XXVII INTERNATIONAL WORKSHOP ON HIV DRUG RESISTANCE AND TREATMENT STRATEGIES

22 - 23 October 2018 Johannesburg, South Africa

27th International Workshop on HIV Drug Resistance and Treatment Strategies

Monday, 22 October to Tuesday, 23 October 2018

Gallagher Convention Centre, Midrand, Johannesburg, South Africa

www.hivresistance2018.co.za

SOUTHERN AFRICAN HIV CLINICIANS SOCIETY

CONFERENCE 2018

24 - 27 OCTOBER

4th Southern African HIV Clinicians Society Conference 2018

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THIRD LINE ART IN SA

Yunus Moosa

20th September 2018

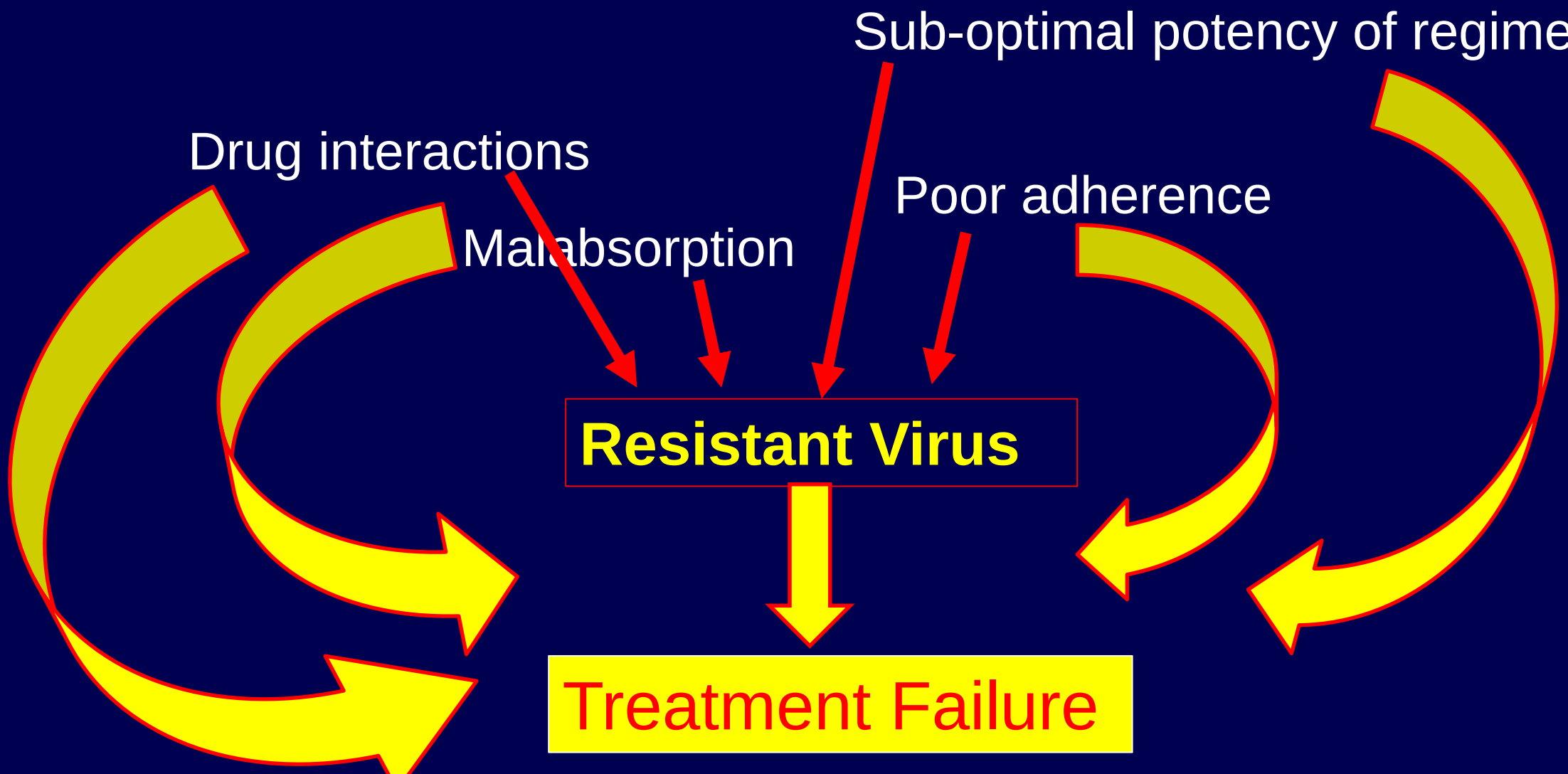
Dept of Infectious Diseases

UKZN

Acknowledgements

- Richard Lessells: KRISP
- Jay Brijkumar: RKK hospital
- Nithen Manickchund: IDU
- Bernadett Gosnell: IDU

Factors that Contribute to Resistance also cause Failure



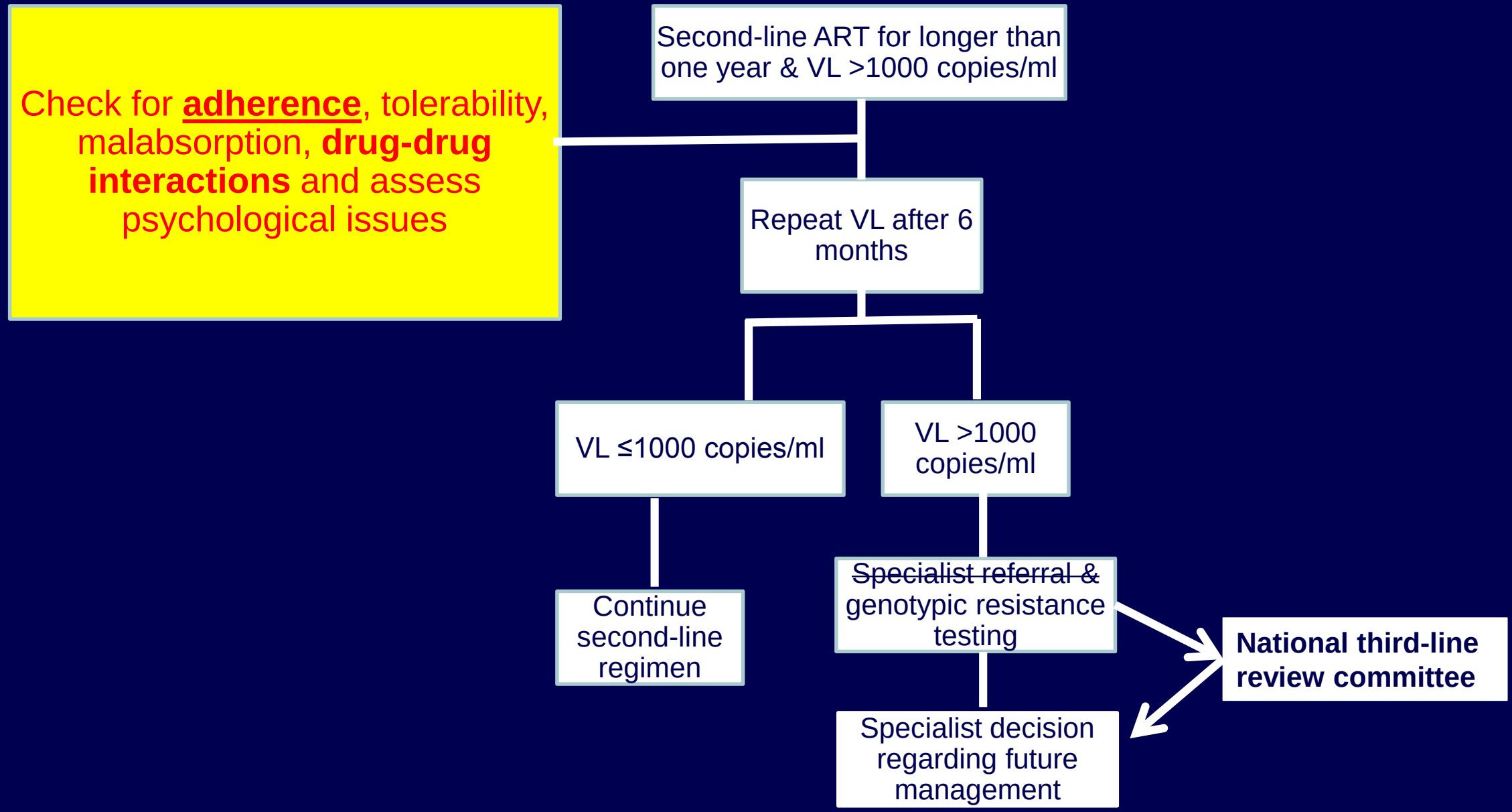
Factors to Consider when deciding on a new regimen (in addition to Genotype)

