UNIVERSITY OF KWAZULU-NATAL ™

INYUVESI YAKWAZULU-NATALI

Clinical skills building - HIV drug resistance

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UKZN INSPIRING GREATNESS

Clinical case

44-year old HIV-positive male

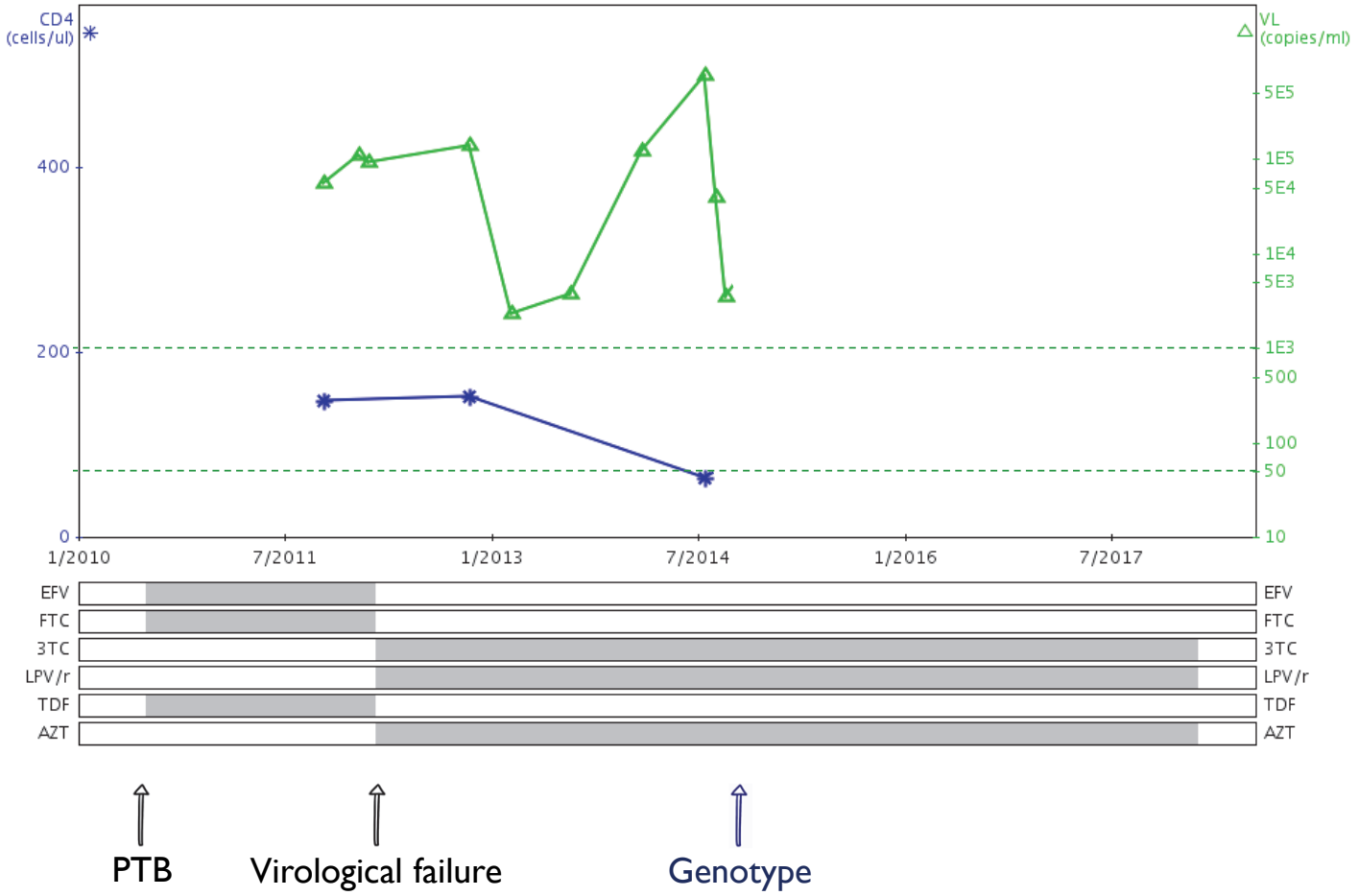
HIV diagnosis 2010

Pre-treatment CD4+ count not known

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

4 x episodes pulmonary TB (last 2010)

Clinical chart



Genotypic resistance test report

Antiretroviral experience: TDF, FTC, EFV, AZT, 3TC, LPVr
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

Question

Does the genotypic resistance test help you to understand this man's ART adherence?

