HIV drug resistance testing in treatment experienced patients including advanced disease

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Outline

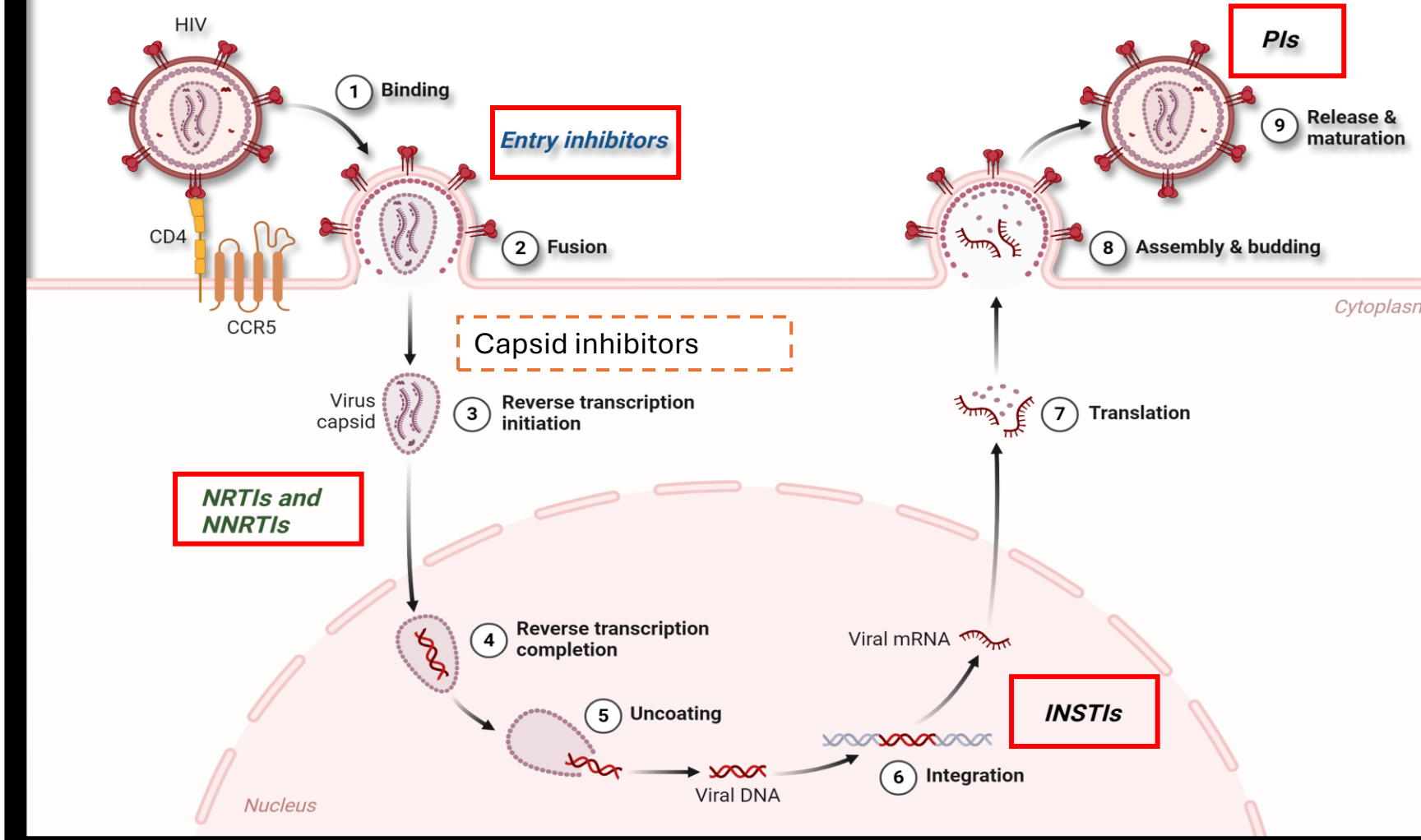
- HIV replication and antiretroviral treatment (ART)
- The success of combination ART
- Drug resistance testing
- HIV evolution, fitness and genetic barrier of drugs
- The rationale for changing national regimens
- Dolutegravir regimens and drug resistance
- Treatment and testing algorithms and evidence-based changes
- Third-line regimen selection
- The importance of drug resistance in patients with advanced disease

Background

Concepts and principles

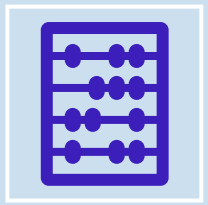
BioRender Disease Mechanisms – Infectious Diseases

HIV Replication Cycle



The success of combination antiretroviral therapy (1)

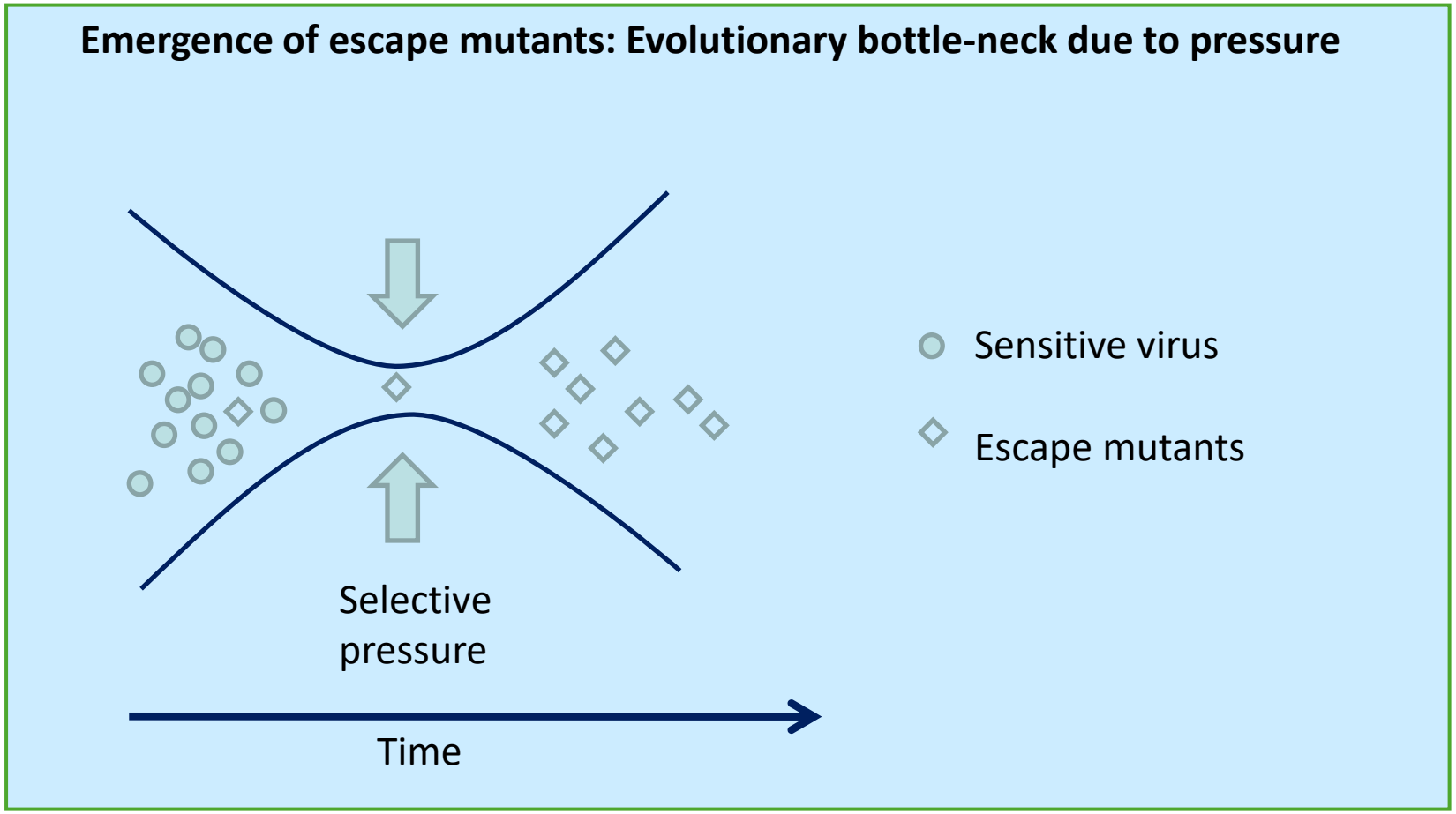
Viral reverse transcriptase lacks proofreading – mutations therefore happen frequently – about one mutation for each round of replication



Evolution however requires multiple rounds of viral replication

Resistance on monotherapy develops fast: not able to stop viral replication and halt evolution

Drug resistance selection



Rapid mutation and pressure:

Evolution in real-time: most “fit” variants will survive

Virus will tend to escape pressures by evolution

- Immune pressure
- Drug pressure

The success of combination antiretroviral therapy (2)

- Combination antiretroviral therapy, initially called highly active antiretroviral therapy (HAART) since 1996 (initially PI + 2 NRTIs, followed by NNRTI + 2 NRTIs) and later including INSTIs
- Combination ART effectively blocks viral replication:
  - multiple drugs target different steps in viral replication and have additive (or possibly synergistic) effect on viral load suppression
- Joint probability of having resistance to all drug components is low for combination therapy
- Regimens include drugs with high genetic barrier and fitness price of mutations

The success of combination ART (3)

- Patients with suppressed HIV viral loads are very unlikely to develop drug resistance as they are very unlikely to have any viral evolution
- However, drug resistance can occur when there are persistent low level viraemia
- Achieving viral load suppression through good adherence is key

Van Zyl GU, Katusiime MG, Wiegand A, McManus WR, Bale MJ, Halvas EK, *et al*. **No evidence of HIV replication in children on antiretroviral therapy**. *J Clin Invest* 2017; **127**:3827–3834.