ARVs experienced in the past

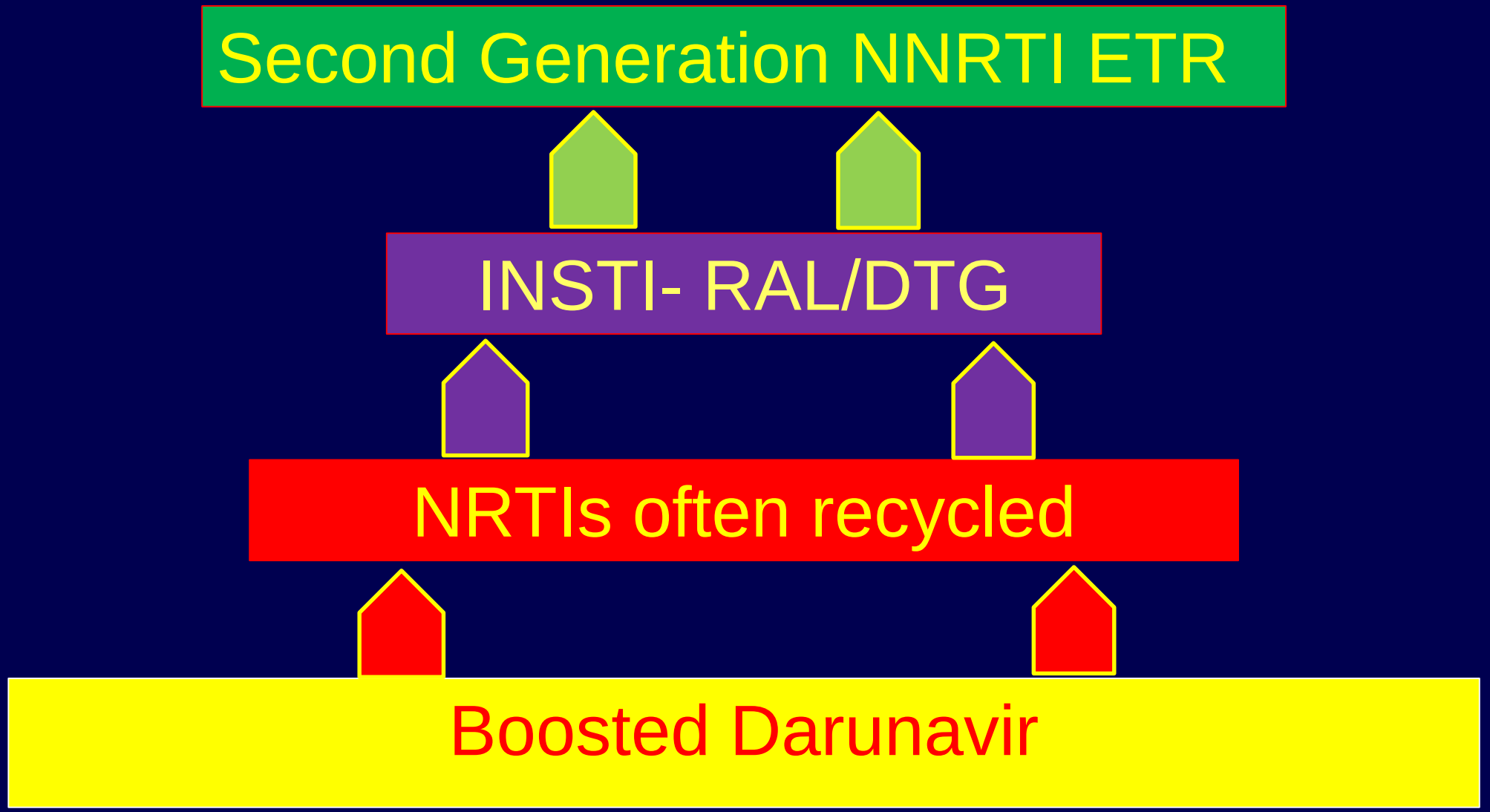
Reasons for discontinuation of ARVs

Regimen at time of resistance testing

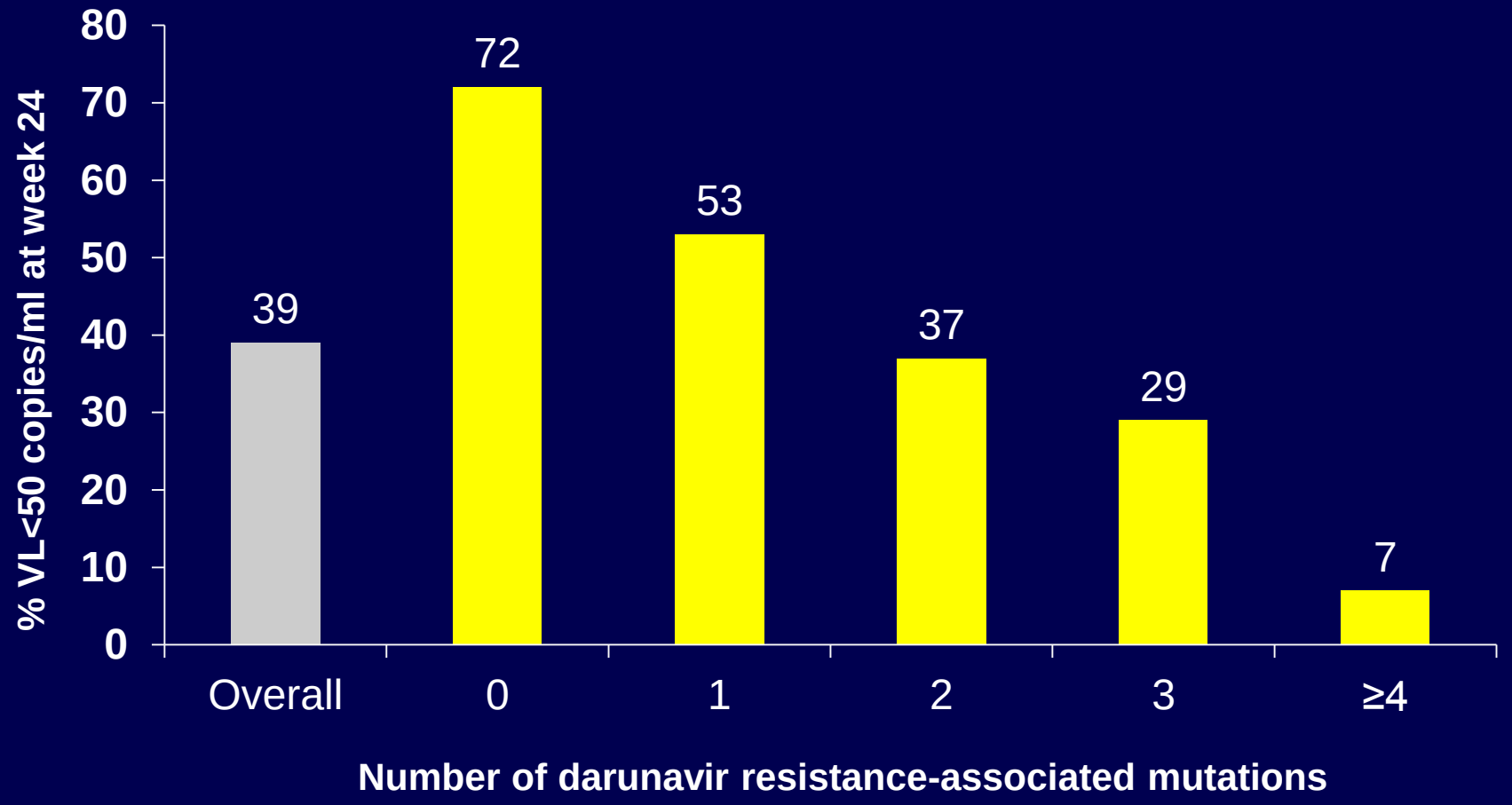
National ART Guidelines: Second Line Treatment Failure