A. Yes - he must be completely non-adherent to ART

B. Yes - he must have differential adherence, i.e. he is taking AZT/3TC but not LPVr

C. Yes – he must have poor adherence but difficult to say more than that

D. No - it doesn't help at all

Routine genotypic resistance test data

NHLS, KwaZulu-Natal, 2015-16

- All genotypic resistance tests performed for adult second-line ART failure 2015-16 (N = 353)

- Median age 34 yrs (IQR 19-42)
- 59% female
- 93% LPVr-based regimens

- Median duration second-line ART 30 months (IQR 18-48)
- Median duration all ART 72 months (IQR 50-95)

Question

In KwaZulu-Natal 2015-2016, approximately what proportion of adults with a resistance test done for virological failure on second-line ART had at least one major PI mutation?

A. 10%

B. 20%

C. 33%

D. 50%

E. 75%

Routine HIV drug resistance testing

NHLS, KwaZulu-Natal, 2015-2016

33% at least one major protease mutation

So the majority were failing without protease resistance

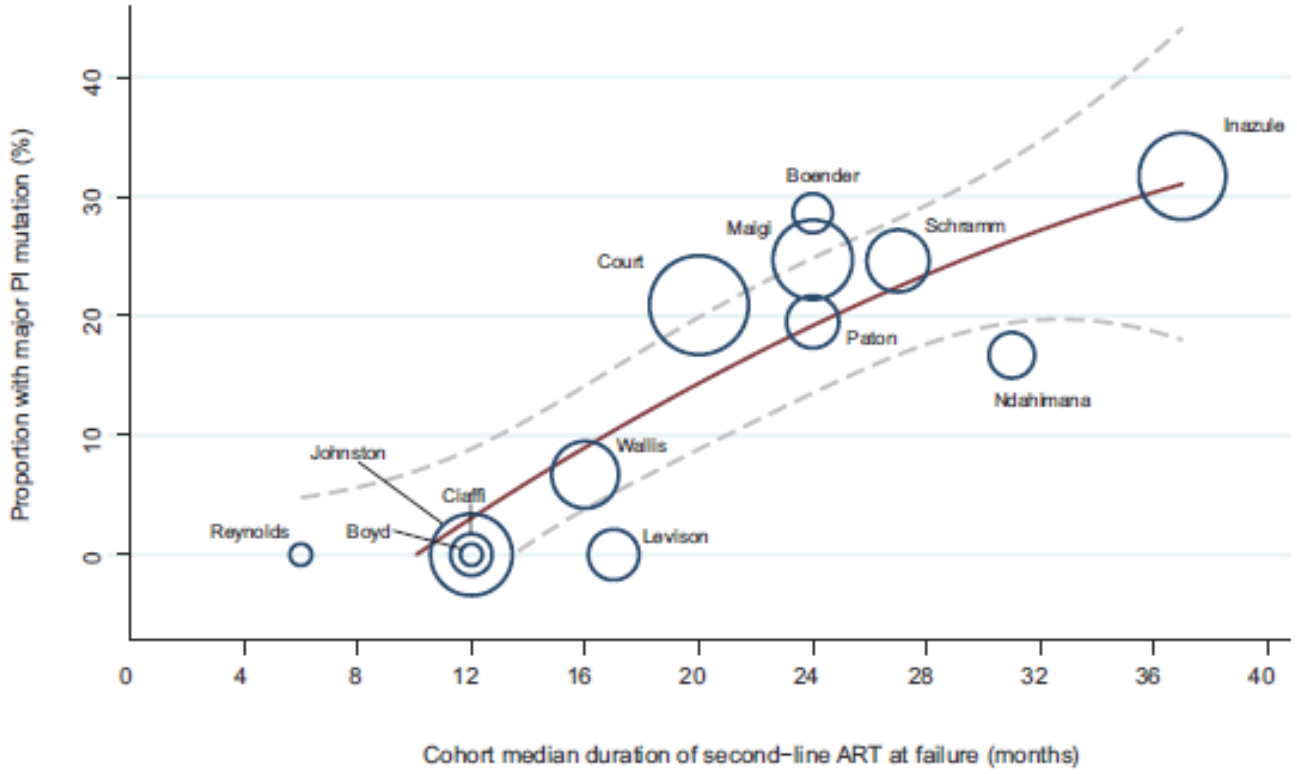
66% NRTI mutations

64% NNRTI mutations

19% no drug resistance mutations

PI resistance at second-line ART failure

Meta-analysis of 13 studies from sub-Saharan Africa



At a cohort level, proportion with major PI mutations is closely associated with median time on second-line ART

Stockdale CID 2018

Why do most adults with virological failure on second-line ART have no major PI mutations?

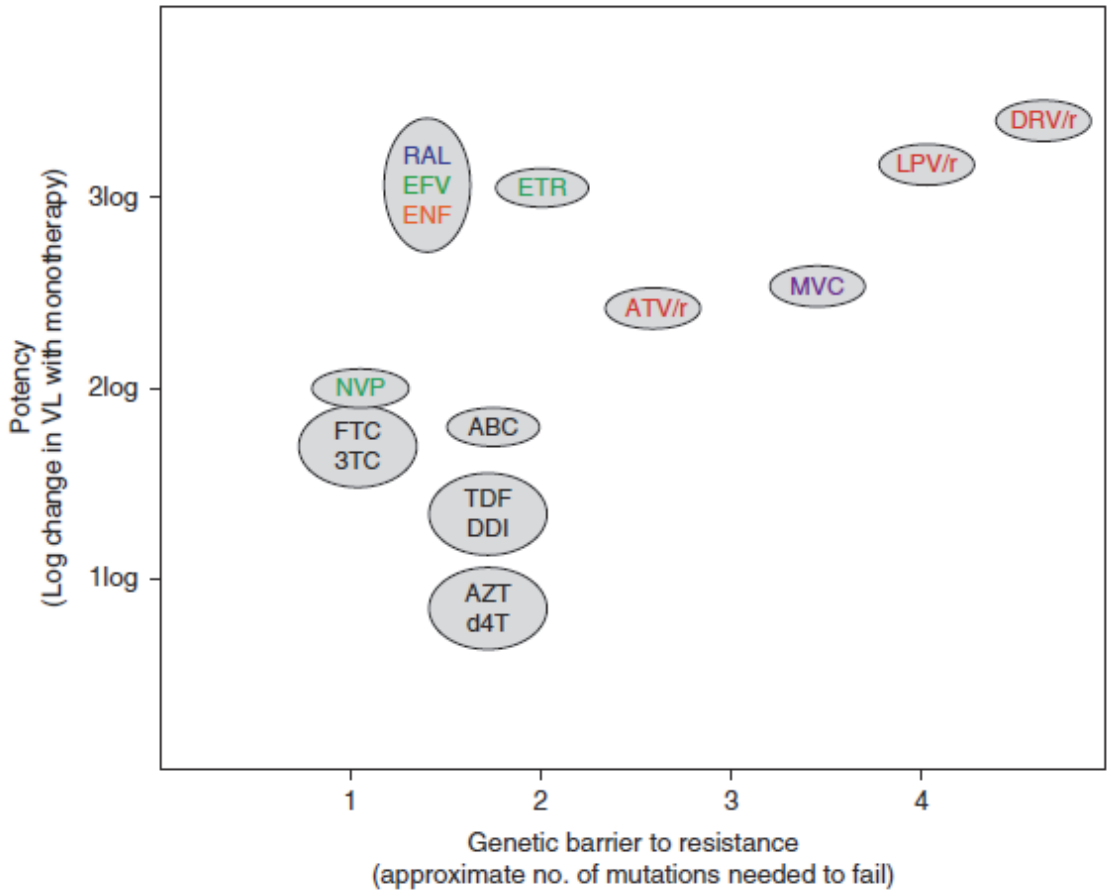
The development of protease inhibitor resistance is relatively uncommon at all adherence levels