Fitness

- Fitness = ability of a particular virus to survive in a **particular environment**
- Fitness is measured by determining the reproductive number (number of cells infected per virus generation)

Drug resistance and relative fitness

- Drug resistance = higher concentration of drug is required to achieve the same effect
- Resistant viral strain able to replicate better than a wild-type strain in the presence of the drug – relatively more fit in the presence of the drug than wild-type virus
- Drug resistance mutations often have a cost = e.g. decreased replication rate in the **absence of the drug**
- Therefore, most drug resistant strains are relatively less fit than wild-type in the absence of a drug

Fitness interactions

- Tenofovir, Lamivudine, Dolutegravir (TLD)
- Mutations that confer drug resistance to TDF (K65R) and lamivudine/3TC (M184V) reduce the acquisition of INSTI resistance mutations e.g. R263K

Oliveira M, Ibanescu RI, Pham HT, Brenner B, Mesplède T, Wainberg MA. **The M184I/V and K65R nucleoside resistance mutations in HIV-1 prevent the emergence of resistance mutations against dolutegravir**. *AIDS* 2016; **30**:2267.

Drug resistance testing methods

Phenotypic testing:

- expensive, time consuming
- valuable when a drug is new or resistance pattern is complex
- in ZA: rare outside clinical trials

Genotypic HIV drug resistance testing

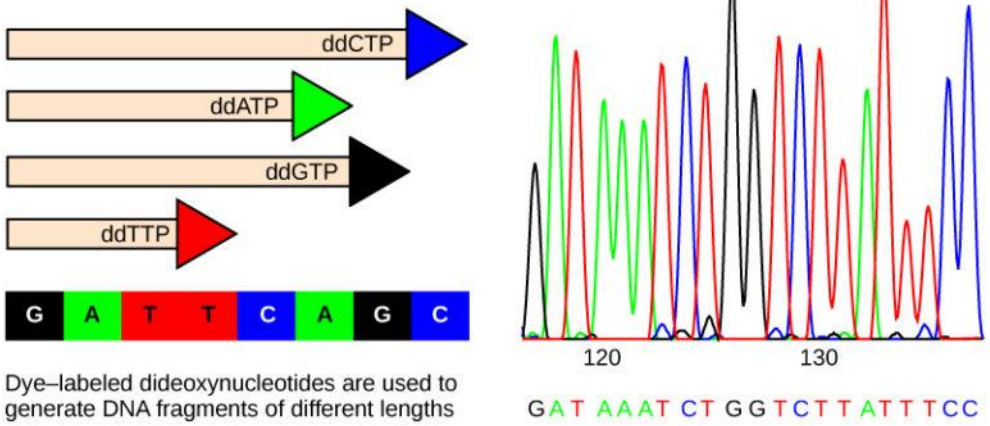
- Target genes are amplified by PCR
- Followed by sequencing (Sanger and recently more next generation sequencing) - > drug resistance interpretation

Genotypic HIV drug resistance testing process

RT-PCR of patient specimen

Automated Sanger/ next generation/ third generation sequencing

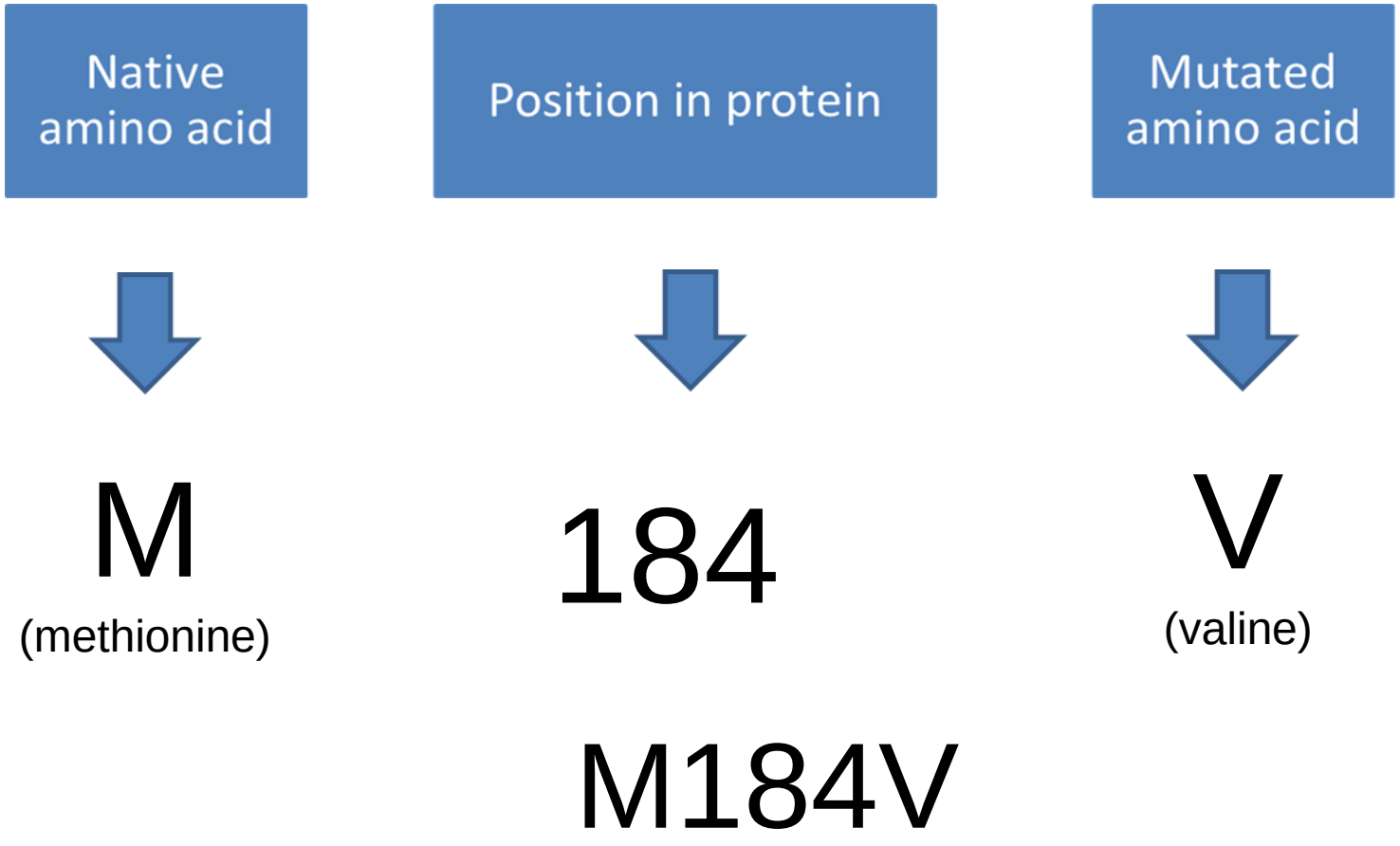
Resistance interpretation



Dye–labeled dideoxynucleotides are used to generate DNA fragments of different lengths

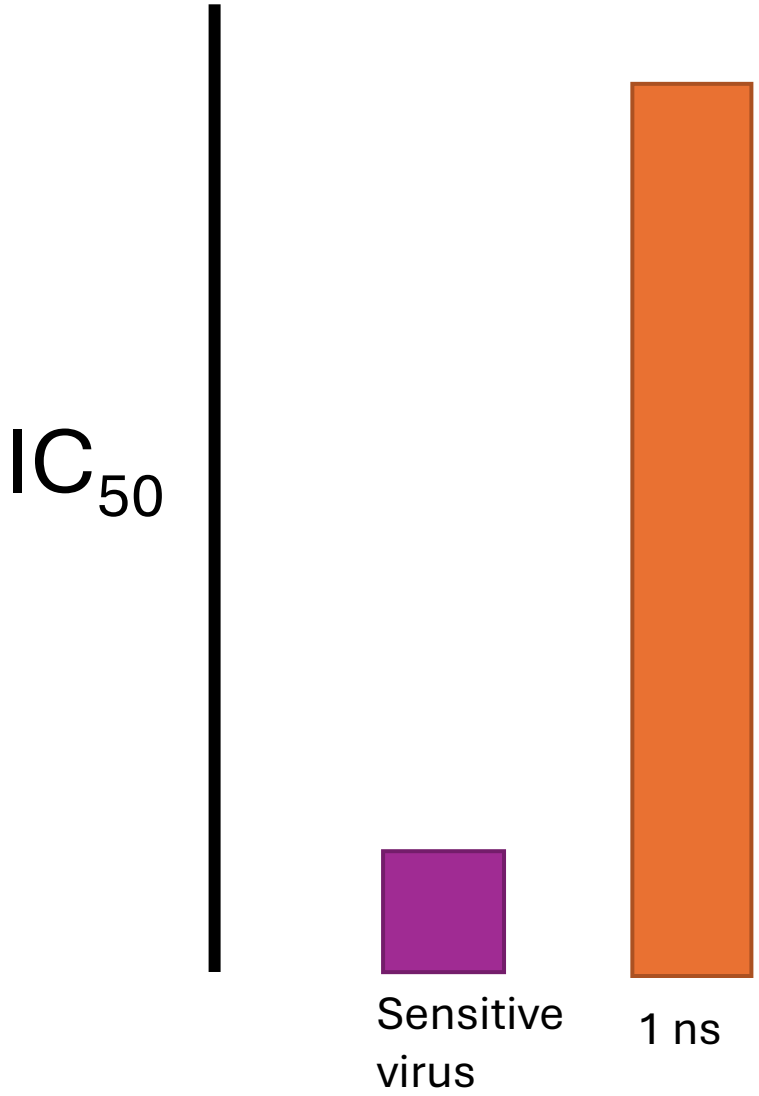
Stanford HIV Drug Resistance database; others