Drugs Used in Third-line Treatment



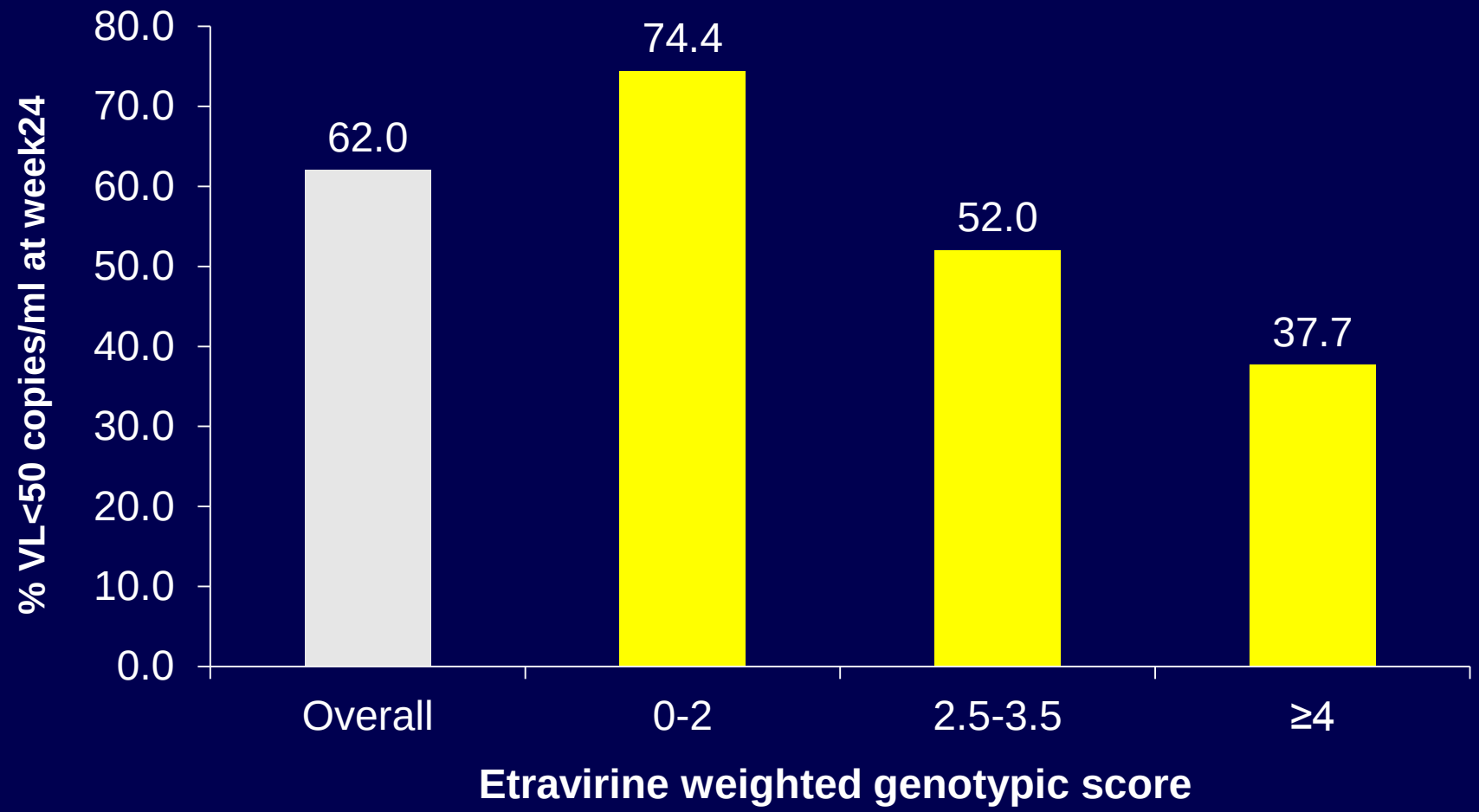
Response to darunavir/ritonavir



DRV mutations: V11I, V32I, L33F, I47V, I50V, I54L, I54M, G73S, L76V, I84V, and L89V

