofovir	181C 184V	Susceptible	1	1.0
nevirapine	101Q 103N 138K 181C	High-level resistance	5	0.0
delavirdine	101Q 103N 138K 181C	High-level resistance	5	0.0
efavirenz	101Q 103N 138K 181C	High-level resistance	5	0.0
etravirine	101Q 103N 138K 181C	High-level resistance	5	0.0
saquinavir	N/A	N/A	N/A	N/A
saquinavir/r		Susceptible	1	1.0
ritonavir	N/A	N/A	N/A	N/A
indinavir	N/A	N/A	N/A	N/A
indinavir/r		Susceptible	1	1.0
nelfinavir		Susceptible	1	1.0
fosamprenavir	N/A	N/A	N/A	N/A
fosamprenavir/r		Susceptible	1	1.0
lopinavir/r		Susceptible	1	1.0
atazanavir	N/A	N/A	N/A	N/A
atazanavir/r		Susceptible	1	1.0
tipranavir/r		Susceptible	1	1.0
darunavir/r		Susceptible	1	1.0

Question 4: Will you change this patient's treatment?

A. Yes

B. No

Question 5: What will be your next regimen of choice?

A. d4T, 3TC, EFV

B. d4T, 3TC, LPV/r

C. AZT, 3TC, LPV/r

D. TDF, FTC, LPV/r

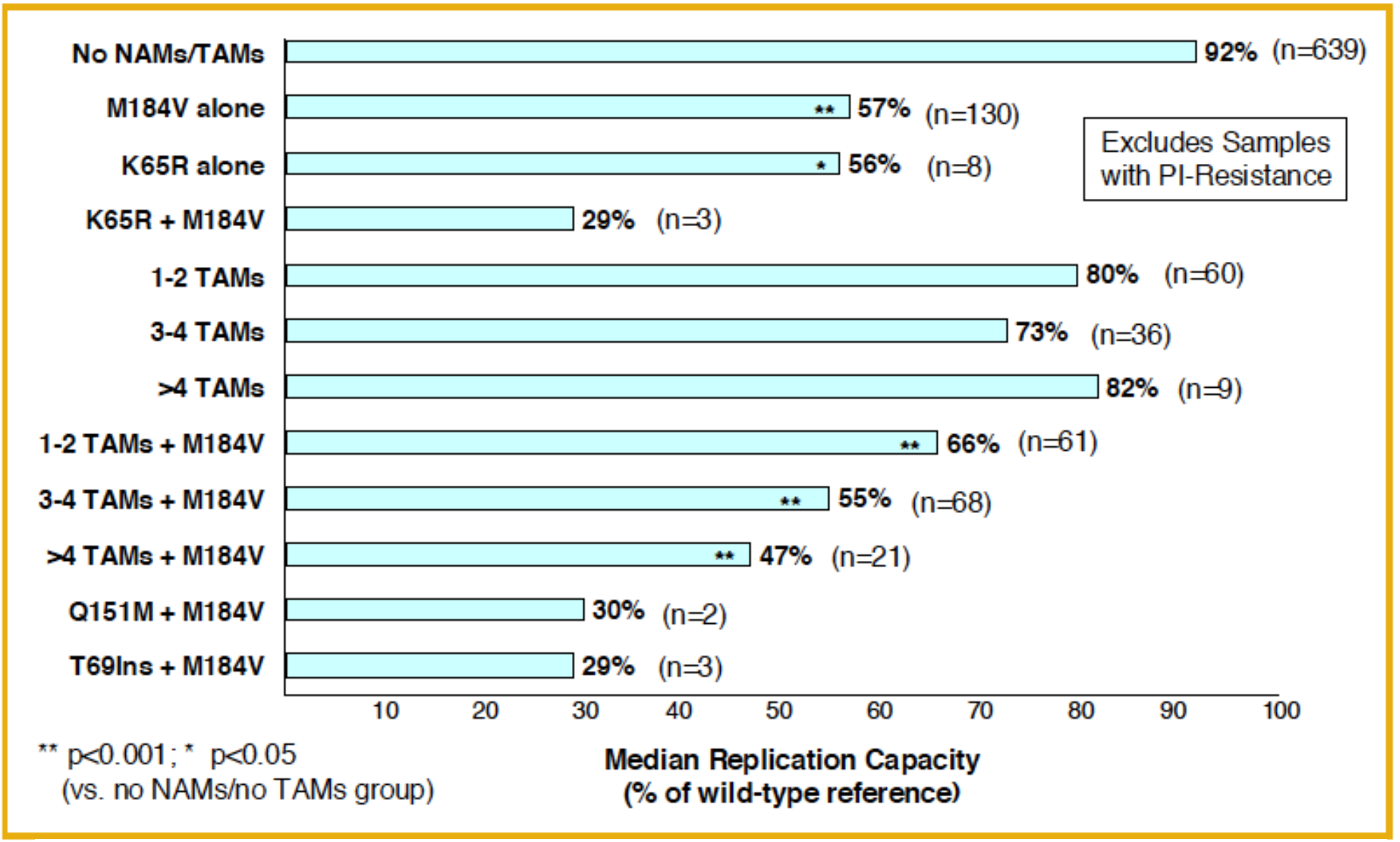
E. AZT, ABC, LPV/r

Questions to Consider

- Why do we recycle 3TC?
- Why can we get away with using only 2 active drugs?
- Why do we not recycle NNRTIs?

Poster Number
616
10th Conference on Retroviruses and Opportunistic Infections
February 10-14, 2003
Boston, Massachusetts

Figure 5 • Replication Capacity of HIV without Protease Inhibitor Resistance Mutations (n=1040)



Decreased Replication Capacity of HIV-1 Clinical Isolates Containing K65R or M184V RT Mutations

MD Miller[1], KL White[1], CJ Petropoulos[2], NT Parkin[2]

Mutation	Drug Affected	Effect
Reverse Transcriptase		
K65R, L74V, W88G, Y181C, and/or M184V*	Zidovudine, possibly stavudine†	Increased sensitivity of wild-type virus; partially reverse effects of TAMs
K65R, T69X, M184IV, and/or K65R/M184IV	Efavirenz	Hypersusceptibility
TAMs (V118I, H208Y, T215Y)‡	NNRTIs	Hypersusceptibility; uncertain effect on NNRTI resistance
Protease		
D30N (with or without N88S)§	Amprenavir	Hypersusceptibility
I47A in HIV-1 and V47A in HIV-2	Saquinavir	Hypersusceptibility
I50L and I50L/A71V	PIs (except atazanavir)	Hypersusceptibility; partially reverses resistance to other PIs
V82T§	Saquinavir	Hypersusceptibility
N88S	Amprenavir	Hypersusceptibility

*The M184V mutation also enhances susceptibility to tenofovir, but K65R reverses this hypersusceptibility.
†The Y181C and M184V mutations enhance susceptibility to stavudine, but the effect of L74V and W88G on stavudine susceptibility is not well documented. The K65R mutation confers cross-resistance to stavudine.
‡In some analyses, the M41L, D67N, T69D, L74V, V75, K103R, V179I, M184V, L210W, T215Y, and K219Q mutations have been implicated in NNRTI hypersusceptibility.
§Not confirmed in clinical isolates.