Mutation notation



Low genetic barrier drugs

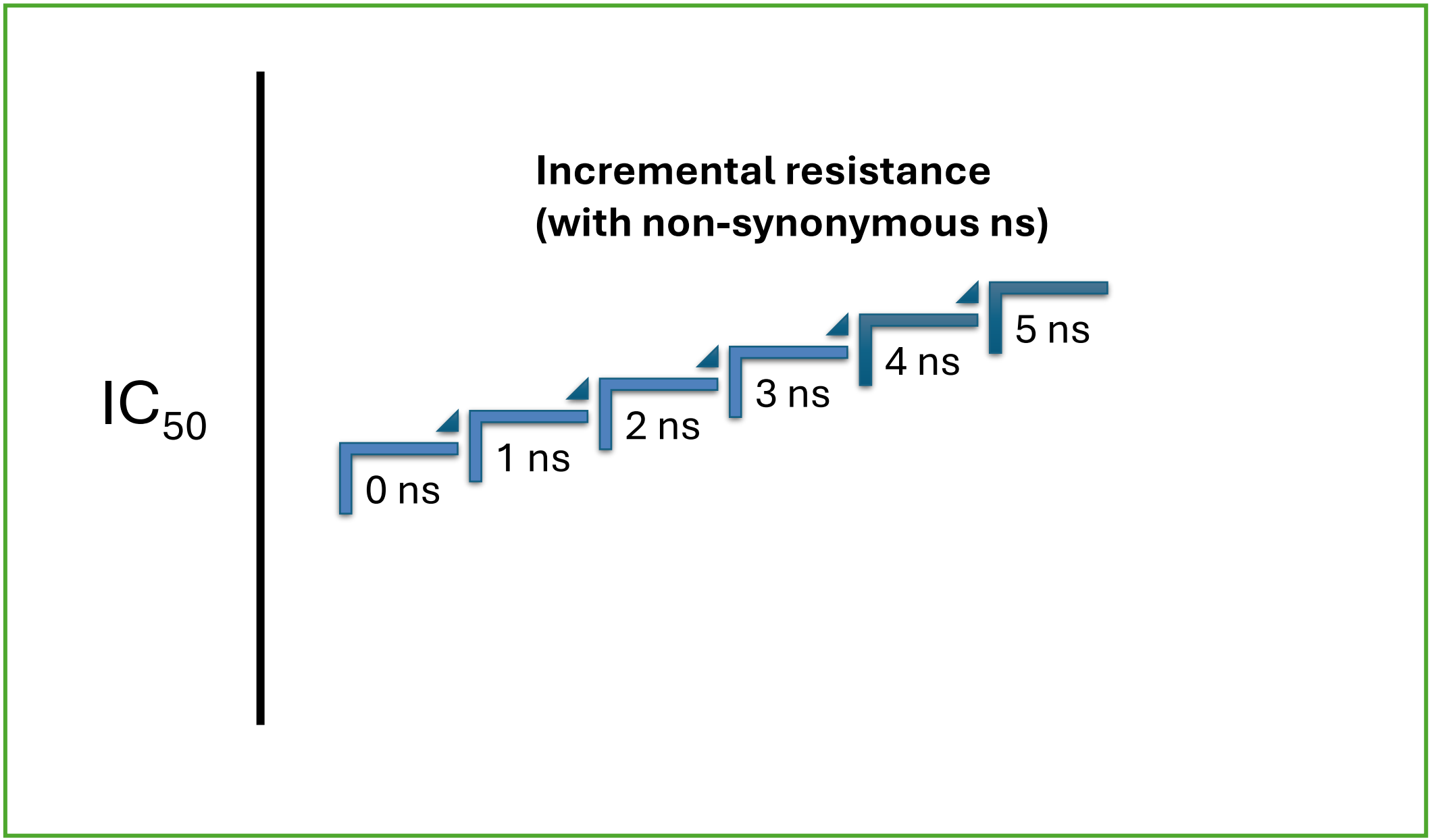
Single mutation results in large “fold change”