Source: AIDS Res Hum Retrovir 2008; 24: 379-88

Response to etravirine



Source: AIDS 2010; 24: 503-14

Clinical case

44-year old HIV-positive male

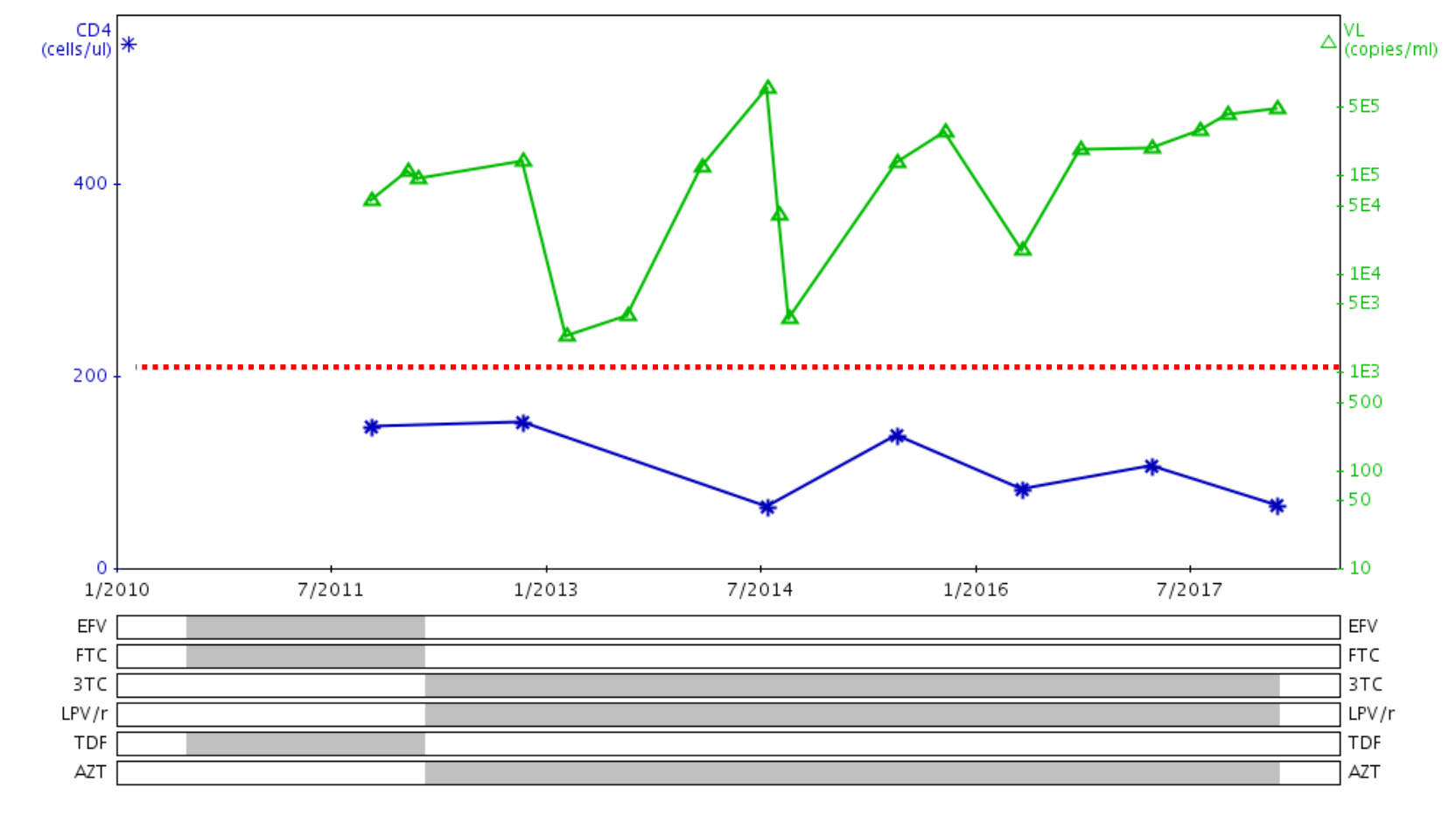
HIV diagnosis 2010

Pre-treatment CD4+ count not known

Initiated first-line ART (TDF/FTC/EFV) in private sector 2010 – transferred public sector Oct 2011

4 x episodes pulmonary TB

Clinical chart



TDF/FTC/EFV

PTB

virologic failure

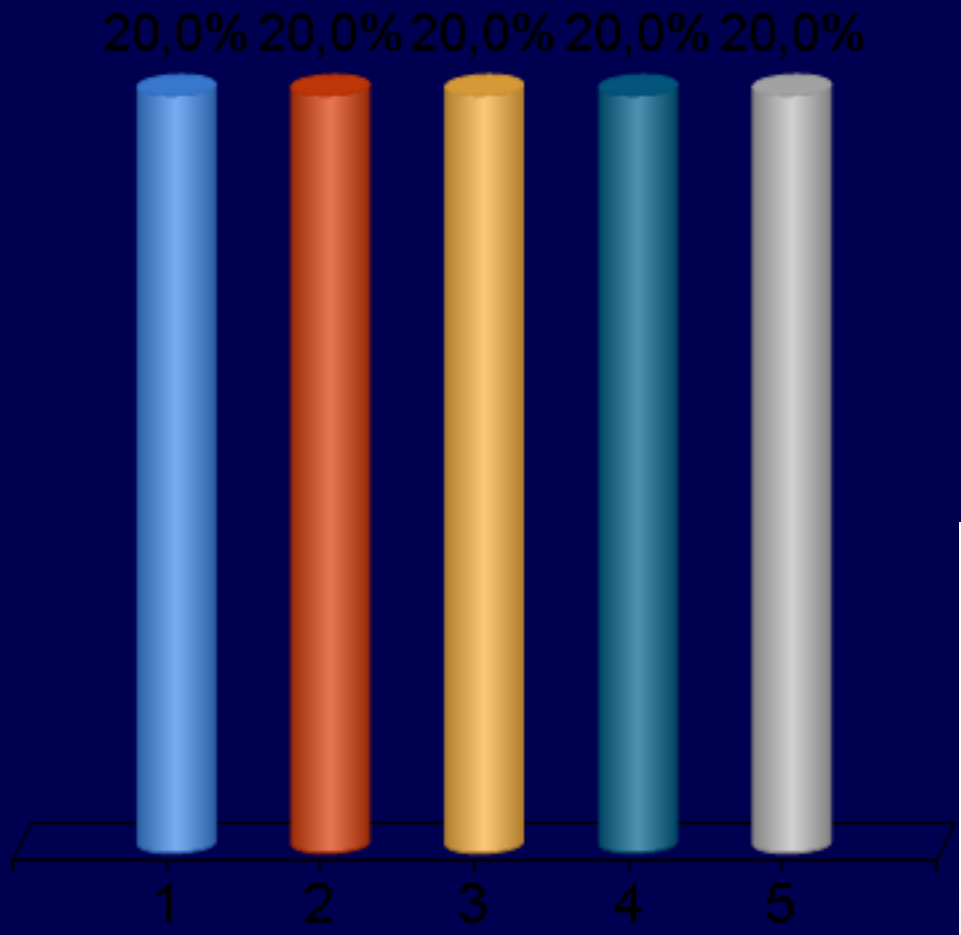
AZT/3TC/LPV/r

Genotype

2.5 yrs. into 2nd line

Why is this patient failing treatment?

1. Poor adherence
2. Drug-drug interactions
3. Malabsorption
4. Drug Resistance
5. All of the above



The following is true about Resistance Testing?

1. Threshold for doing test is a VL of 500 cpm
2. PCR is a very sensitive test therefore the limit for detecting mutations is as low as 5% of the quasispecies.
3. Gives a fair reflection of mutations in viruses within all body compartments.
4. Should only be interpreted with a good drug history.

Genotypic resistance test report

Antiretroviral experience: TDF, FTC, EFV, **AZT, 3TC, LPV/r**
Subtype: HIV-1 Subtype C
Resistance interpretations: HIVdb 8.6

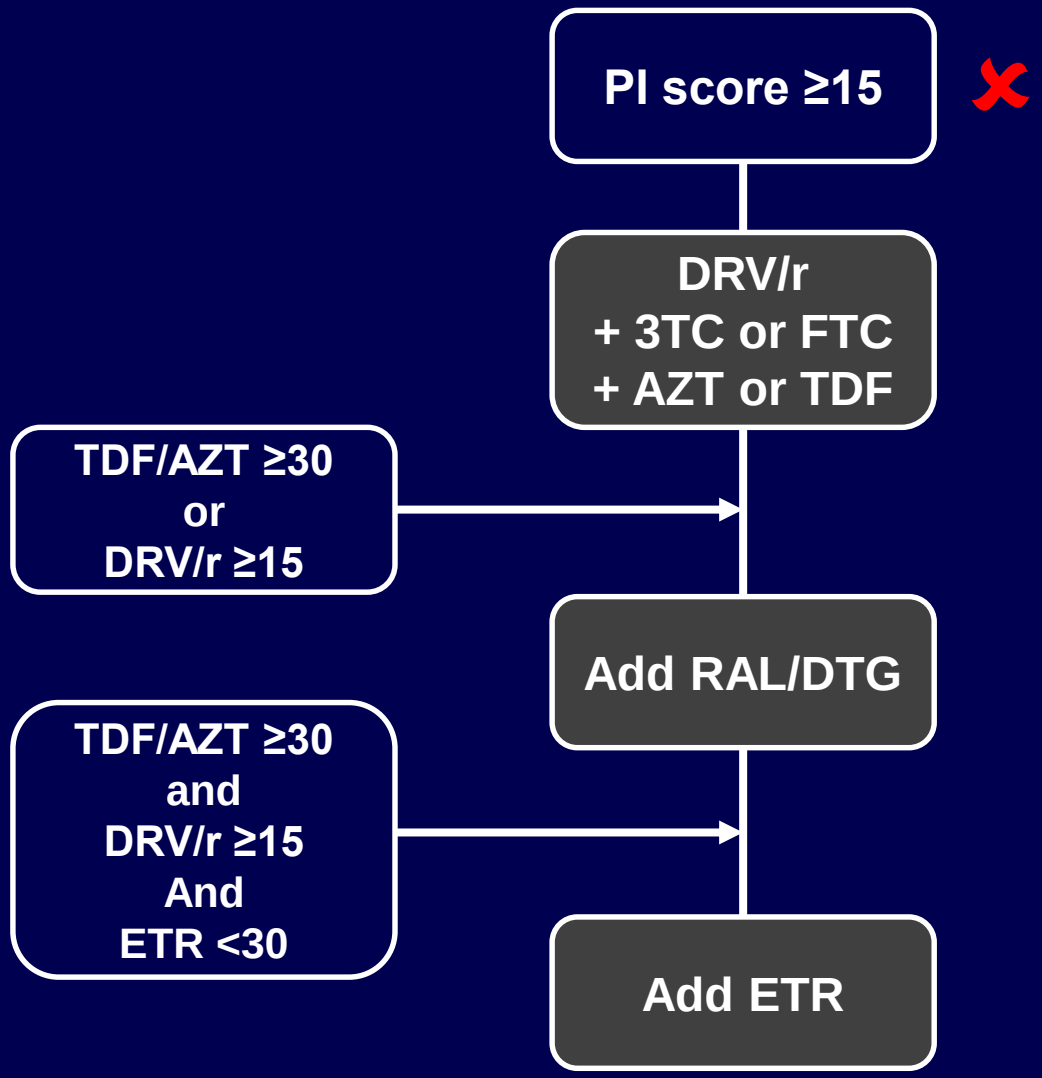
Drug	Mutations	Description	Score
Zidovudine	M184V, T215S	Potential low-level resistance	10
Lamivudine	M184V	High-level resistance	60
Abacavir	M184V, T215S	Low-level resistance	20
Emtricitabine	M184V	High-level resistance	60
Tenofovir	M184V, T215S	Susceptible	-5
Nevirapine	-	Susceptible	0
Efavirenz	-	Susceptible	0
Etravirine	-	Susceptible	0
Lopinavir/r	-	Susceptible	0
Atazanavir/r	-	Susceptible	0
Darunavir/r	-	Susceptible	0