Resistance to AZT

M184V–induced Hypersusceptibility

- M184V & Y181C (and L74V) are close to active site of HIV-1 RT
- Reduce the rate of nucleotide excision → called primer unblocking
- This increases the sensitivity of RT to inhibition by AZT
- Also suppresses effects of AZT mutations (re-sensitisation)
- Similar effect on susceptibility to TDF & d4T
- But effect may be transient and followed by evolution towards highly-mutated strains with broad resistance patterns

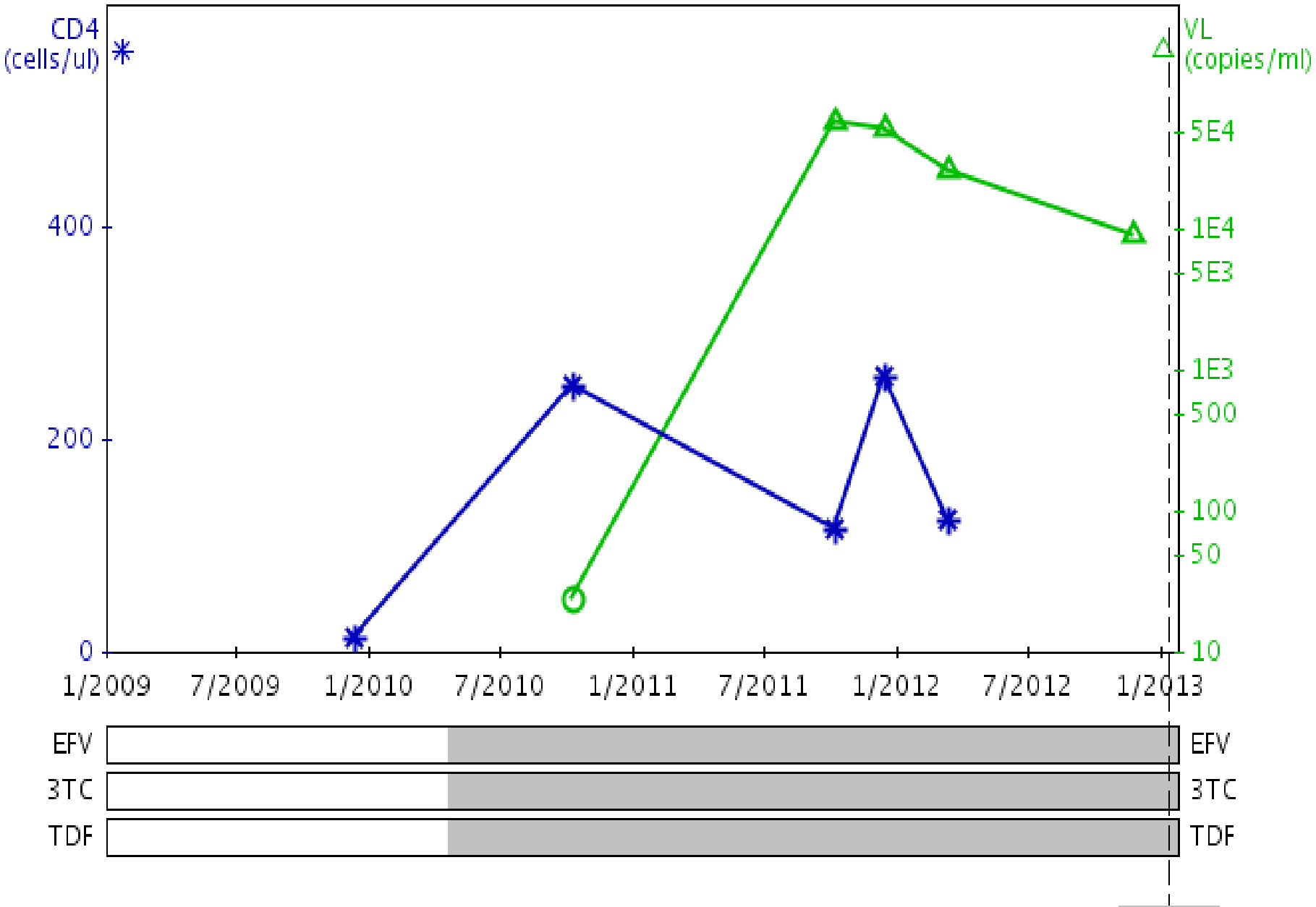
Outcome of 2nd-line regimens

- In patients with M184V as sole NRTI resistance mutation (± NNRTI mutations), comparable rates of VL suppression after switch to any of the following regimens:
  - 3TC/FTC + NRTI + boosted PI
  - 3TC/FTC + NRTI + boosted PI + additional active agent(s)
  - 3TC-sparing regimen
    - 2 NRTIs + boosted PI ± other active agent(s)
- Early detection of isolated M184V & switch to boosted PI + 3TC/FTC-based regimen can achieve VL suppression without the need to switch to more complex regimens

Why don't we recycle NNRTIs?

- Continuing NNRTI when K103N is present provides little clinical benefit
- May complicate use of PI because of drug interactions
- May select for additional NNRTI mutations that can affect 2nd gen NNRTIs
- Secondary (compensatory) mutations emerge to restore the replicative capacity of the virus
- Similar to other NRTIs and PIs
- This is unlike the M184V mutation which is an evolutionary dead end for the virus

+ Patient 2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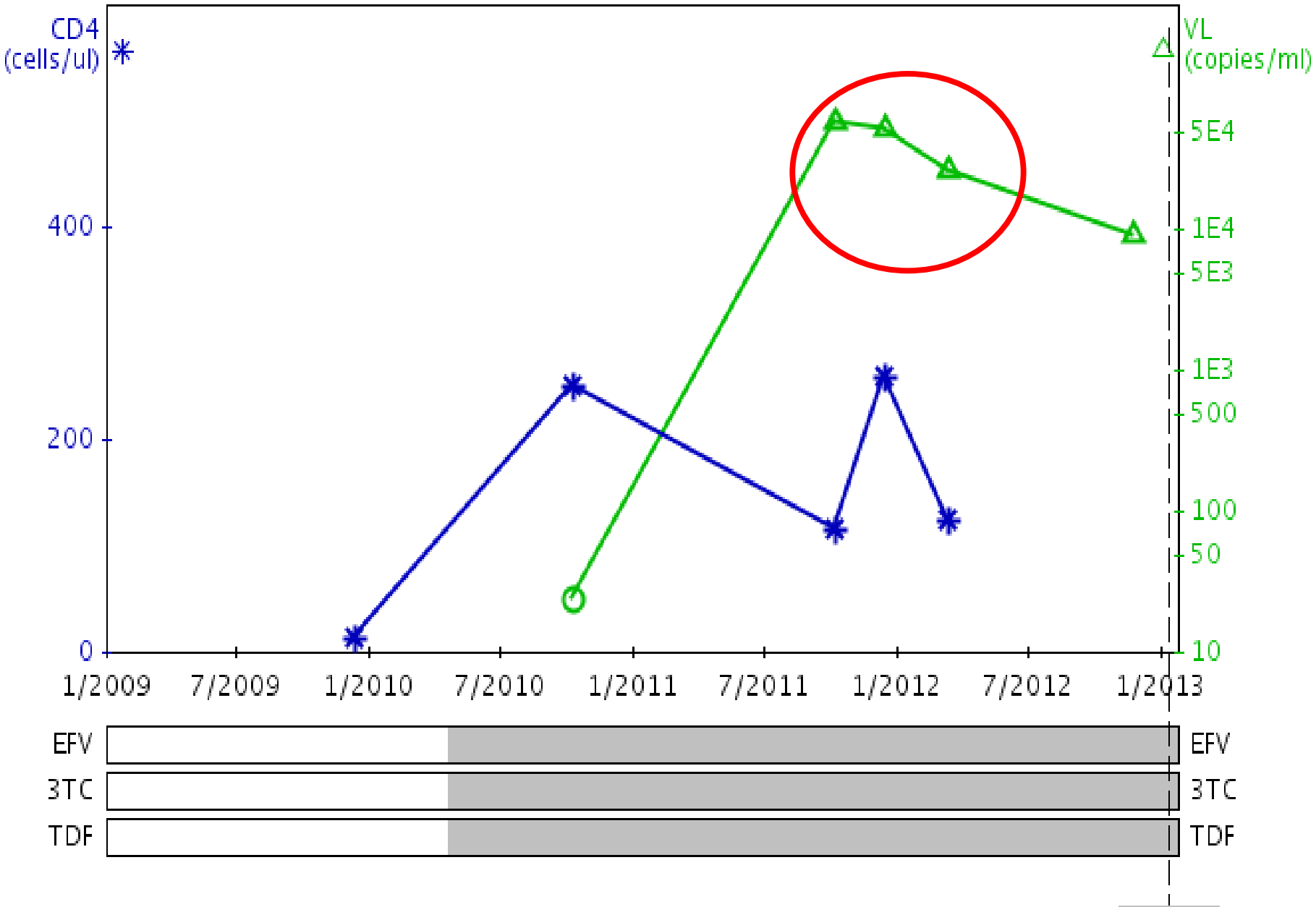
EFV
3TC
TDF
EFV
3TC
TDF