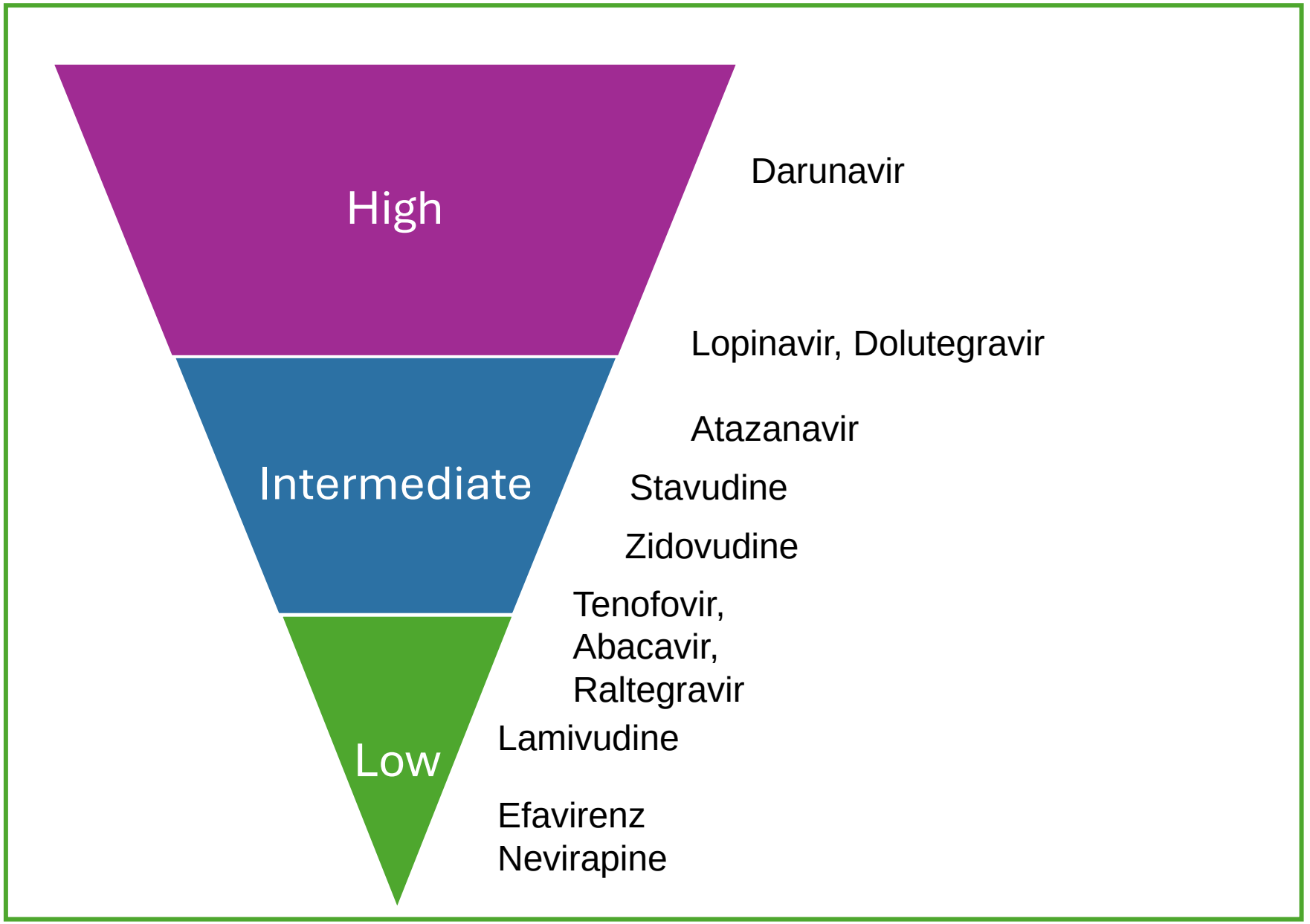
ns= nucleotide substitution

<u>Examples:</u>
K103N – EFV /NVP
M184V – 3TC/FTC

High genetic barrier drugs

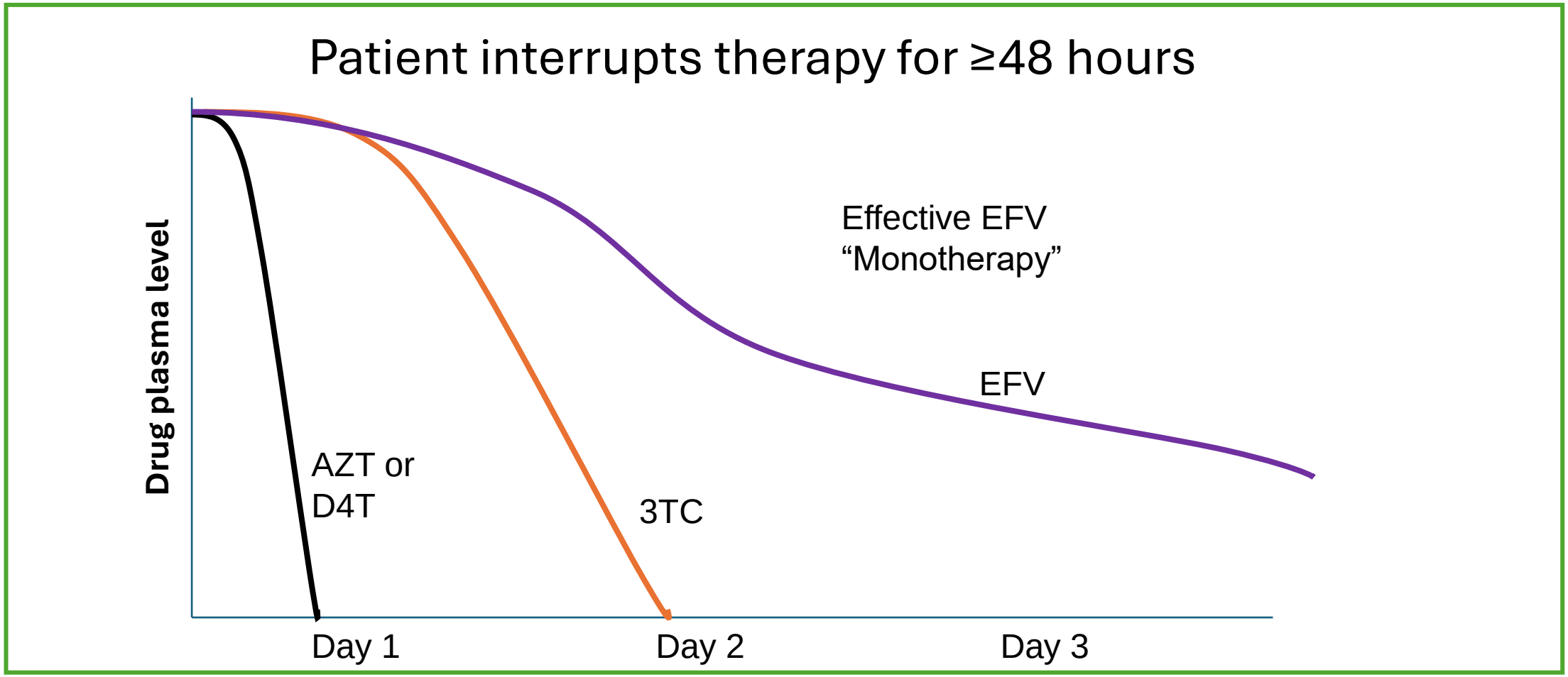


Arbitrary genetic barrier comparison



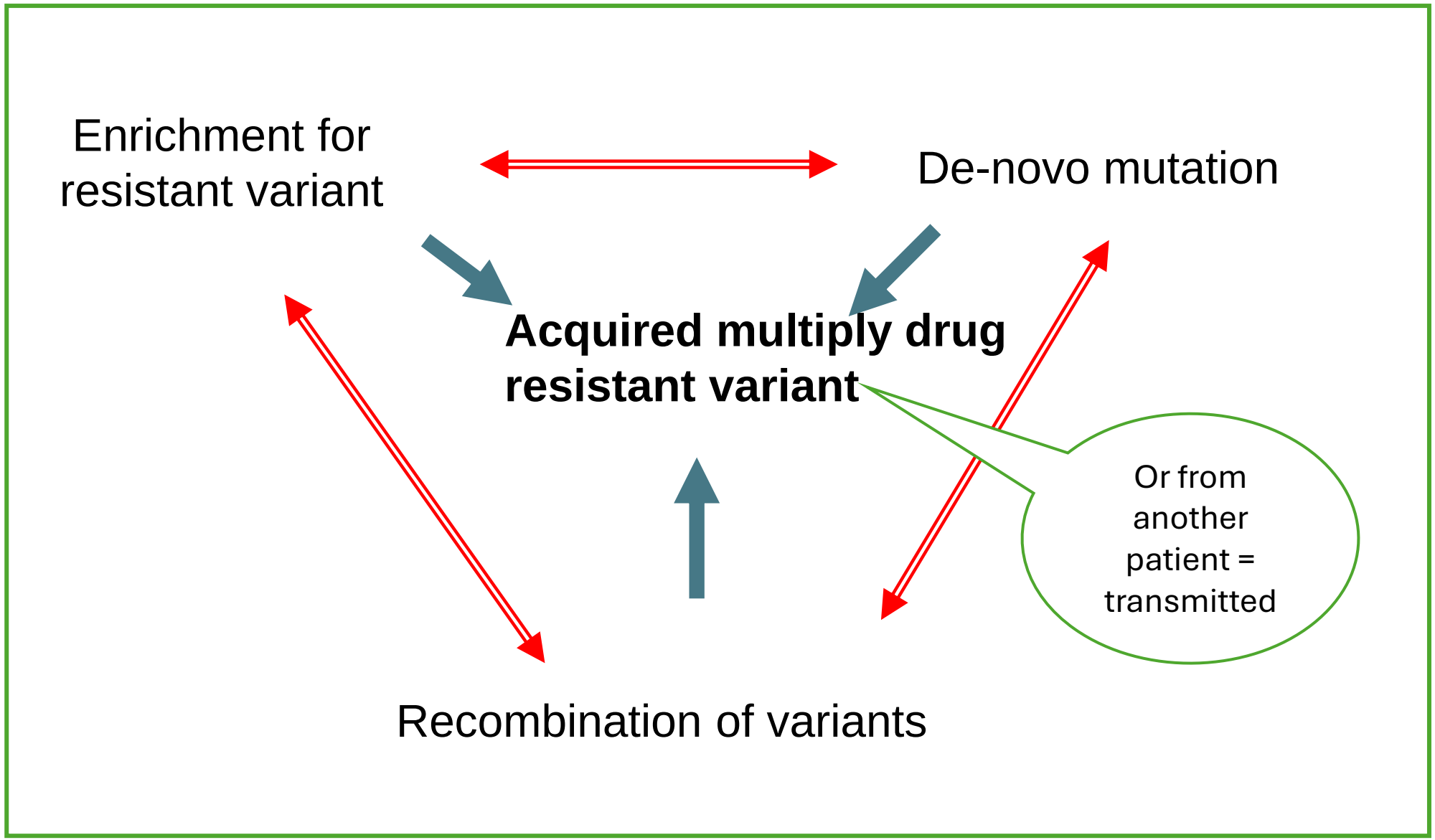
Mutations required, the difficulty of their evolution, and their fitness cost