Viral fitness of resistant virus

Genetic barrier to resistance

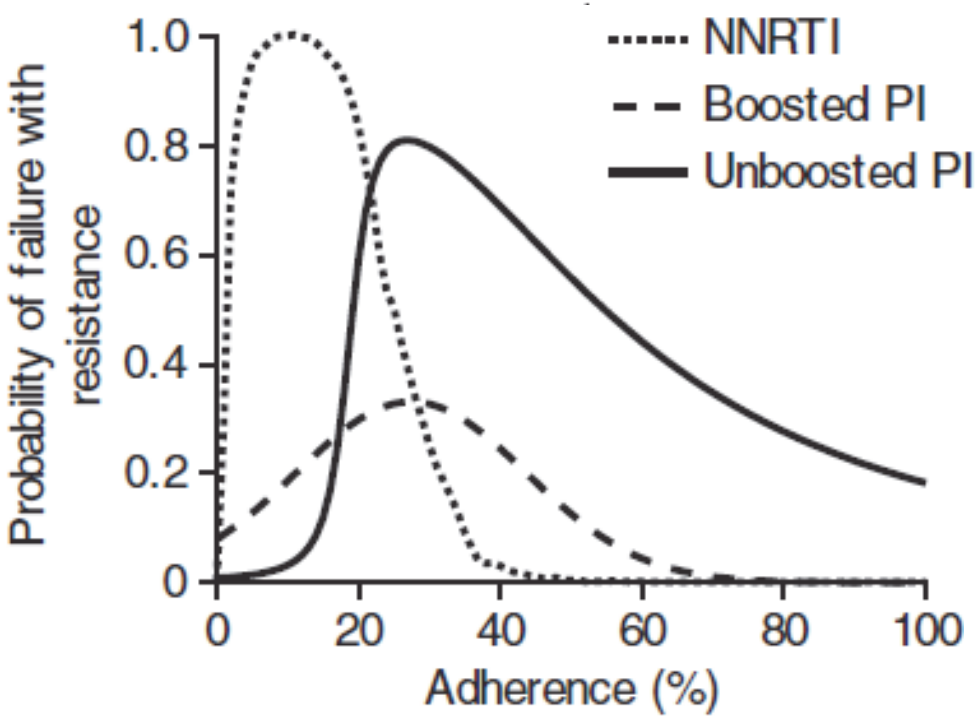
Potency

Why do most adults with virological failure on second-line ART have no major PI mutations?