+ Resistance Profile

Drug	Mutations	Description	Level	GSS
zidovudine	65R 69S 118I 184V	Susceptible	1	1.0
zalcitabine	N/A	N/A	N/A	N/A
didanosine	65R 69S 118I 184V	Intermediate resistance	4	0.5
lamivudine	65R 69S 118I 184V	High-level resistance	5	0.0
stavudine	65R 69S 118I 184V	Potential low-level resistance	2	1.0
abacavir	65R 69S 115F 118I 184V	High-level resistance	5	0.0
emtricitabine	65R 69S 118I 184V	High-level resistance	5	0.0
tenofovir	65R 69S 115F 118I 184V	Intermediate resistance	4	0.5
nevirapine	106M 188L	High-level resistance	5	0.0
delavirdine	106M 188L	High-level resistance	5	0.0
efavirenz	106M 188L	High-level resistance	5	0.0
etravirine	106M 188L	Intermediate resistance	4	0.5
saquinavir	N/A	N/A	N/A	N/A
saquinavir/r		Susceptible	1	1.0
ritonavir	N/A	N/A	N/A	N/A
indinavir	N/A	N/A	N/A	N/A
indinavir/r		Susceptible	1	1.0
nelfinavir		Susceptible	1	1.0
fosamprenavir	N/A	N/A	N/A	N/A
fosamprenavir/r		Susceptible	1	1.0
lopinavir/r		Susceptible	1	1.0
atazanavir	N/A	N/A	N/A	N/A
atazanavir/r		Susceptible	1	1.0
tipranavir/r		Susceptible	1	1.0
darunavir/r		Susceptible	1	1.0

+ Patient 2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EFV
3TC
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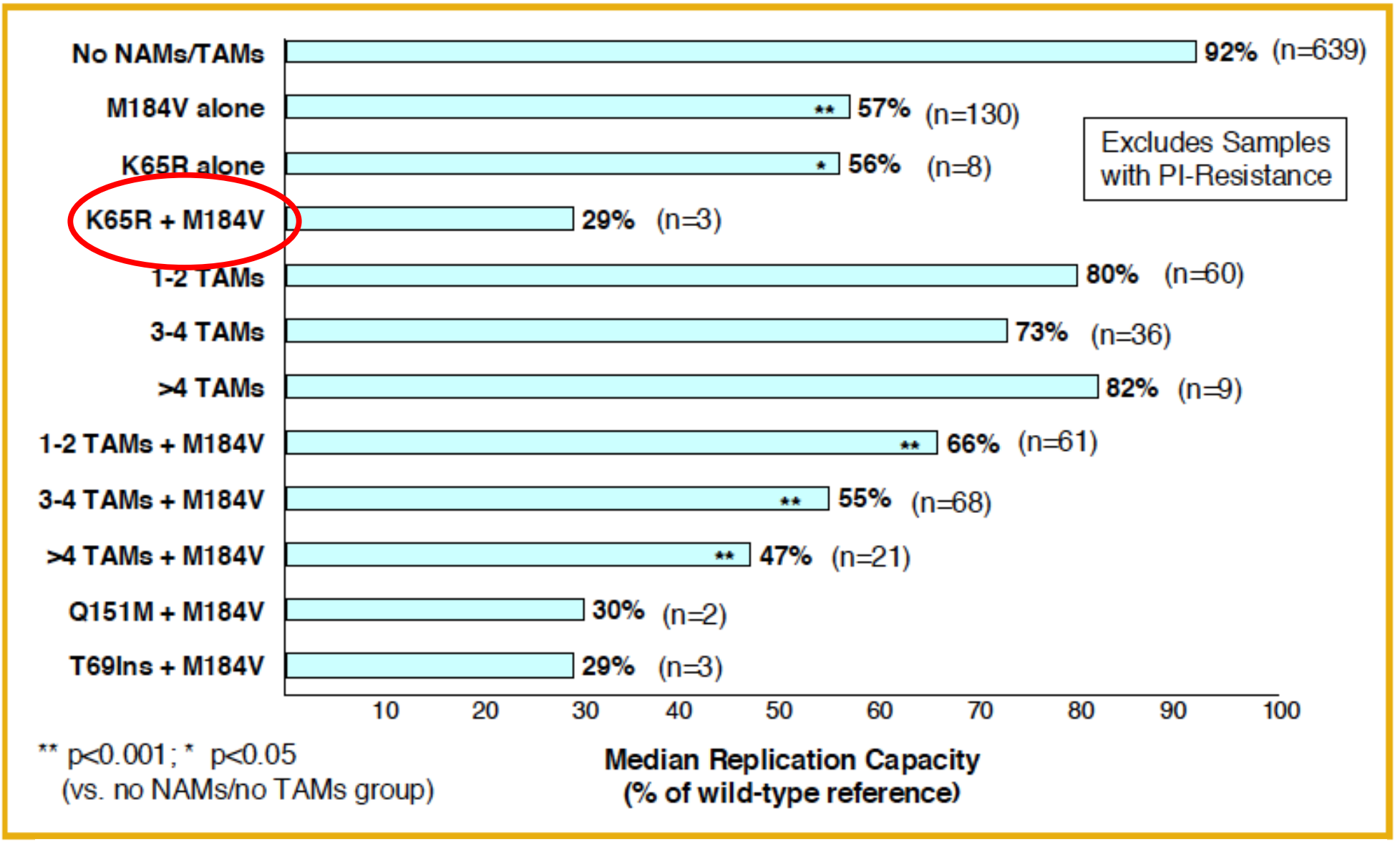
Figure 5 • Replication Capacity of HIV without Protease Inhibitor Resistance Mutations (n=1040)