NNRTI regimens: “Weekend interruptions” and effective monotherapy



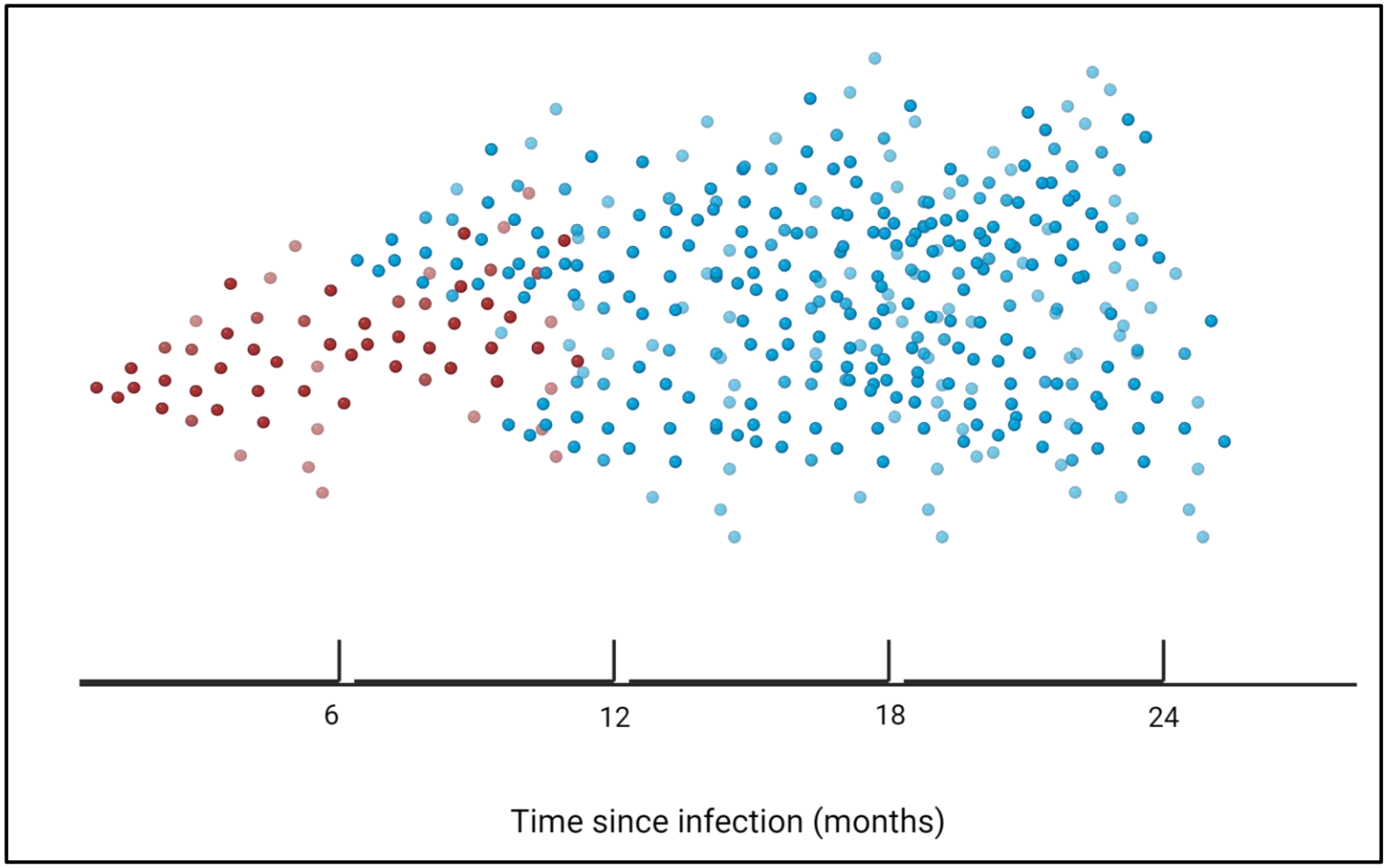
Parienti et al. (2004) Predictors of virologic failure and resistance in HIV-infected patients treated with nevirapine- or efavirenz-based antiretroviral therapy. *Clin Infect Dis,* 38**,** 1311-6
Parienti J-J, Das-Douglas M, Massari V, Guzman D, Deeks SG, et al. (2008) Not All Missed Doses Are the Same: Sustained NNRTI Treatment Interruptions Predict HIV Rebound at Low-to-Moderate Adherence Levels. PLoS ONE 3(7): e2783

How does acquired drug resistance arise?



Pre-treatment (or transmitted HIV drug resistance)

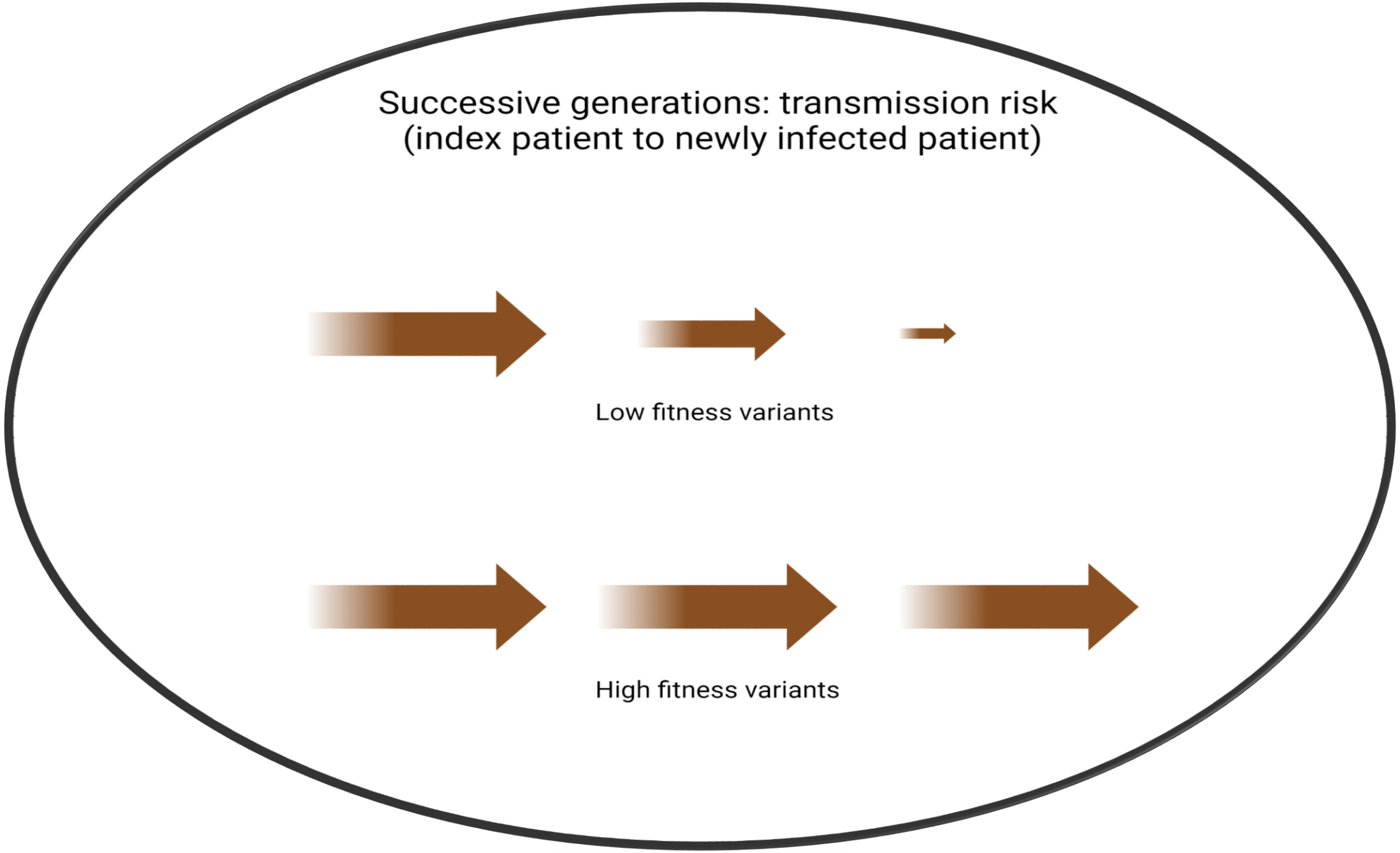
Drug resistance reversion



Less fit variants may revert faster

Testing soon after infection to detect transmitted resistance

Bennett et al 2008 The World Health Organization global strategy for prevention and assessment of HIV drug resistance. Antiviral Therapy 13 Suppl 2:1-13


Successive generations: transmission risk
(index patient to newly infected patient)
Low fitness variants
High fitness variants

Current ART treatment guidelines (WHO)

- **Dolutegravir in combination with two NRTIs**
  - **Preferred first-line ART** (alternative 400 m
  - **Preferred second-line ART after NN** boosted PI regimens for patients who have failed a first-li
- In practice:
  - Generic fixed dos d adherence benefit
  - Tenofovir, lamiv vir (TLD) for first-line = TLD-1
  - Therapy experien (second-line): TLD-2

Second generation INSTIs especially DTG-including regimens predominate world-wide in ART treatment

World Health Organization, “Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach,” World Health Organization, 2021

The recent need to change guidelines

01

High levels of pre-treatment NNRTI resistance

02

DTG-based ART success ≥ EFV-based regimens in several studies

03

Longer expected durability of DTG-based first line ART due to very low risk of drug resistance

- Few virologic failures
- Drug resistance very rare when used as part of triple combination therapy

M. V. Meireles, A. R. P. Pascom, E. C. Duarte, and W. McFarland, “Comparative effectiveness of first-line antiretroviral therapy: results from a large real-world cohort after the implementation of dolutegravir,” AIDS, vol. 33, no. 10, pp. 1663–1668, Aug. 2019
J.-M. Molina et al., “Once-daily dolutegravir versus darunavir plus ritonavir for treatment-naive adults with HIV-1 infection (FLAMINGO): 96 week results from a randomised, open-label, phase 3b study,” Lancet HIV, vol. 2, no. 4, pp. e127-136, Apr. 2015
J. van Lunzen et al., “Once daily dolutegravir (S/GSK1349572) in combination therapy in antiretroviral-naive adults with HIV: planned interim 48 week results from SPRING-1, a dose-ranging, randomised, phase 2b trial,” Lancet Infect Dis, vol. 12, no. 2, pp. 111–118, Feb. 2012
W. D. F. Venter et al., “Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV,” New England Journal of Medicine, vol. 381, no. 9, pp. 803–815, Aug. 2019
I. Beesham et al., “High Levels of Pretreatment HIV-1 Drug Resistance Mutations Among South African Women Who Acquired HIV During a Prospective Study,” J Acquir Immune Defic Syndr, vol. 91, no. 2, pp. 130–137, Oct. 2022
Cruciani, M., Parisi, S.G., 2019. Dolutegravir based antiretroviral therapy compared to other combined antiretroviral regimens for the treatment of HIV-infected naive patients: A systematic review and meta-analysis. PLOS ONE 14, e0222229.