How would you alter ART?

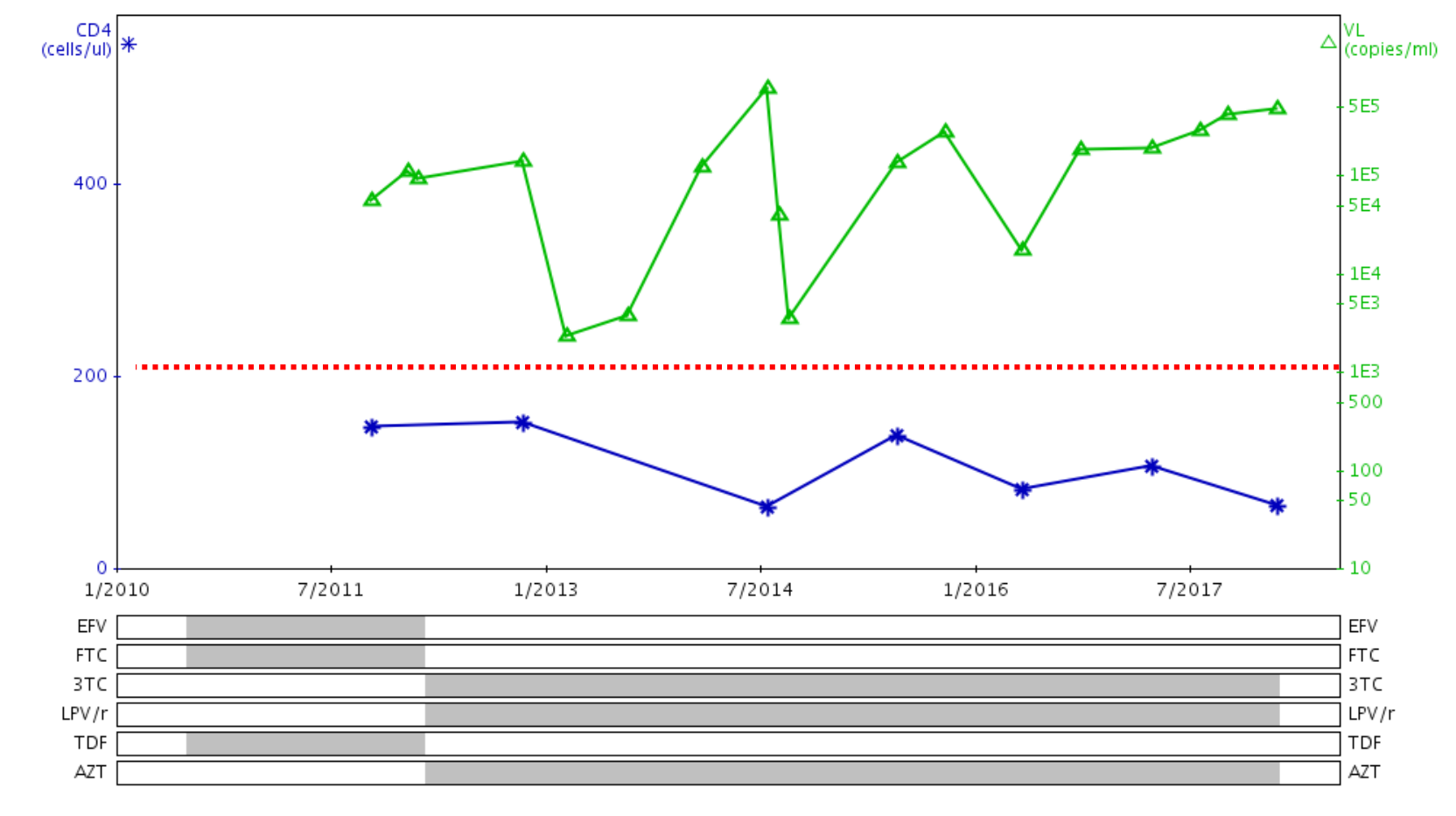
1. Stop all ART
2. Switch to TDF/FTC/EFV
3. Continue AZT/3TC/LPV/r
4. Switch to AZT/3TC/ATV/r
5. Switch to AZT/FTC/DRV/r

Third-line ART algorithm

TDF: -5 (S)
LPV/r: 0 (S)
AZT: 10 (S)



Clinical chart



PTB

virologic failure
TDF/FTC/EFV

AZT/3TC/LPV/r

Genotype
2.5 yrs. into 2nd line

PTB (Xpert +)

Genotype

Genotypic resistance test report

Antiretroviral experience: TDF, FTC, EFV, AZT, 3TC, LPV/r
Subtype: HIV-1 Subtype C
Resistance interpretations: HIVdb 8.6