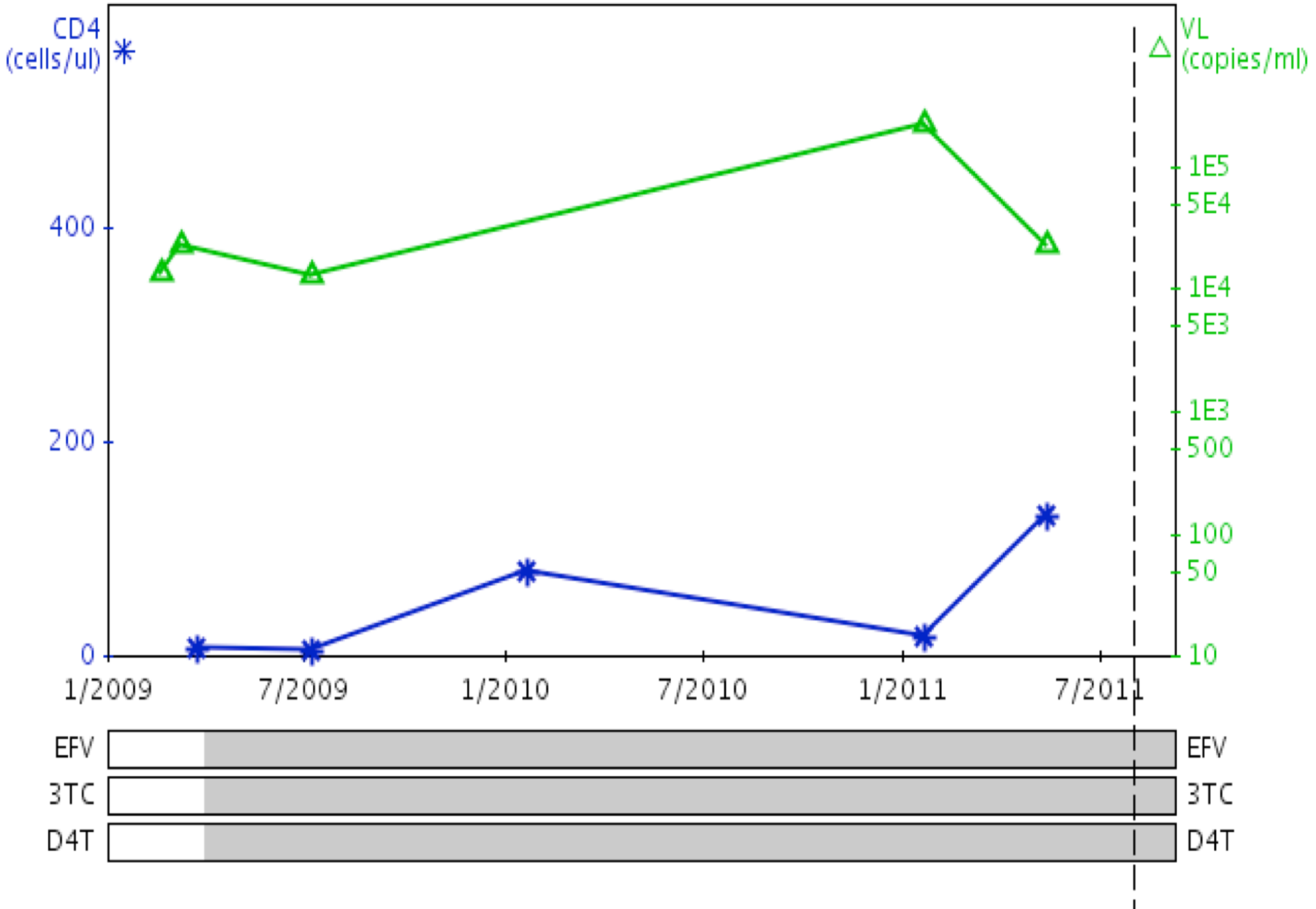
Decreased Replication Capacity of HIV-1 Clinical Isolates Containing K65R or M184V RT Mutations

MD Miller[1], KL White[1], CJ Petropoulos[2], NT Parkin[2]

K65R mutation

- Confers resistance to TDF, ABC, 3TC, FTC, ddI and ?d4T
- But sensitizes virus to AZT
- Mechanism similar to 3TC – reduced primer excision
- Tips balance in favour of hypersusceptibility to AZT and not towards resistance to other NRTIs
- Reverses M184V-induced hypersusceptibility to TDF

+ Patient 3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7/2011
EFV
3TC
D4T
EFV
3TC
D4T