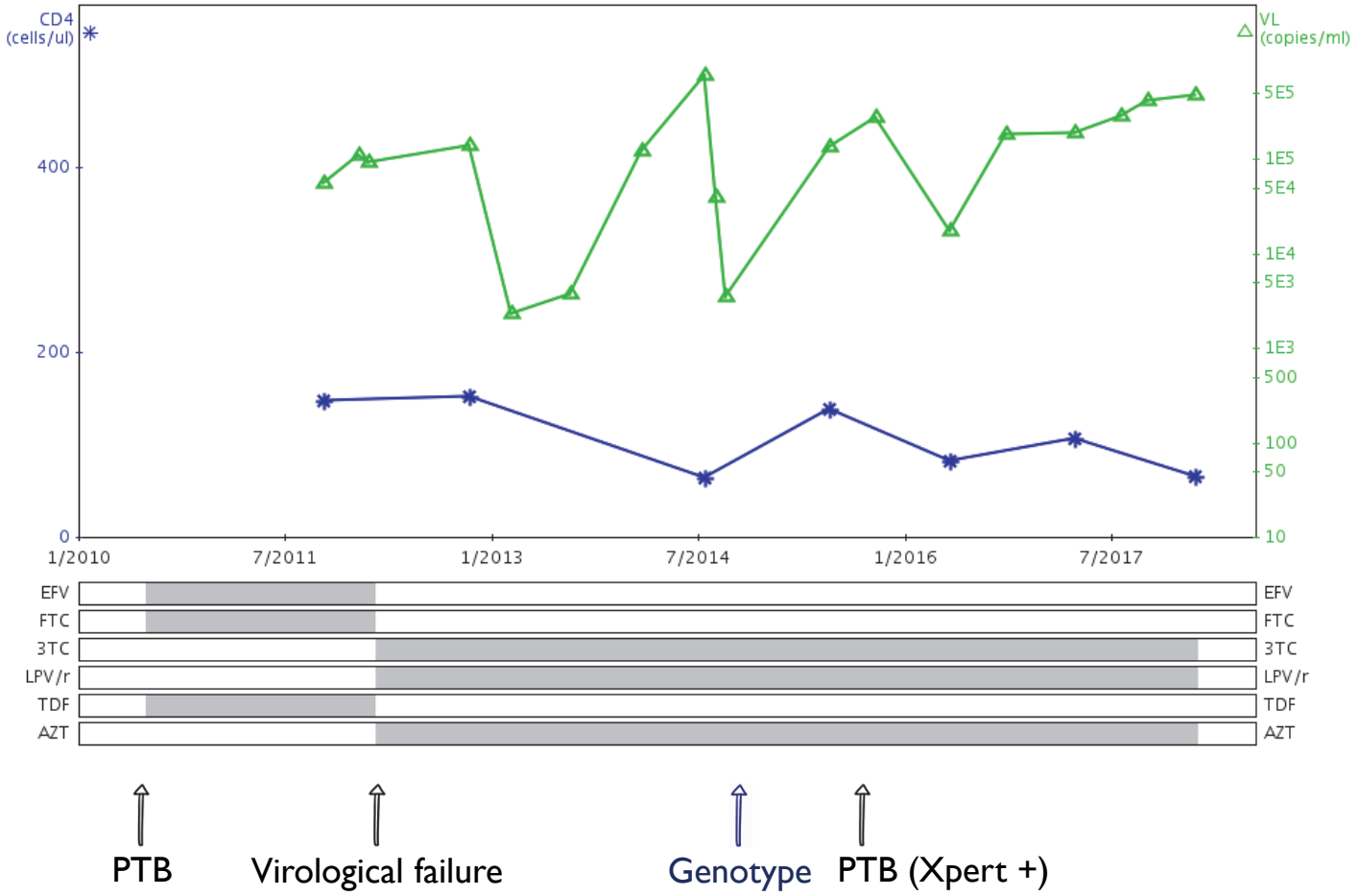
Why do most adults with virological failure on second-line ART have no major PI mutations?

Association between adherence and drug resistance quite different for PIs compared to NNRTIs



Rosenbloom Nature Med 2012

Clinical chart



Question

When would you repeat a resistance test in an adult patient who has no major PI mutations, continues on second-line ART and has persistent viraemia despite enhanced adherence counselling?