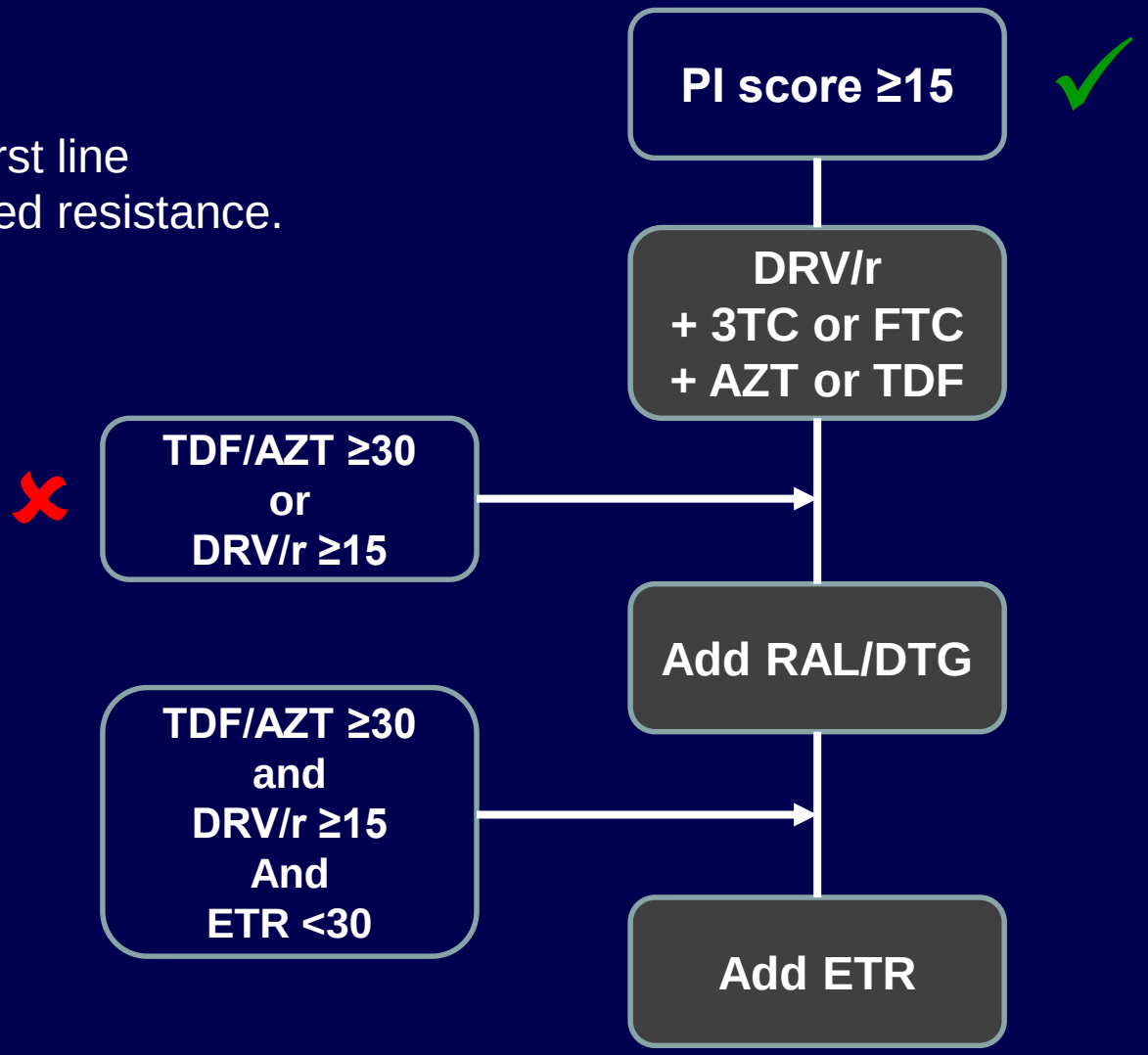
Drug	Mutations	Description	Score
Zidovudine	M41L, M184V, T215S	Intermediate resistance	55
Lamivudine	M41L, M184V, T215S	High-level resistance	65
Abacavir	M41L, M184V, T215S	Intermediate resistance	45
Emtricitabine	M41L, M184V, T215S	High-level resistance	65
Tenofovir	M41L, M184V, T215S	Low-level resistance	15
Nevirapine	A98G	Intermediate resistance	30
Efavirenz	A98G	Low-level resistance	15
Etravirine	A98G	Potential low-level resistance	10
Lopinavir/r	L10F, M46I, I54V, V82A	High-level resistance	80
Atazanavir/r	M46I, I54V, V82A	High-level resistance	60
Darunavir/r	L10F	Susceptible	5

Would you submit a request for third-line antiretroviral therapy r

1. Yes
2. No
3. I would phone adult ID hotline for advice first

Third-line ART algorithm

TDF: 15 (L)
DRV: 5 (S)
AZT: 55 (I)
TDF was used in first line treatment: ?archived resistance.



Clinical case

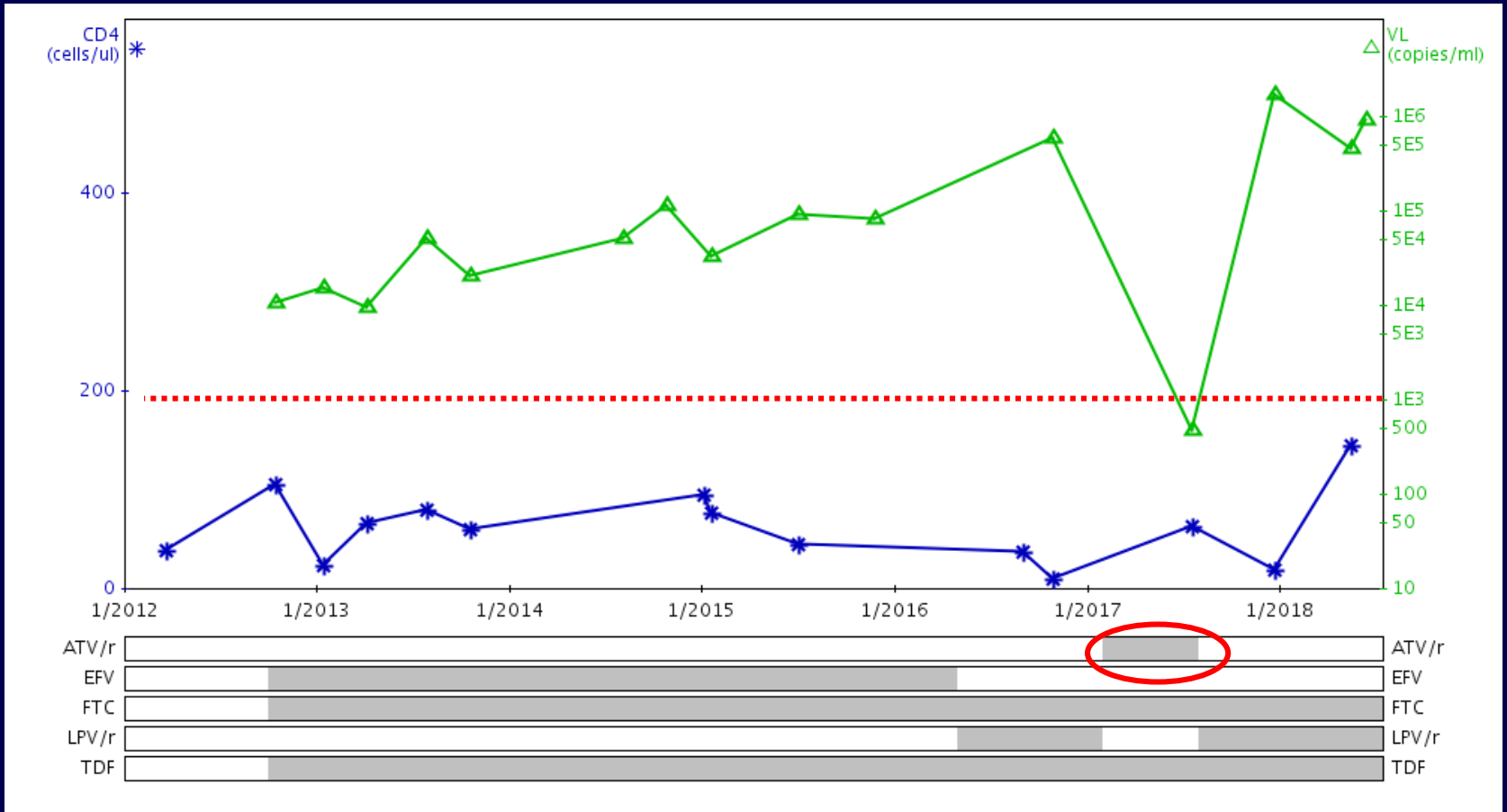
34-year old HIV-positive female

HIV diagnosis 2012

Pre-treatment CD4+ count 40 cells/µL

First-line regimen TDF/FTC/EFV 2012-2016

Clinical chart



TDF/FTC/EFV

TDF/FTC/LPV/r

Virological failure

Diarrhoea

PTB (Xpert neg)

Shigellosis

Genotype

Genotypic resistance test report

Antiretroviral experience:	TDF, FTC, EFV, LPVr, ATV/r
Subtype:	HIV-1 Subtype C
Resistance interpretations:	HIVdb 8.6