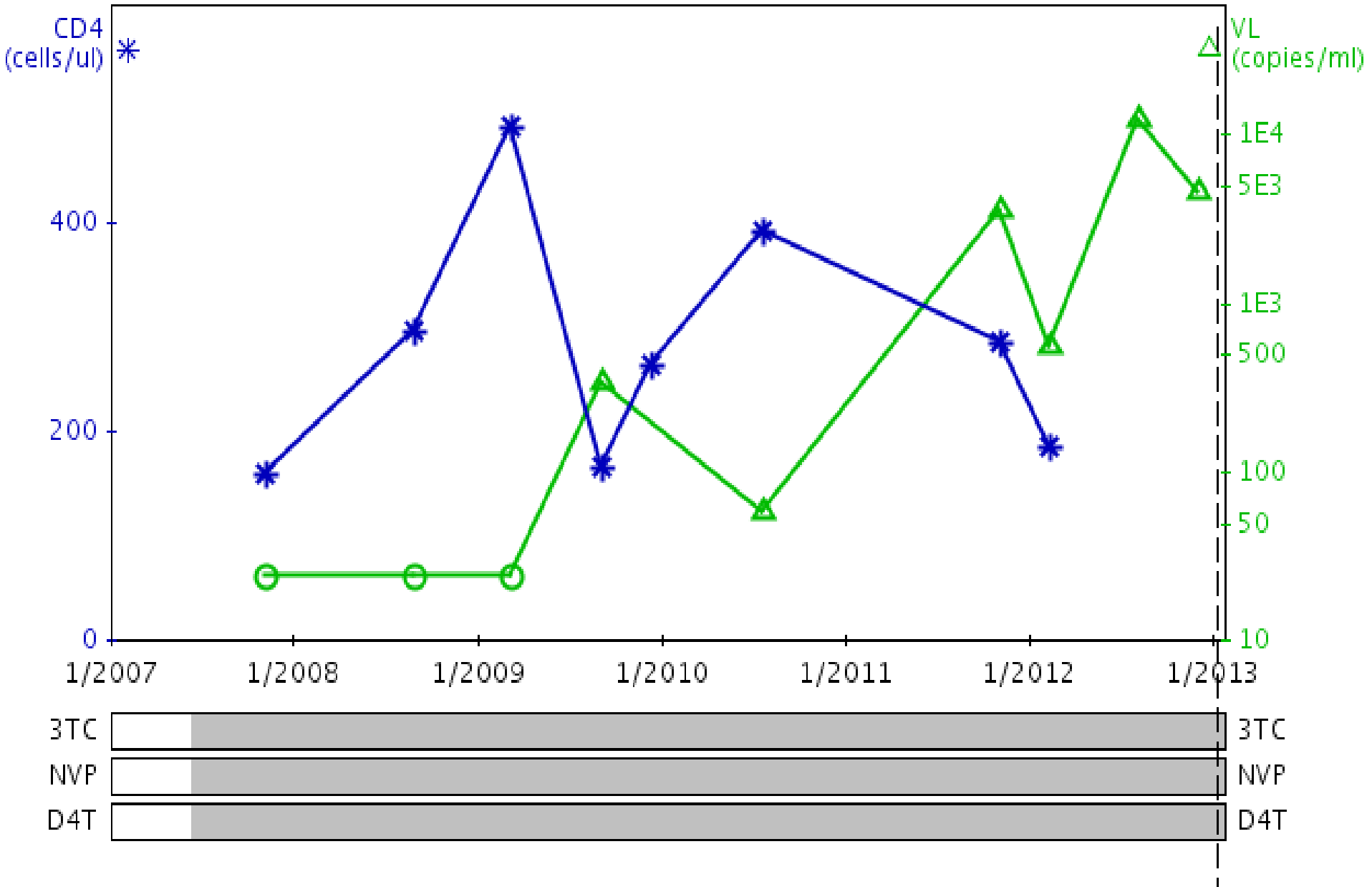
+ Resistance Profile

Drug	Mutations	Description	Level	GSS
zidovudine	67N 70R 184V	Low-level resistance	3	0.5
zalcitabine	N/A	N/A	N/A	N/A
didanosine	67N 184V	Potential low-level resistance	2	1.0
lamivudine	184V	High-level resistance	5	0.0
stavudine	67N 70R 184V	Low-level resistance	3	0.5
abacavir	67N 184V	Low-level resistance	3	0.5
emtricitabine	184V	High-level resistance	5	0.0
tenofovir	67N 70R 184V	Susceptible	1	1.0
nevirapine	103N	High-level resistance	5	0.0
delavirdine	103N	High-level resistance	5	0.0
efavirenz	103N	High-level resistance	5	0.0
etravirine	103N	Potential low-level resistance	2	1.0
saquinavir	N/A	N/A	N/A	N/A
saquinavir/r		Susceptible	1	1.0
ritonavir	N/A	N/A	N/A	N/A
indinavir	N/A	N/A	N/A	N/A
indinavir/r		Susceptible	1	1.0
nelfinavir		Susceptible	1	1.0
fosamprenavir	N/A	N/A	N/A	N/A
fosamprenavir/r		Susceptible	1	1.0
lopinavir/r		Susceptible	1	1.0
atazanavir	N/A	N/A	N/A	N/A
atazanavir/r		Susceptible	1	1.0
tipranavir/r		Susceptible	1	1.0
darunavir/r		Susceptible	1	1.0

Question 6: What would be your next regimen of choice?

A. AZT, 3TC, LPV/r
B. TDF, FTC, LPV/r
C. ABC, 3TC, LPV/r
D. FDC

+ Patient 3 +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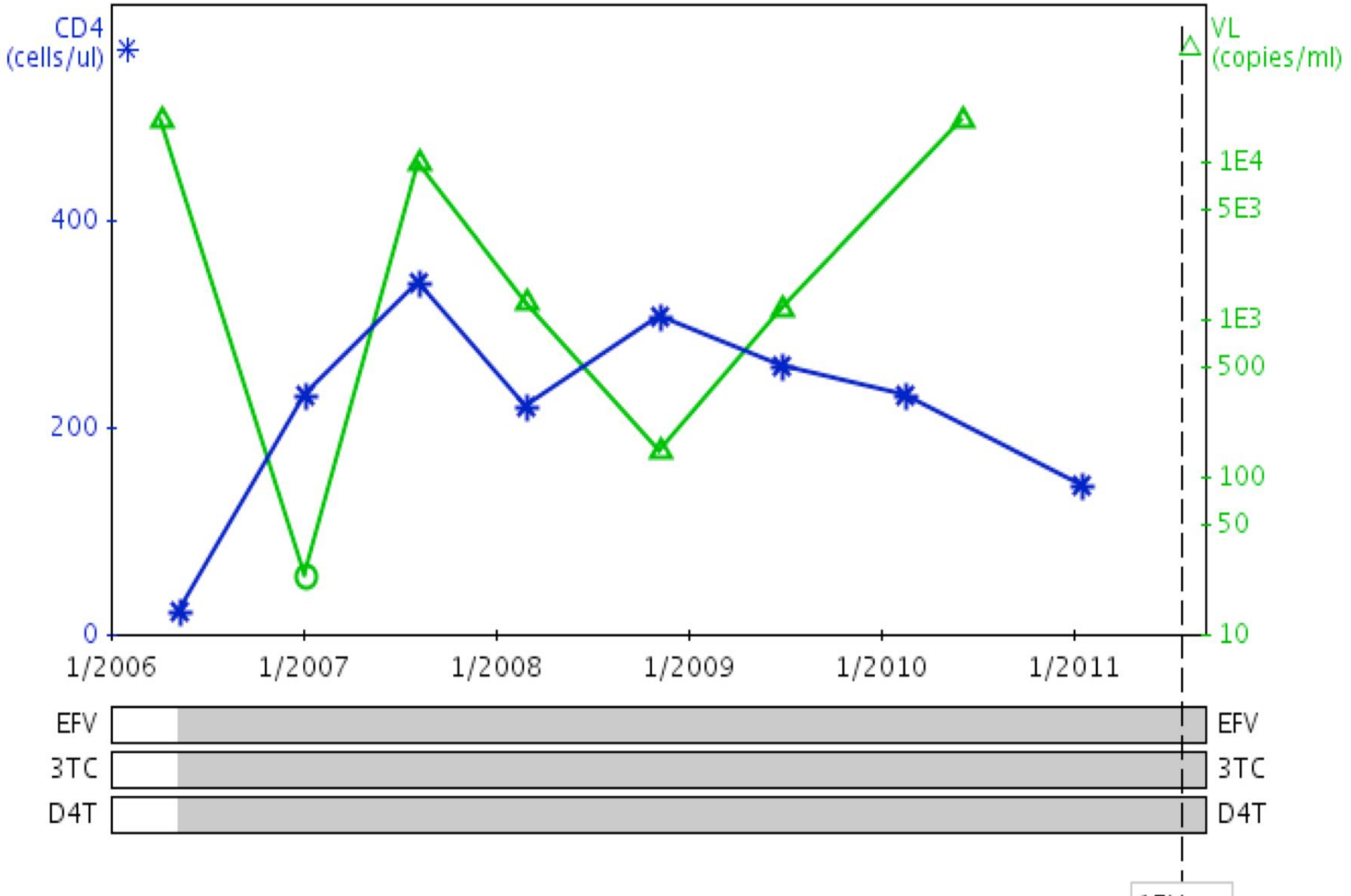
+ Resistance Profile

Drug	Mutations	Description	Level	GSS
zidovudine	69N 70R 181C 184V 219Q	Low-level resistance	3	0.5
zalcitabine	N/A	N/A	N/A	N/A
didanosine	69N 184V	Low-level resistance	3	0.5
lamivudine	69N 184V	High-level resistance	5	0.0
stavudine	69N 70R 184V 219Q	Low-level resistance	3	0.5
abacavir	69N 184V	Low-level resistance	3	0.5
emtricitabine	69N 184V	High-level resistance	5	0.0
tenofovir	69N 70R 181C 184V	Susceptible	1	1.0
nevirapine	103N 181C	High-level resistance	5	0.0
delavirdine	103N 181C	High-level resistance	5	0.0
efavirenz	103N 181C	High-level resistance	5	0.0
etravirine	103N 181C	Intermediate resistance	4	0.5
saquinavir	N/A	N/A	N/A	N/A
saquinavir/r		Susceptible	1	1.0
ritonavir	N/A	N/A	N/A	N/A
indinavir	N/A	N/A	N/A	N/A
indinavir/r		Susceptible	1	1.0
nelfinavir		Susceptible	1	1.0
fosamprenavir	N/A	N/A	N/A	N/A
fosamprenavir/r		Susceptible	1	1.0
lopinavir/r		Susceptible	1	1.0
atazanavir	N/A	N/A	N/A	N/A
atazanavir/r		Susceptible	1	1.0
tipranavir/r		Susceptible	1	1.0
darunavir/r		Susceptible	1	1.0

+ Patient 3 ++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EFV
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EFV
3TC
D4T