A. After 3 months if VL >1000 copies/mL

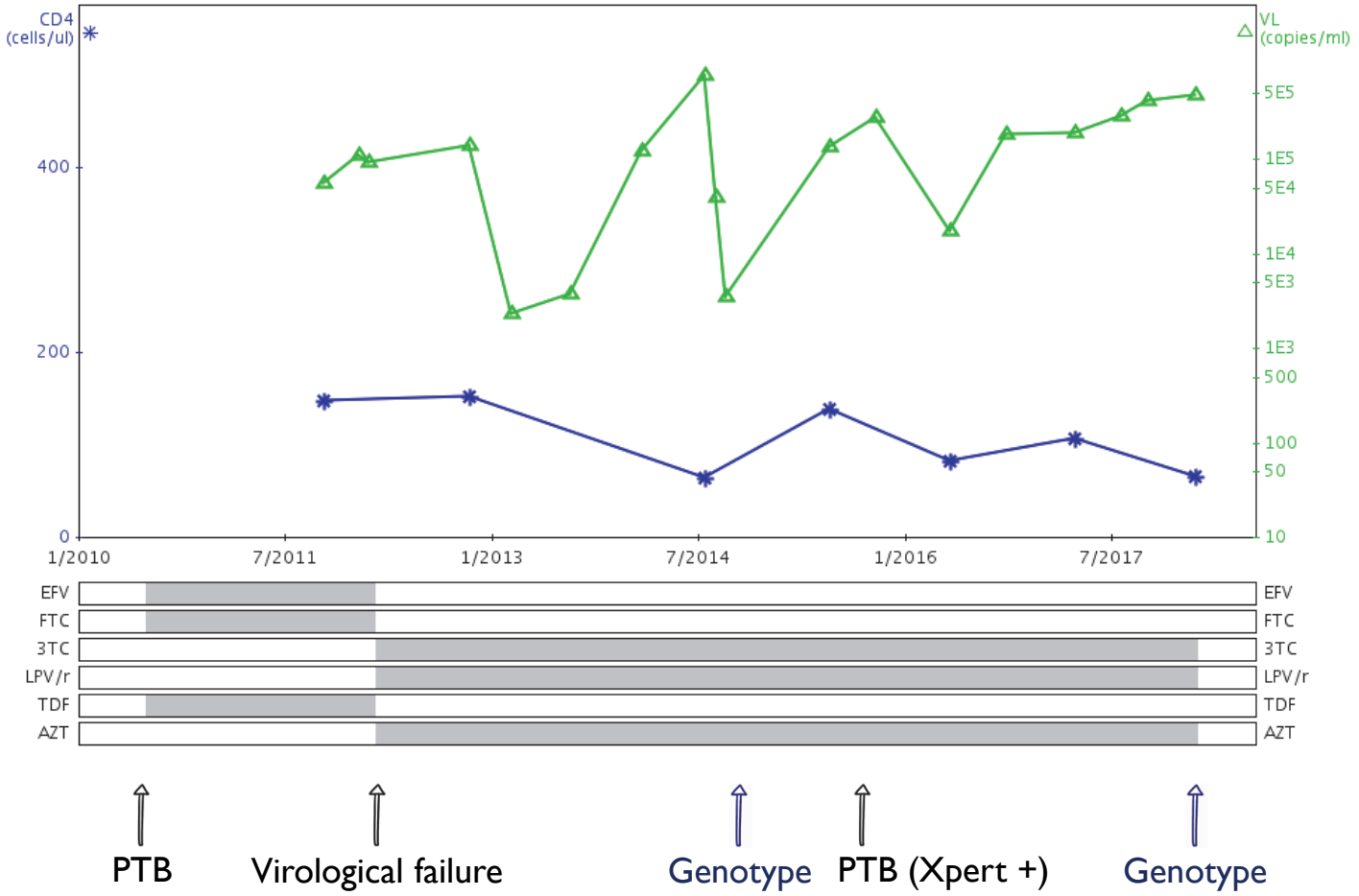
B. After 3 months if <1 $\log_{10}$ copies/mL decrease in VL