Drug	Mutations	Description	Score
Zidovudine	K65R, M184V, K219E	Susceptible	-15
Lamivudine	K65R, M184V	High-level resistance	90
Abacavir	K65R, M184V, K219E	High-level resistance	65
Emtricitabine	K65R, M184V	High-level resistance	90
Tenofovir	K65R, M184V, K219E	Intermediate resistance	55
Nevirapine	L100I, K103N	High-level resistance	120
Efavirenz	L100I, K103N	High-level resistance	120
Etravirine	L100I, K103N	Intermediate resistance	30
Lopinavir/r	L10F, M46I, I54V, L76V, V82A	High-level resistance	120
Atazanavir/r	M46I, I54V, V82A	High-level resistance	60
Darunavir/r	L10F, L76V	Low-level resistance	25

Third-line ART algorithm

AZT: -15 (S) - AZT naïve
TDF: 15 (L)
DRV: 25 (L)

PI score ≥15 ✓

DRV/r
+ 3TC or FTC
+ AZT or TDF

✓ TDF/AZT ≥30
or
DRV/r ≥15

✗ TDF/AZT ≥30
and
DRV/r ≥15
And
ETR <30

Add RAL/DTG

Add ETR

DRV/r
3TC
AZT
DTG

Clinical case

45-year old HIV-positive female

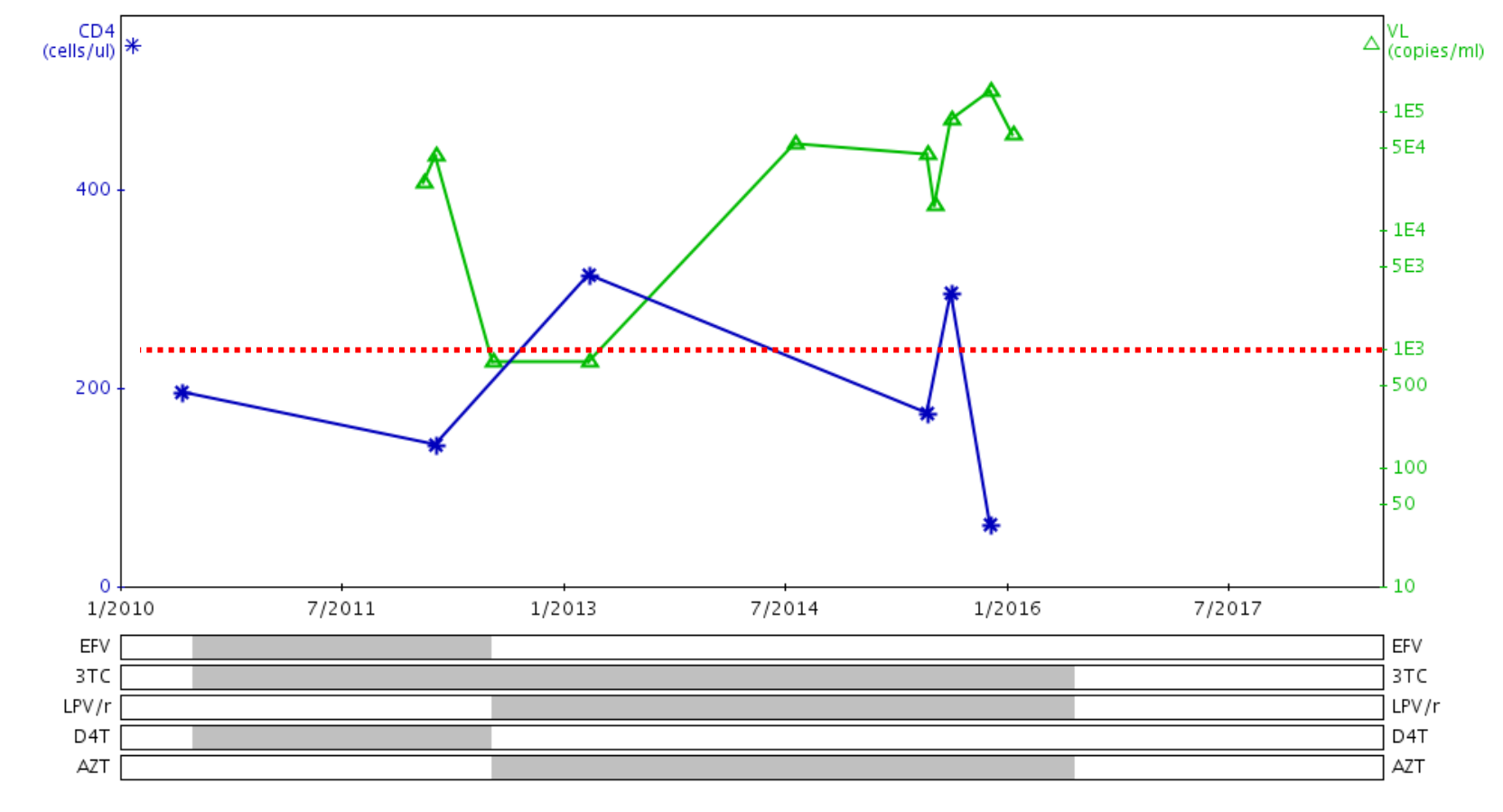
HIV diagnosis 2010

Pre-treatment CD4+ count 198 cells/µL

First-line regimen d4T/3TC/EFV 2010-2012

Second-line regimen AZT/3TC/LPV/r 2012-2016

Clinical chart



d4T/3TC/EFV → Virological failure

AZT/3TC/LPV/r x 3 yrs

→ Pregnancy

→ PTB (Xpert +)

→ Genotype

Genotypic resistance test report

Antiretroviral experience:	d4T, 3TC, EFV, AZT, LPVr
Subtype:	HIV-1 Subtype C
Resistance interpretations:	HIVdb 8.6

Drug	Mutations	Description	Score
Zidovudine	A62V, K65R, D67GNS, V75I, F116Y, Q151M, M184V, K219E	High-level resistance	100
Lamivudine	A62V, K65R, V75I, F116Y, Q151M, M184V	High-level resistance	120
Abacavir	A62V, K65R, D67GNS, V75I, F116Y, Q151M, M184V, K219E	High-level resistance	150
Emtricitabine	A62V, K65R, V75I, F116Y, Q151M, M184V	High-level resistance	120
Tenofovir	A62V, K65R, D67GNS, V75I, F116Y, Q151M, M184V, K219E	High-level resistance	110
Nevirapine	K103N	High-level resistance	60
Efavirenz	K103N	High-level resistance	60
Etravirine	K103N	Susceptible	0
Lopinavir/r	L10F, I54V, L76V, V82A	High-level resistance	90
Atazanavir/r	I54V, V82A	Intermediate resistance	40
Darunavir/r	L10F, L76V	Low-level resistance	25

Third-line ART algorithm

AZT: -100 (H)
TDF: 110 (H)
DRV: 25 (L)