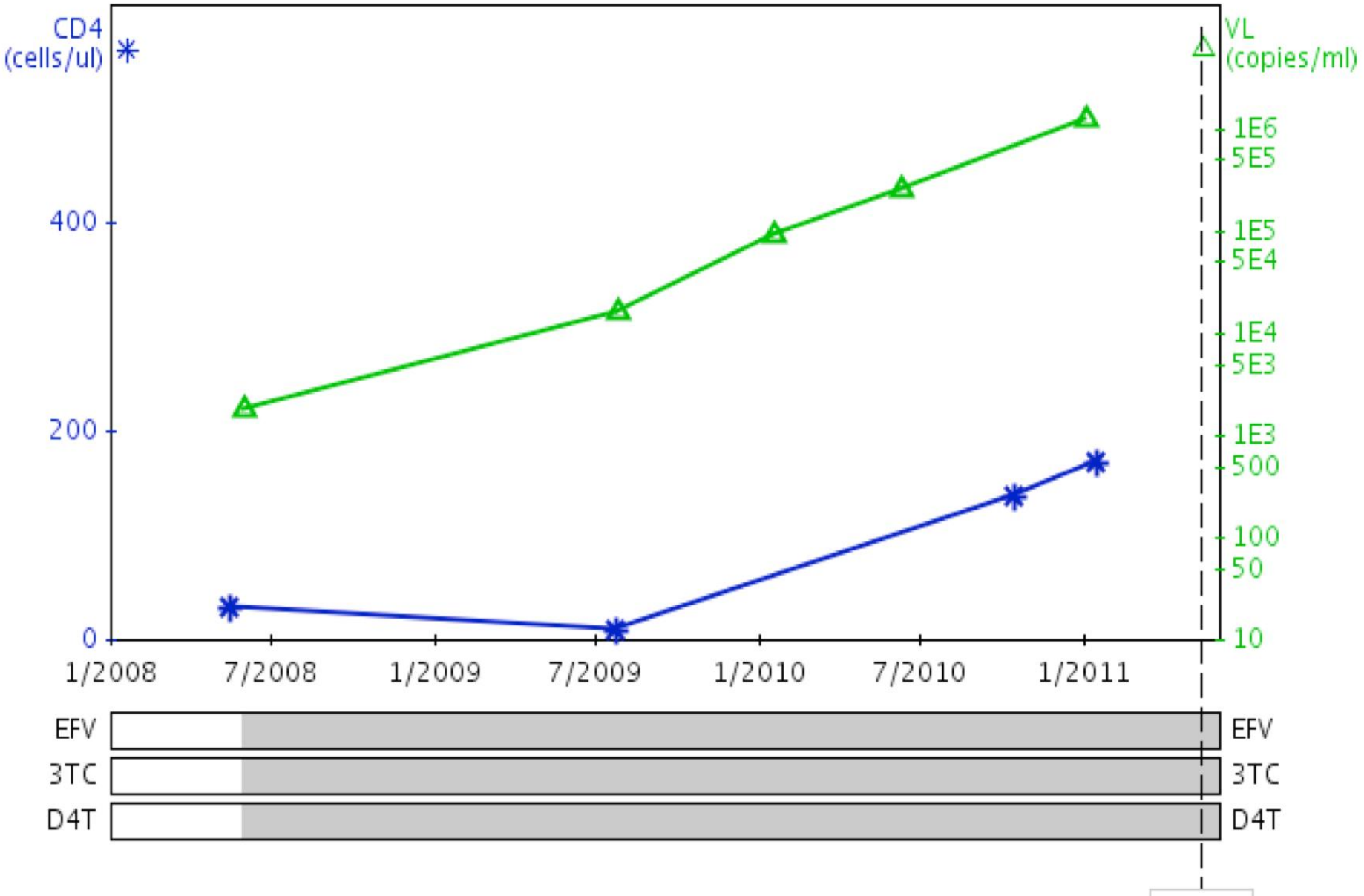
+ Resistance Profile

Drug	Mutations	Description	Level	GSS
zidovudine	67G 70R 75I 184V 215F 219Q	High-level resistance	5	0.0
zalcitabine	N/A	N/A	N/A	N/A
didanosine	67G 75I 184V 215F	Intermediate resistance	4	0.5
lamivudine	75I 184V 215F	High-level resistance	5	0.0
stavudine	67G 70R 75I 184V 215F 219Q	High-level resistance	5	0.0
abacavir	67G 75I 184V 215F	Intermediate resistance	4	0.5
emtricitabine	75I 184V 215F	High-level resistance	5	0.0
tenofovir	67G 70R 75I 184V 215F	Low-level resistance	3	0.5
nevirapine	106M 190A	High-level resistance	5	0.0
delavirdine	106M	High-level resistance	5	0.0
efavirenz	106M 190A	High-level resistance	5	0.0
etravirine	106M 190A	Low-level resistance	3	0.5
saquinavir	N/A	N/A	N/A	N/A
saquinavir/r		Susceptible	1	1.0
ritonavir	N/A	N/A	N/A	N/A
indinavir	N/A	N/A	N/A	N/A
indinavir/r		Susceptible	1	1.0
nelfinavir	74S	Potential low-level resistance	2	1.0
fosamprenavir	N/A	N/A	N/A	N/A
fosamprenavir/r		Susceptible	1	1.0
lopinavir/r		Susceptible	1	1.0
atazanavir	N/A	N/A	N/A	N/A
atazanavir/r		Susceptible	1	1.0
tipranavir/r		Susceptible	1	1.0
darunavir/r		Susceptible	1	1.0

Question 7: What would be your next regimen of choice?

A. AZT, 3TC, LPV/r
B. TDF, FTC, LPV/r
C. ABC, 3TC, LPV/r
D. RAL, ETV, LPV/r,
E. RAL, ETV, DRV/r

+ Patient 3 +++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7/2010
1/2011
EFV
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EFV
3TC
D4T

+ Resistance Profile

Drug	Mutations	Description	Level	GSS
zidovudine	65R 75I 77L 116Y 151M 184V	High-level resistance	5	0.0
zalcitabine	N/A	N/A	N/A	N/A
didanosine	65R 75I 77L 116Y 151M 184V	High-level resistance	5	0.0
lamivudine	65R 75I 77L 116Y 151M 184V	High-level resistance	5	0.0
stavudine	65R 75I 77L 116Y 151M 184V	High-level resistance	5	0.0
abacavir	65R 75I 77L 116Y 151M 184V	High-level resistance	5	0.0
emtricitabine	65R 75I 77L 116Y 151M 184V	High-level resistance	5	0.0
tenofovir	65R 75I 77L 116Y 151M 184V	High-level resistance	5	0.0
nevirapine	103N 225H	High-level resistance	5	0.0
delavirdine	103N 225H	High-level resistance	5	0.0
efavirenz	103N 225H	High-level resistance	5	0.0
etravirine	103N 225H	Low-level resistance	3	0.5
saquinavir	N/A	N/A	N/A	N/A
saquinavir/r		Susceptible	1	1.0
ritonavir	N/A	N/A	N/A	N/A
indinavir	N/A	N/A	N/A	N/A
indinavir/r		Susceptible	1	1.0
nelfinavir		Susceptible	1	1.0
fosamprenavir	N/A	N/A	N/A	N/A
fosamprenavir/r		Susceptible	1	1.0
lopinavir/r		Susceptible	1	1.0
atazanavir	N/A	N/A	N/A	N/A
atazanavir/r		Susceptible	1	1.0
tipranavir/r		Susceptible	1	1.0
darunavir/r		Susceptible	1	1.0


TROUBLE
Maker

Question 8: What now?