UNAIDS 95-95-95 targets

At least 95% of people living with HIV know their HIV status

At least 95% of people who know their HIV status are on treatment

At least 95% of people on treatment have a suppressed viral load

L. Frescura *et al.*, “Achieving the 95 95 95 targets for all: A pathway to ending AIDS,” *PLOS ONE*, vol. 17, no. 8, p. e0272405, Aug. 2022

UNAIDS, “Fast-Track: ending the AIDS epidemic by 2030,” Geneva, Switzerland, 2014

Undetectable = Untransmittable

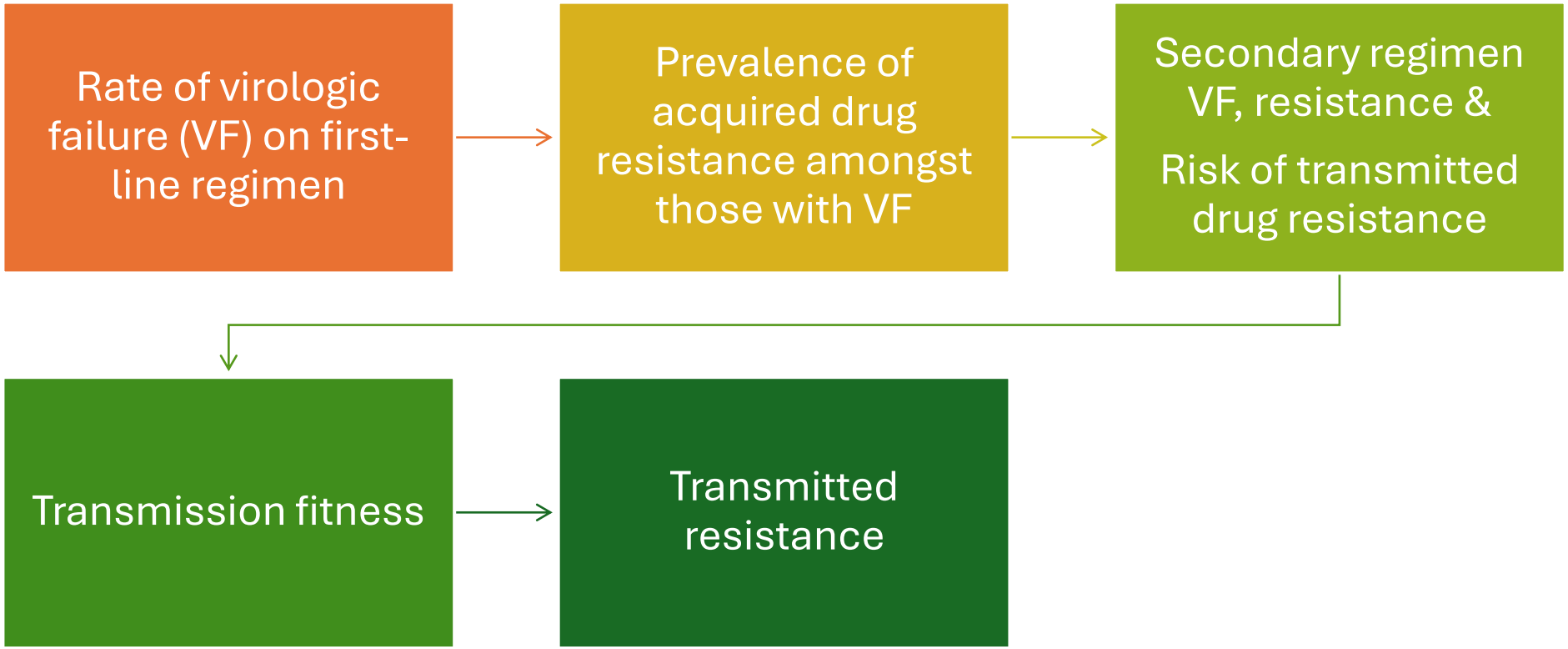
Biological intervention with the best evidence of preventing HIV transmission on population level is **antiretroviral therapy to infected individuals**

- Treating infected individuals -> achieving undetectable viral loads
- These individuals are no longer a source of transmission
- **Programmatically true, but there may be exceptions

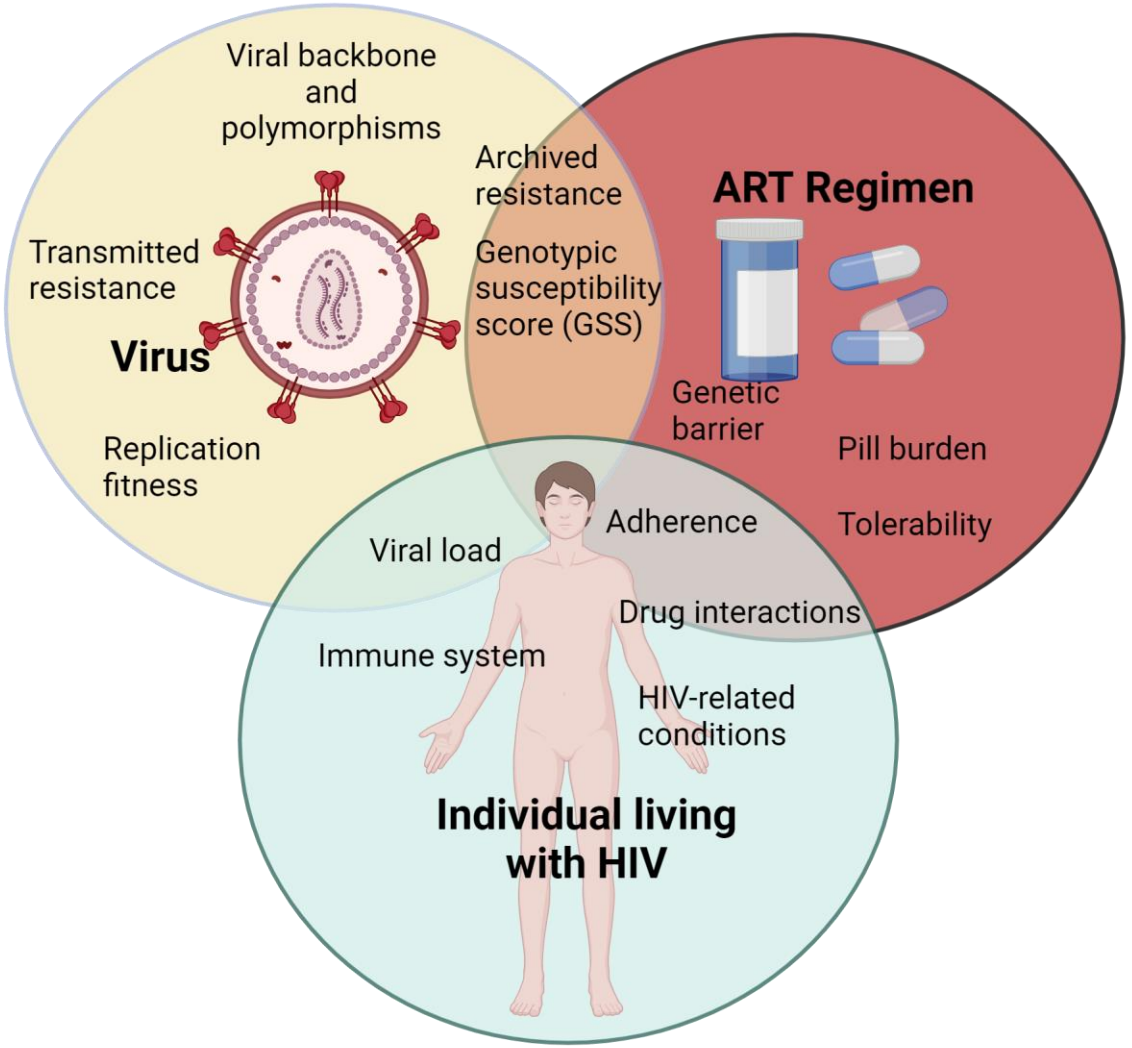
Cohen, M. S., Gamble, T. & McCauley, M. Prevention of HIV Transmission and the HPTN 052 Study. Annu. Rev. Med. (2019). doi:10.1146/annurev-med-110918-034551

**Ndirangu J, Viljoen J, Bland RM, Danaviah S, Thorne C, Perre PV de, et al. Cell-Free (RNA) and Cell-Associated (DNA) HIV-1 and Postnatal Transmission through Breastfeeding. PLOS ONE 2012; 7:e51493.