PI score ≥15 ✓

DRV/r
+ 3TC or FTC
+ AZT or TDF

✓ TDF/AZT ≥30
or
DRV/r ≥15

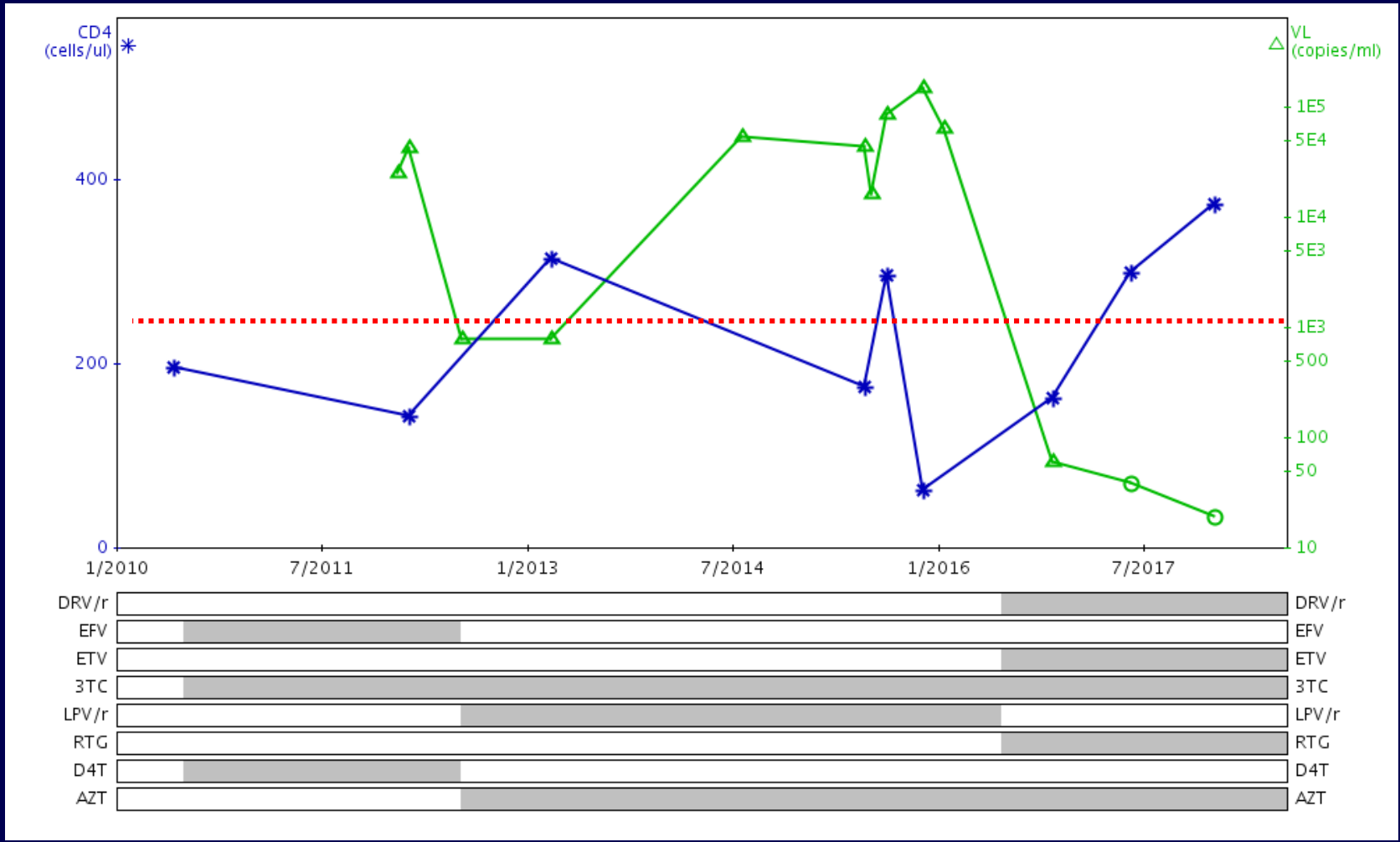
Add RAL/DTG

✓ TDF/AZT ≥30
and
DRV/r ≥15
And
ETR <30

Add ETR

DRV/r
3TC
AZT
RAL
ETR

Clinical chart



Virological failure

PTB (Xpert +)

Pregnancy

3rd Line ART

Third-line Antiretroviral Therapy Programme in the South African Public Sector: cohort description and virological outcomes

M Moorhouse, G Maartens, WDF Venter, MYS Moosa, K Steegen, K Jamaloodien, MP Fox, F Conradie.

Description of the third-line cohort

August 2013 to July 2014 - **144** approved for third-line ART

Factor		Median	IQR
Age (years)		41	19-47
CD4+ count at submission (cells/uL)		172	128 -351
Viral load at submission (copies/mL)		14759	314-90378
		N	%
Women		85	60
Year of ART initiation	<2004	19	13.2
	2004-2007	75	52.1
	2008-2011	48	33.3
	Unknown	2	1.4
Year of PI/r initiation	<2004	4	2.8
	2004-2007	16	11.1
	2008-2011	45	31.3
	2012-2013	9	6.3
	Unknown	70	48.6

Resistance profiles: 144 patients failing PI based ART

ARV		Resistance		
	N	Median (IQR) Resistance scores*	N resistant Score ≥15	%
NNRTI				
Efavirenz	140	60 (10-90)	104	74
Nevirapine	140	75 (15-110)	108	77
Etravirine	140	5 (0-22.5)	52	37
NRTI				
Lamivudine	140	65 (60-75)	118	84
Zidovudine	141	65 (5-90)	102	72
Tenofovir	141	25 (10-42)	97	69
Abacavir	141	50 (20-70)	129	91
PI				
Lopinavir	144	80 (63.5-95)	139	97
Atazanavir	144	60 (40-70)	141	98
Darunavir	144	20 (5-25)	82	57
Stanford resistance scores*			N	%
Lopinavir score	> 29		134	93
	> 59	High Ω	113	78
Darunavir score	> 29	Intermediate Ω	29	20
	> 59		1	0.7
Etravirine score	> 29	Intermediate Ω	29	21
	> 59		5	3.6

Stanford score

- Low level: 15 -29
- Intermediate level: 30-59
- High level: >59

Treatment and Outcome

- 144 initiated on DRV/r
- 101 on RAL
- 33 on ETR
- At least one VL at 6 months after initiation (n=118)
  - 83% (98/118) had VL <1000
  - 79% (93/118) had VL <400.

Conclusion

A high proportion of third-line patients with follow-up viral loads were virologically suppressed

Third line algorithm is working but important to pick up PI resistance as early as possible.

In cases where one is recycling NRTIs be vigilant for lack of complete suppression and consider bolstering regimen with an INSTI.

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Every Patient presented had TB at some point

Managing TB in the context of second and third line ART

Which TB drug is associated with PI failure

A. Isoniazid

B. Ethambutol

C. Pyrazinamide

D. Rifampicin

Which PI can be used with Rifampicin based ATT

A. Lopinavir/ritonavir

B. Darunavir/ritonavir

C. Atazanavir/ritonavir

D. Indinavir/ritonavir

How should dose adjust when using Rifampicin and Aluvia?

A. Double the dose of aluvia (4 bid)

B. Double dose the Rifafour

C. Dose aluvia three times a day (2 tds)

D. Further increase ritonavir (LPV 400 + ritonavir 400 bid)

E. None of above

Current Strategy

Rifampin[459] (Rifampicin)(Rifadin)	600 mg QD	400/100 mg Q12h x 7 days, 600/150 mg Q12H x 7 days then 800/200 Q12H x 7 days	-	Lopinavir AUC: decreased 71% (on 400/100 mg Q12H); AUC: decreased 40% (on 600/150 mg Q12H); AUC: no significant change (on 800/200 mg Q12H)	Decreased lopinavir effects at lower dosages	Induction of CYP450 3A4 by rifampin	Avoid coadministration. If combination can not be avoided lopinavir/ritonavir dosage of 800/200 mg Q12H appears to compensate for rifampin induced 3A4 induction

These initial positive clinical and experimental experiences with double-dose lopinavir/ritonavir suggest that these regimens may be tolerable and effective among at least some patients with HIV-related tuberculosis, but prospective data to guide patient and dose selection are still limited. ***Higher-dose lopinavir/ritonavir should only be used with close clinical and laboratory monitoring for possible hepatotoxicity in cases where there is a pressing need to start antiretroviral therapy and no other antiretroviral drug options are available.***

What alternate to rifampicin?

A. Rifabutin

B. Double dose rifampicin

C. Rifapentine

D. Riftimaxcid

How do you dose rifabutin?

A. 600mg daily

B. 450mg daily

C. 300mg daily

D. 150mg daily

E. 150mg three time as week

F. I don’t care!

Main toxicities: Rifabutin

- Uveitis
- Hepatotoxicity
- Neutropenia.

Conclusion

- The algorithm based approach to third line is effective and easy to implement
- Managing TB in the context of second line and third line requires treatment modification.

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