A. Refer to 3rd line committee

B. Continue on regimen

C. RAL, ETV, LPV/r

D. AZT, 3TC, LPV/r

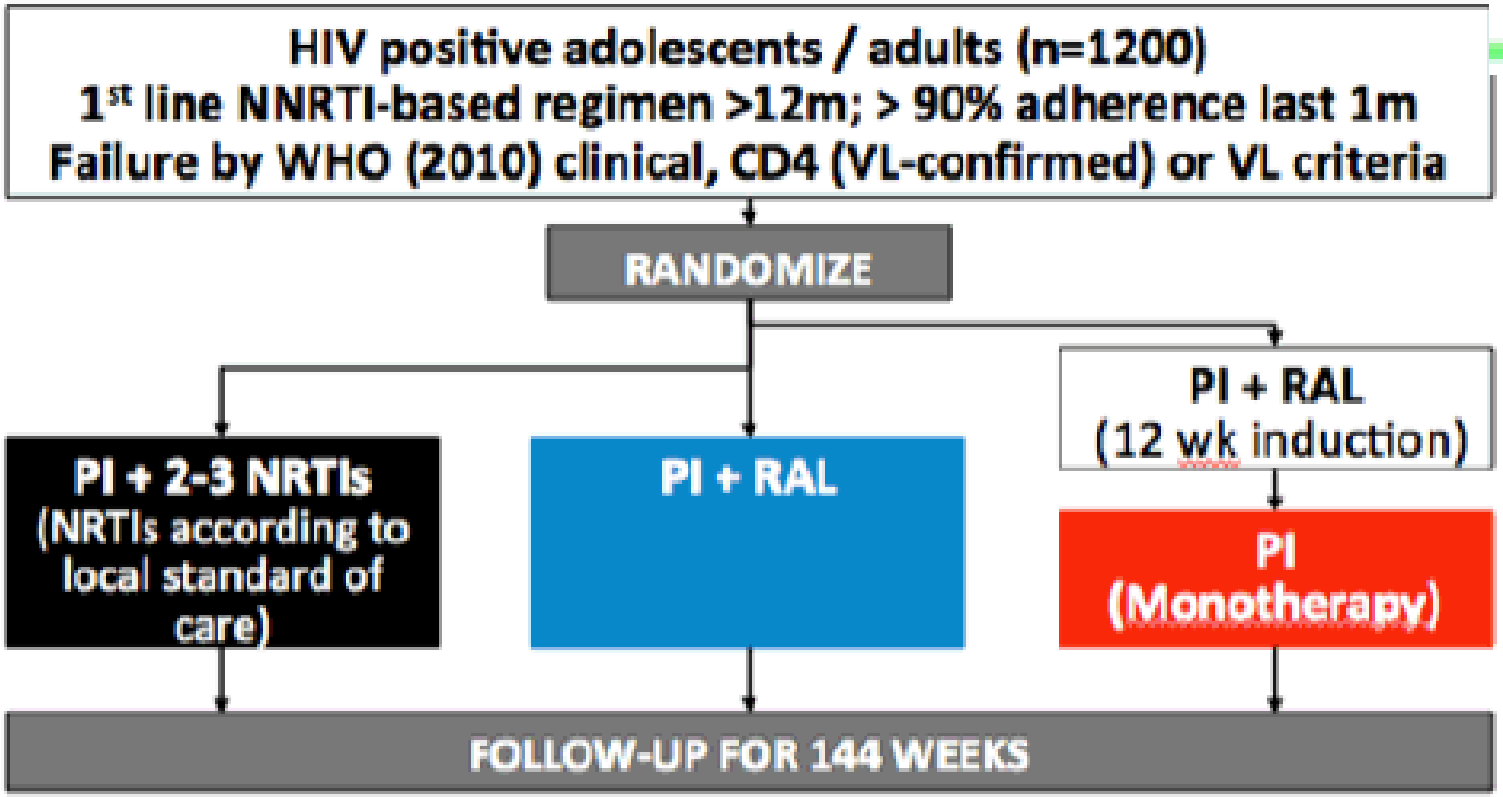
What Does the Literature Say?

- ACTG 5230 trial
  - PI monotherapy after 1st-line treatment failure in low-resource settings
  - 87% virological suppression after 6 months
- Recent meta-analysis
  - Boosted PI monotherapy inferior to standard triple ART regimens
  - Cannot be considered an alternative to standard treatment

What Does the Literature Say?

- PASER cohort: 243 participants who switched to 2nd-line PI-based regimen after 1st-line failure
- ART predicted partially active for 128 (55.2%)
  - drug-resistant virus with ↓ predicted susceptibility to at least 1 drug.
  - Of these, 60 (46.9%) received <2 active drugs
- After 12 months, 208 still on 2nd-line & 201 had VL results – 28 (13.9%) had virological failure
  - 11/80 (13.8%) predicted to receive fully active regimens
  - 17/112 (15.2%) with partially active regimens (P = .782)
  - 7/51 (13.7%) predicted to receive <2 active drugs

What Does the Literature Say?



Primary outcome at week 96:

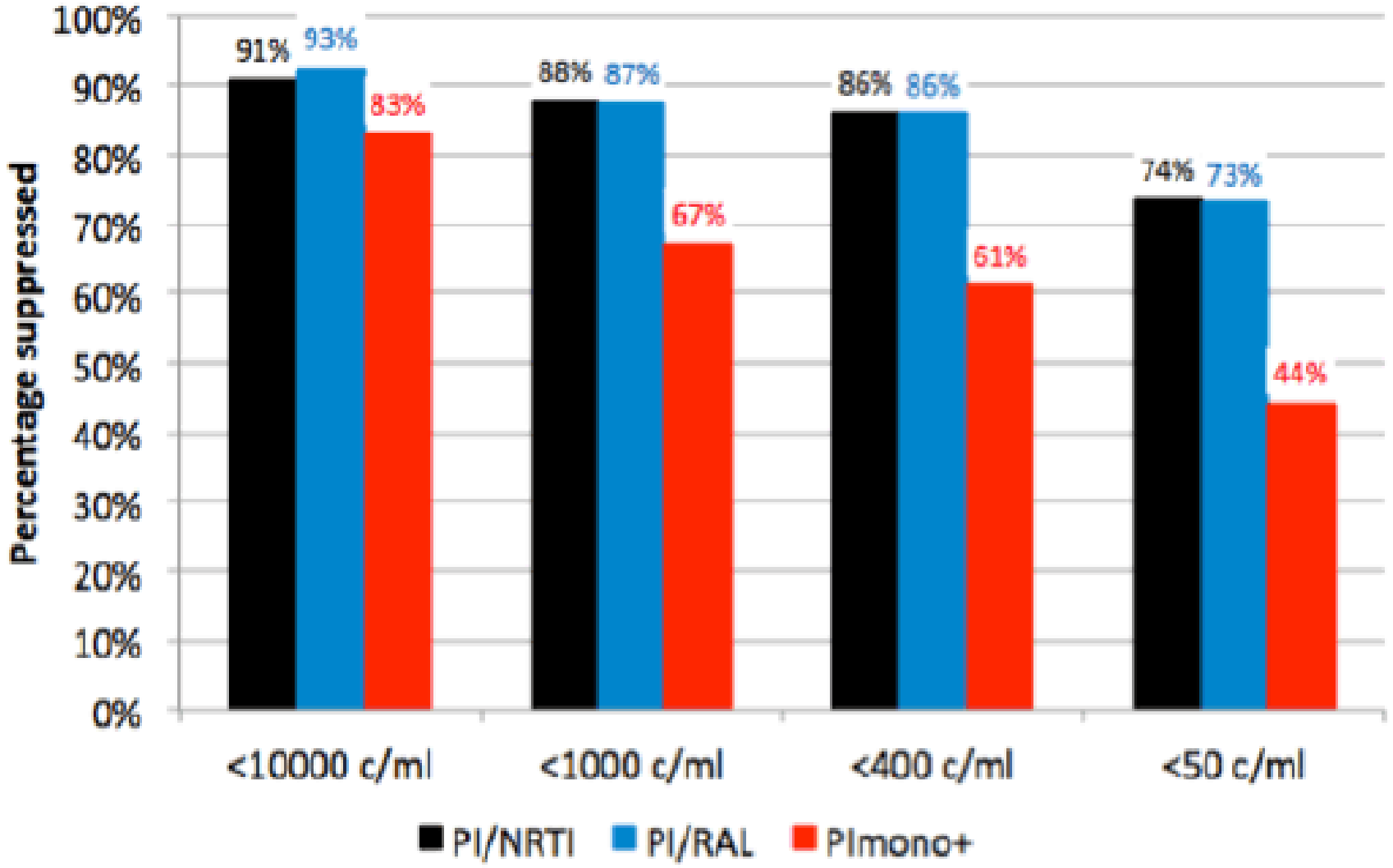
Good HIV disease control **– defined as all of:**