HIV drug resistance threatens the third 95



Resistance emergence: conceptual



Factors affecting HIV-1 drug resistance acquisition

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One drug to rule them all

- DTG and other high genetic barrier INSTI regimens have largely replaced other regimens
- WHO recommends DTG regimens in treatment naïve and experienced patients
  - High treatment success rate in both first and second-line patients (tolerability and efficacy)
- Relatively high genetic barrier (DTG representing DTG, BIC and CAB)
  - Very low risk of resistance in treatment naïve patients starting with TLD or other DTG-based triple regimens

World Health Organization, "Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach," World Health Organization, 2021;
M. Cevik et al. "Emergent Resistance to Dolutegravir Among INSTI-Naïve Patients on First-line or Second-line Antiretroviral Therapy: A Review of Published Cases," Open Forum Infect Dis, vol. 7, no. 6, p. ofaa202, Jun. 2020;
N. I. Paton et al., "Efficacy and safety of dolutegravir or darunavir in combination with lamivudine …(NADIA): week 96 results…," Lancet HIV, vol. 9, no. 6, pp. e381–e393, Jun. 2022

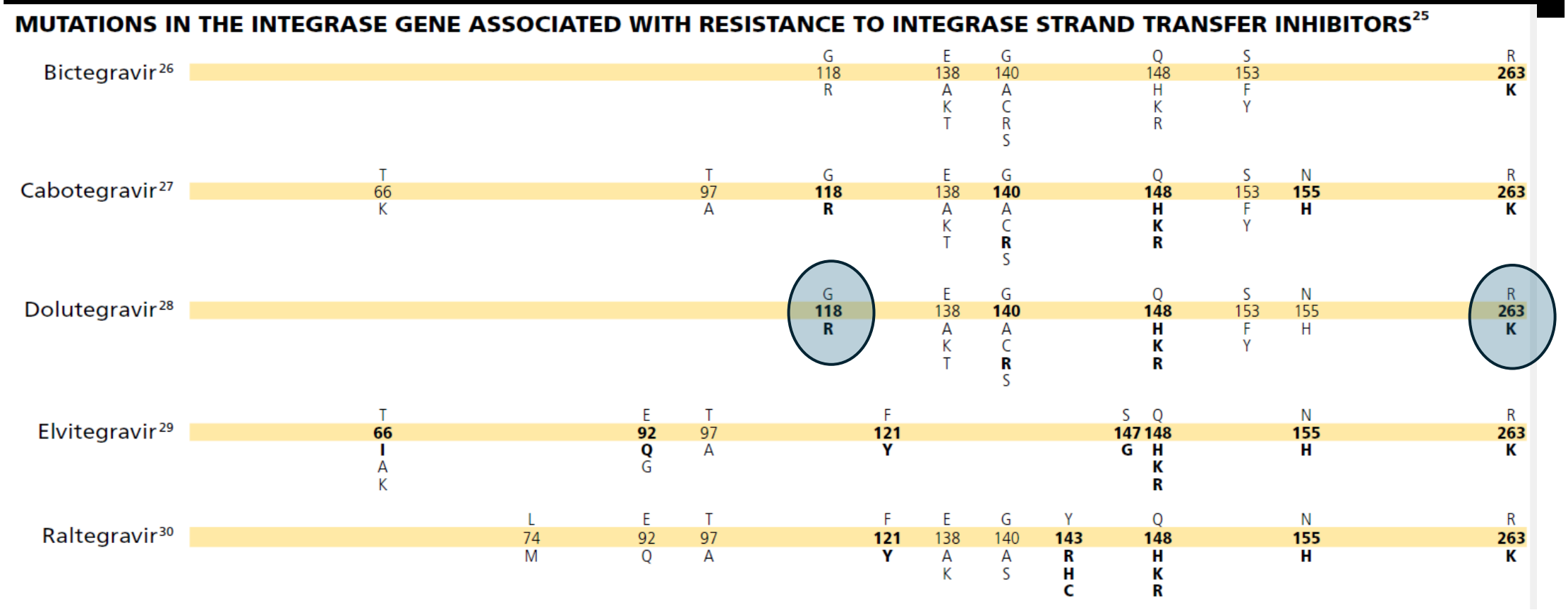
Is DTG facing its “Cracks of Doom”?

XXX INTERNATIONAL WORKSHOP ON HIV DRUG RESISTANCE AND TREATMENT STRATEGIES

20 - 22 September 2023 • Cape Town, South Africa

- Large scale rollout of DTG regimens in RLS
  - TLD and other DTG regimens used in treatment naïve and treatment experienced patients
  - Patients blindly transitioning to DTG irrespective of being viremic
  - Increased time on DTG regimens
  - Limited HIV viral load monitoring
- Emerging reports of a high proportion of drug resistance in some observational and laboratory-based studies

DTG resistance IAS mutation list & DTG as first INSTI



Wensing A.M. et al., "2022 Update of the Drug Resistance Mutations in HIV-1," Top Antivir Med, vol. 30, no. 4, pp. 559–574, Oct. 2022.

Tao K. et al., "Treatment Emergent Dolutegravir Resistance Mutations in Individuals Naïve to HIV-1 Integrase Inhibitors: A Rapid Scoping Review," Viruses, vol. 15, no. 9, p. 1932, Sep. 2023

Stanford HIV DB

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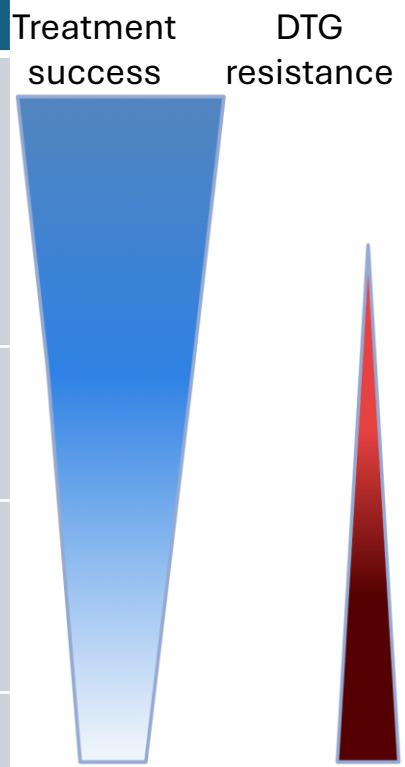
Major Integrase Inhibitor (INSTI) Resistance Mutations

Consensus	66 T	92 E	118 G	138 E	140 G	143 Y	147 S	148 Q	155 N	263 R
Bictegravir (BIC)	K	Q	**R**	KAT	SAC			**HRK**	H	**K**
Cabotegravir (CAB)	K	Q	**R**	KAT	SAC**R**			**HRK**	**H**	**K**
Dolutegravir (DTG)	K	Q	**R**	KAT	SAC			**HRK**	H	**K**
Elvitegravir (EVG)	**AIK**	**Q**	**R**	**KAT**	**SAC**		**G**	**HRK**	**H**	**K**
Raltegravir (RAL)	AI**K**	**Q**	**R**	**KAT**	**SAC**	**RCH**		**HRK**	**H**	K

https://hivdb.stanford.edu/dr-summary/resistance-notes/INSTI/ [from 19 Oct 2022]

Virologic success and drug resistance with different DTG triple combination treatment scenarios

Treatment Scenario	Viral load	Studies
Treatment naive	BL VL < 100 000 copies/mL	SINGLE, SPRING-1&2, FLAMINGO, ADVANCE, NAMSAL, others
	BL VL ≥ 100 000 copies/mL	
Transition from current first-line	Viral load suppressed	Schramm et al. 2022 (Malawi), others
	Viremic	
Treatment experienced: INSTI naïve	BL VL < 100 000 copies/mL	SAILING, DAWNING, NADIA, ARTIST, ODESSEY, IMPAACT P1093
	BL VL ≥ 100 000 copies/mL	
INSTI experienced		VIKING



Studies of HIV drug resistance

Randomized trials	Population based observational studies	Laboratory based studies
• **Allocation is unbiased** • **Strick entry criteria (excluding patients)** • **Relative short follow-up – drug resistance may take long**	• Representative or **convenience** samples • **Regimen allocation not random** • **Information about long-term real-life outcomes**	• **Population denominator unknown** • **Referral biases** • **Low cost and pragmatic** • **Longitudinal trends**

Guidelines and practical approach:

HIV drug resistance testing in treatment experienced patients and patients with advanced disease

Definitions: First-line DTG regimens

Previous ART exposure	Regimens
ART naïve patient who initiated ART on a DTG regimen	Tenofovir/lamivudine/dolutegravir (TLD1)
Patient was switched from a first-line non-DTG regimen, including a first-line PI regimen in children to a DTG-based regimen with a VF < 50 copies/mL withing 6/12 prior to swich	Abacavir/lamivudine/dolutegravir (ALD1)

Western Cape Government Circular H108/2024

Second-line DTG regimens (recent)

Previous ART exposure	Regimens
Patient was switched from a first-line ART regimen (NNRTI or PI based) to a DTG-based regimen with a VL ≥ 50 copies/mL	Tenofovir/lamivudine/dolutegravir (TLD2) Abacavir/lamivudine/dolutegravir (ALD2) Zidovudine/lamivudine/dolutegravir
Patient was switched from a second-line PI based regimen with a VL < 50 copies/mL to a DTG based regimen	
Patient was switched from a PI based regimen with a VL ≥ 50 copies/mL to a DTG based regimen without a resistance test	

Third-line DTG regimens

Previous ART exposure	Regimens
Patient was switched to a third-line DTG-based regimen based on the results of a genotypic resistance test showing resistance mutations to PI in previous second line regimen	Individualised DTG based regimen

Non VL-dependent regimen switches Regimens where the VL result will not influence nor delay the decision to switch to a DTG-containing regimen			
VL considerations	**Current Regimen**	**Criteria for switch**	**Regimen if change indicated**
Switching regardless of VL result	**TEE** ABC/3TC/EFV (or NVP*) AZT/3TC/EFV (or NVP*) AZT/3TC/DTG Any LPV/r or ATV/r regimen for **less than 2 years**	**Switch all to a DTG-containing regimen, regardless of VL result** Review VL in last 12 months. If VL in last 12 months was not suppressed, continue to switch same day, but do ABCDE assessment and provide enhanced adherence counseling (EAC) if needed. If VL was not done in last 12 months, do it at this visit, but do not wait for the result to switch	**TLD** provided no renal dysfunction and age ≥ 10 yrs and weight ≥ 30 kg If client does not qualify for TDF **ABC[1]/3TC/DTG** If client does not qualify for TDF and has ABC hypersensitivity **AZT/3TC/DTG**

2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. June 2023 Version 4; Republic of South Africa National Department of Health

Zhao Y, Voget J, Singini I, Omar Z, Mudaly V, Boulle A, et al. Virologic outcomes with tenofovir-lamivudine-dolutegravir in adults failing PI-based second-line ART. Southern African Journal of HIV Medicine 2024; 25:8.