C. After 6 months if VL >1000 copies/mL

D. After at least 12 months if persistent VL >1000 copies/mL

E. When immunological or clinical failure develops

Clinical chart



Genotypic resistance test report

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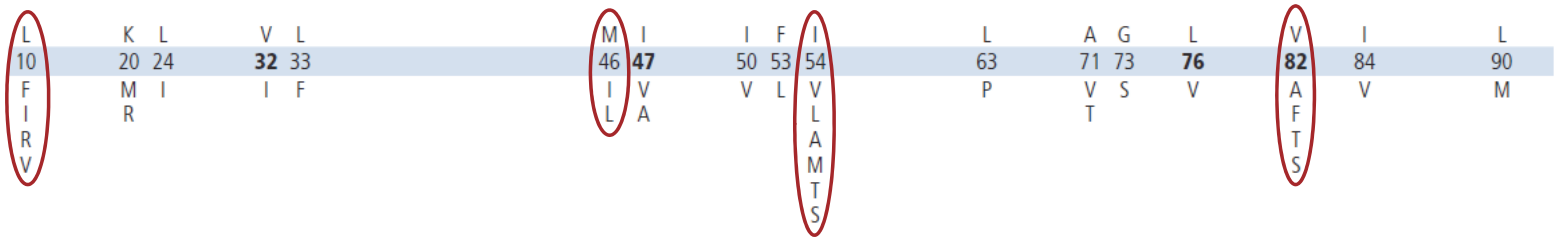
Subtype: HIV-1 Subtype C
Resistance interpretations: HIVdb 8.6