- Alive and no new WHO4 events from 0-96 weeks AND
- CD4 cell count > 250 cells/mm^3 at 96 weeks AND
- VL<10,000 c/ml OR >10,000 c/ml without PI res. mutations at 96 weeks

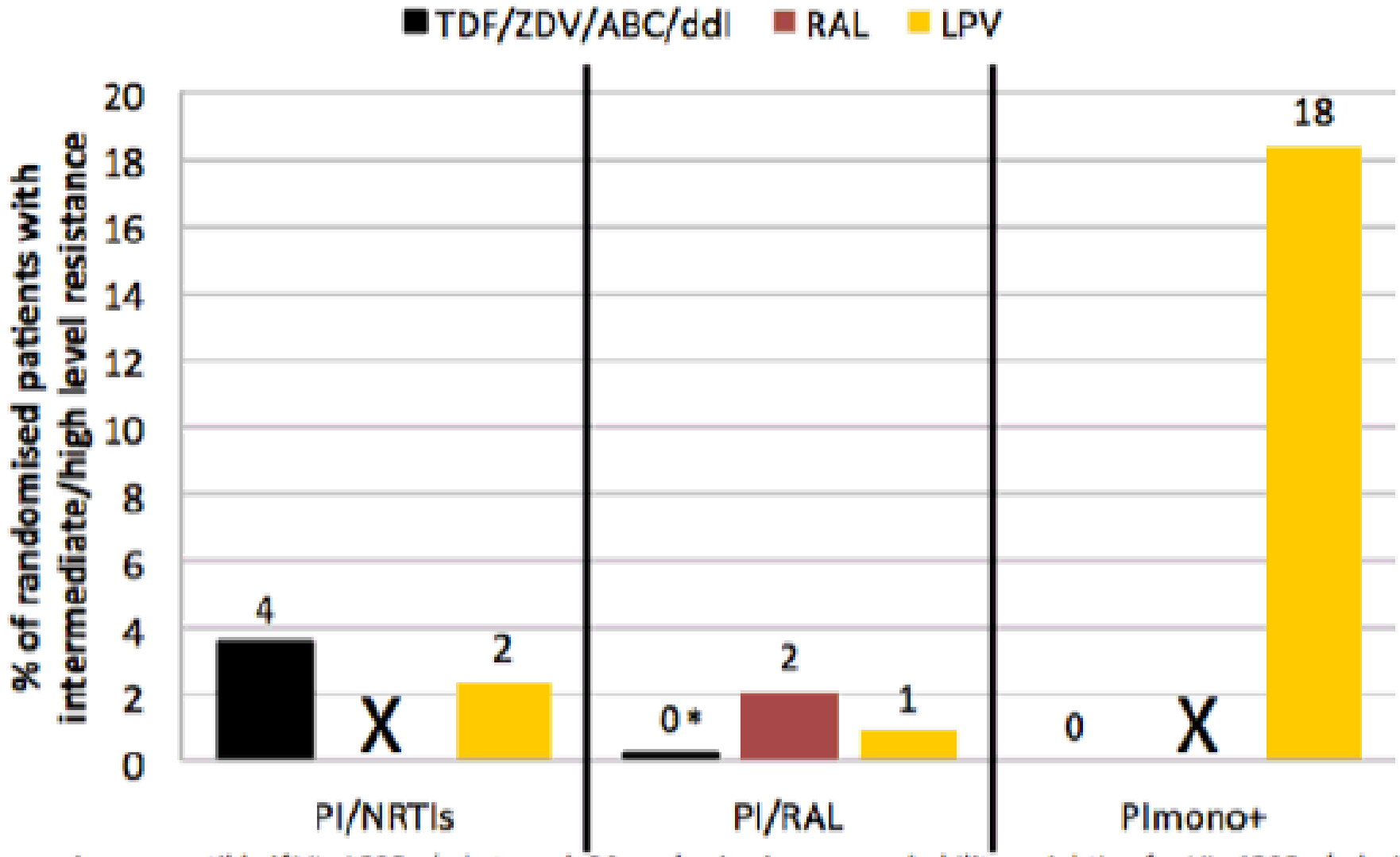
	PI/NRTI participants N (%)
Total with baseline genotypes available	391 (100%)
Intermediate-high level resistance to	
- Tenofovir	223 (57%)
- Zidovudine	290 (74%)
- Lamivudine	371 (95%)
- Emcitrabine	71 (95%)
- Abacavir	318 (81%)
- Didanosine	301 (77%)
- Stavudine	309 (79%)
Number of NRTIs in initial second-line regimen with no more than low-level resistance	
- 0	230 (59%)
- 1	128 (33%)
- 2	33 (8%)

VL suppression at 96 weeks

	<10000 c/ml	<1000 c/ml	<400 c/ml	<50 c/ml
PI/RAL vs PI/NRTI	P=0.36	P=0.87	P=0.97	P=0.88
PImono+ vs PI/NRTI	P=0.002	P<0.0001	P<0.0001	P<0.0001



Resistance at 96 weeks
(predicted in whole population)



Note: assuming susceptible if VL<1000 c/ml at week 96; and using inverse probability weighting for VL>1000 c/ml with missing genotype at week 96 based on those with observed genotypes

*One patient in RAL/PI with intermediate/high level resistance to TDF had moved to 3TC TDF ALV at week 4 due to rash

TREATMENT

NRTI regimen prescribed:

- TDF+3/FTC 70%
- TDF/3TC/ZDV 9% (Malawi national guidelines)
- ddI+ABC 12% ZDV+3TC 4% Other 4%

LPV/r used throughout in >99%

Regimen consistent with randomised strategy at w96: >97%

Complete adherence (0 missed pills/last 1m): 88% of visits

FOLLOW UP

Protocol-mandated visits attended: > 95%

Withdrawal / lost to follow up before w96: 1.3%

Lessons Learned

- The best option is to have a fully active regimen with no resistance
- When resistance has occurred, use it to your best advantage
- Remember that compensatory mutations can occur at any time and will restore viral fitness
- HIV sequence differs significantly between patients due to:
  - random, divergent evolution,
  - host variation (immune response, genetic background, target cell availability)
  - viral factors (replication capacity, mutation rate, host cell tropism)
    - (Nijhuis et al., 2001; Clavel et al., 2000)