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

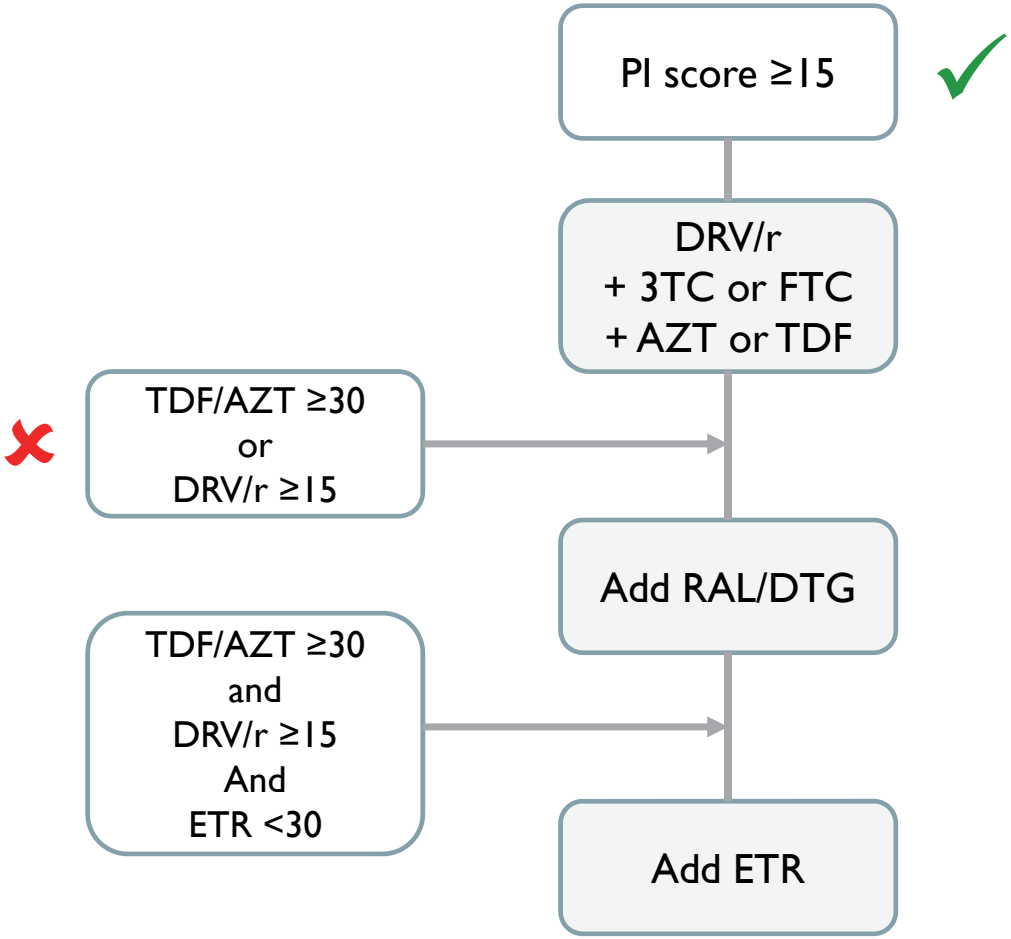
Protease mutations

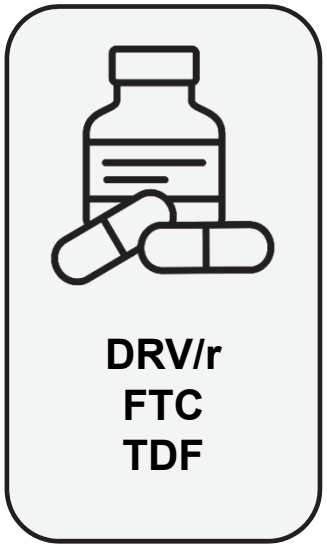


Major PI mutations – mutations occurring within the active binding site of protease enzyme which disrupt PI binding; have the greatest impact on PI susceptibility

Minor PI mutations – mutations outside the active binding site; can enhance resistance and can be compensatory, i.e. restore enzyme activity or reverse viral fitness defects

Third-line ART algorithm





Case progress

Admitted to hospital while waiting for third-line ART

Treated for chest infection & gastroenteritis (antibiotics, fluids)

Sputum Xpert Ultra negative

Attends clinic one week post-discharge to start third-line ART

Case progress

Admitted to hospital while waiting for third-line ART

Treated for chest infection & gastroenteritis (antibiotics, fluids)

Sputum Xpert Ultra negative

Attends clinic one week post-discharge to start third-line ART

Blood chemistry:		
Sodium	**132 L**	mmol/L
Potassium	3.8	mmol/L
Chloride	103	mmol/L
Bicarbonate	**20 L**	mmol/L
Anion gap	13	mmol/L
Urea	**8.6 H**	mmol/L
Creatinine and estimated GFR:		
Creatinine	**120 H**	umol/L
eGFR (MDRD formula)	57	mL/min/1.73 m^2
Liver function tests:		
Total protein	**79 H**	g/L
Albumin	**31 L**	g/L
Total bilirubin	8	umol/L
Alanine transaminase (ALT)	**144 H**	U/L
Alkaline phosphatase (ALP)	**267 H**	U/L
Gamma-glutamyl transferase (GGT)	**259 H**	U/L

Calculated CrCl 61 mL/min

Question

What would you do now?

A. Start recommended third-line ART regimen (TDF/FTC/DRV/r) immediately

B. Start modified third-line ART regimen (ABC/3TC/DRV/r) immediately

C. Re-admit to hospital for further investigation

D. Review in one week with repeat U&Es, LFTs

E. Phone local ID specialist for advice

Case progress

Admitted to hospital while waiting for third-line ART

Treated for chest infection & gastroenteritis (antibiotics, fluids)

Sputum Xpert Ultra negative

Attends clinic one week post-discharge to start third-line ART

Repeat U&Es, LFTs one week later

Blood chemistry:		
Sodium	**134 L**	mmol/L
Potassium	3.5	mmol/L
Chloride	101	mmol/L
Bicarbonate	25	mmol/L
Anion gap	12	mmol/L
Urea	**8.2 H**	mmol/L
Creatinine and estimated GFR:		
Creatinine	100	umol/L
eGFR (MDRD formula)	>60	mL/min/1.73 m^2
Liver function tests:		
Albumin	**31 L**	g/L
Total bilirubin	10	umol/L
Alanine transaminase (ALT)	24	U/L
Alkaline phosphatase (ALP)	112	U/L
Gamma-glutamyl transferase (GGT)	**128 H**	U/L

Key learning points

- Most adults with virological failure on second-line ART do not have major PI mutations
- Adherence measurement, support and interventions remain critical to prevent development of drug resistance
- Genotypic resistance testing should be repeated in people with persistent viraemia despite good adherence on second-line ART, but optimal timing not clear
- Once PI resistance occurs, most have high-level LPVr resistance and at least low-level DRV/r resistance