3 Paton NI, Musaazi J, Kityo C, Walimbwa S, Hoppe A, Balyegisawa A, et al. Efficacy and safety of dolutegravir or darunavir in combination with lamivudine plus either zidovudine or tenofovir for second-line treatment of HIV infection (NADIA): week 96 results from a prospective, multicentre, open-label, factorial, randomised, non-inferiority trial. Lancet HIV 2022; 9:e381–e393.

VL-dependent regimen switches

Relevant to all clients who have been on PI-based regimens for more than two years: their VL result in the last 12 months will influence the decision of how and when to switch to a DTG-containing regimen

VL considerations	Current Regimen	Criteria for switch	Regimen if change indicated
VL < 1000 c/mL	**Any LPV/r or ATV/r regimen** for **more than 2 years**	**Switch all to a DTG-containing regimen** If VL in last 12 months was ≥ 50 c/mL, continue to switch same day, but do ABCDE assessment, provide EAC if needed, and repeat the VL after 3 months as per ***"The VL non-suppression algorithm" on page 21***	**TLD** provided no renal dysfunction and age ≥ 10 yrs and weight ≥ 30 kg If clients does not qualify for TDF **ABC[1]/3TC/DTG**
[2] Two or more consecutive VLs ≥ 1000 c/mL taken **two or more years** after starting PI regimen	Adult or adolescent on any **LPV/r or ATV/r** regimen and adherence **less than 80%[3]**	**Switch all to a DTG-containing regimen** **Do not do a resistance test** These clients are unlikely to have PI resistance mutations. Rather switch to a more tolerable once daily FDC regimen which is likely to support adherence. Manage as per ***"The VL non-suppression algorithm" on page 21***	**TLD** provided no renal dysfunction and age ≥ 10 yrs and weight ≥ 30 kg If clients does not qualify for TDF **ABC[1]/3TC/DTG**
	Adult or adolescent on any **LPV/r or ATV/r** regimen and adherence **more than 80%[3]**	Clients who meet the definition of confirmed virological failure and have confirmed adherence more than 80% may need a resistance test **These clients do not qualify for a same-day switch.** Discuss with an HIV expert[4] to authorise and interpret a resistance test. Provide individualised regimen as recommended by HIV expert. Repeat VL 3 months after the regimen change to confirm re-suppression, as per the ***"Management of Confirmed Virological Failure on TLD" on page 23***	
	Child < 10 years, or weight < 30 kg on any **LPV/r or ATV/r regimen**	These clients do not yet qualify for TLD and may require a resistance test. Refer to algorithm ***"Switching children on PI-containing regimens to DTG-containing regimens" on page 16***	

2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. June 2023 Version 4; Republic of South Africa National Department of Health

VL Monitoring Algorithm for Clients on TLD

(also applicable to ALD and other DTG-containing regimens)

Routine VL monitoring for virally suppressed clients as outlined in the algorithm
"Routine HIV VL Monitoring on ART" on page 20
VL monitoring should happen every 6 DCs in a breastfeeding woman

VL < 50 c/mL

VL unsuppressed (VL ≥ 50 c/ml)
(This includes previous VL level of 50-999 and VL > 1000 c/ml)

Do a thorough assessment of the cause of an elevated VL. Consider the possibility of:
A. Adherence problems *(see**"Enhanced Adherence Support" on page 22**)*
B. Bugs (Intercurrent infections)
C. In-Correct ART dosage *(see Annexure 5 **"Drug Dosing Chart" on page 34**)*
D. Drug Interactions *(see**"Drug Interactions with DTG and Rifampicin-containing TB Treatment" on page 13**)*
E. REsistance (if > 2 years on treatment)

Implement interventions to re-suppress the VL, including **Enhanced Adherence Support** if indicated
(See Annexure 3 Enhanced Adherence Counselling)
Recommend **condom use and contraception** as appropriate

Repeat VL after 3 months

Repeat VL after 3 months

Repeat VL **unsuppressed** [1] **(VL > 50 c/ml)**

Re-assess and resolve adherence issues! [2]

*(See **"ABCDE assessment of an Elevated Viral Load" on page 22** and Annexure 3 **"Enhanced Adherence Support" on page 22**)*

On TLD for **at least 2 years**

On TLD **less than** 2 years [3]

If **Adherence > 80%** [4], and
Two or more consecutive **VLs ≥ 1000 c/mL**
taken two or more years after starting TLD regimen
or at least one VL ≥ 1000 c/mL and either
CD4 < 200 cells/mm3 or an opportunistic infection

If adherence still
suboptimal [4],
or persistent low-level viraemia
(2 or more consecutive VLs between
50 and 999 c/mL)

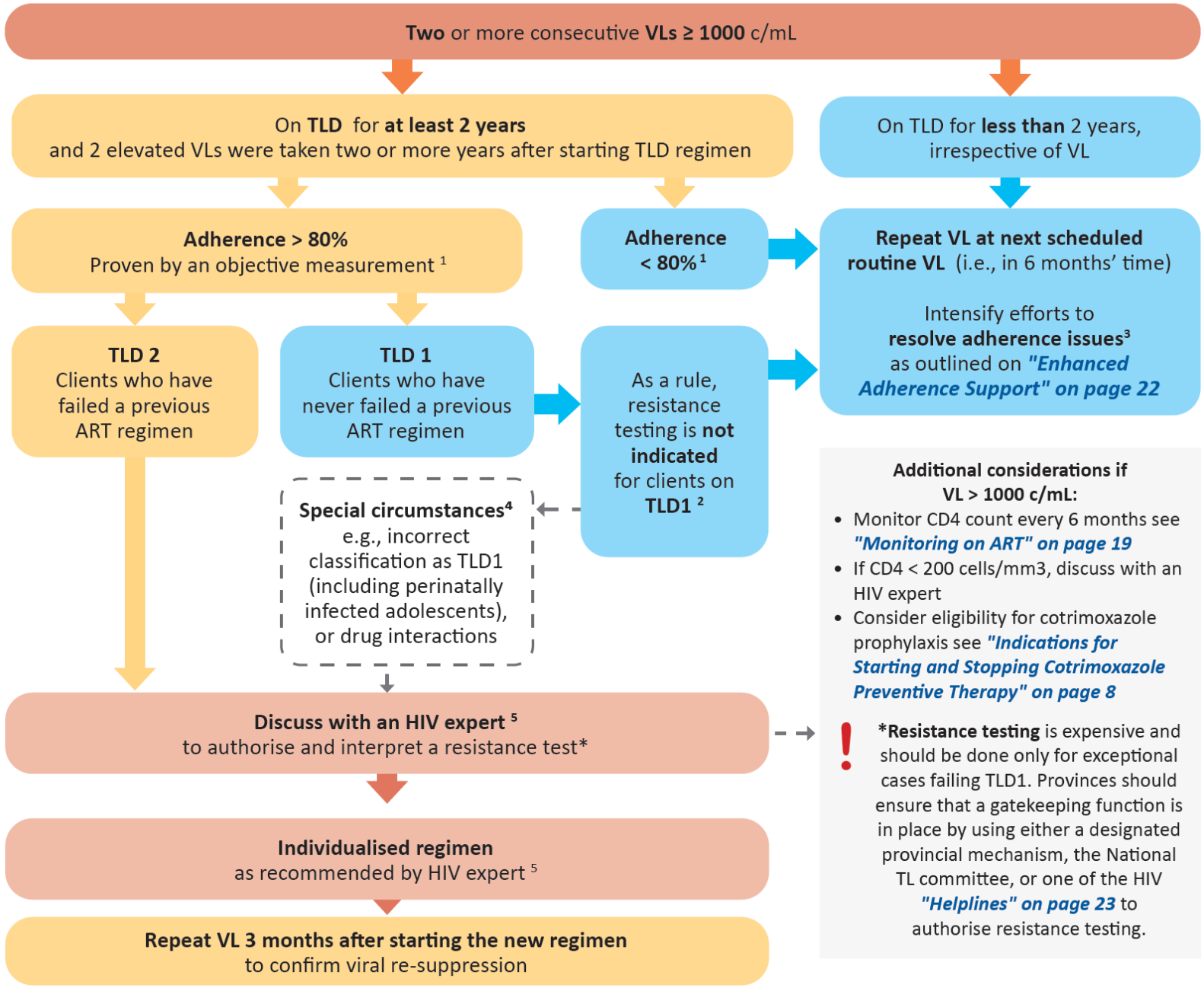
Go to the algorithm for
"Management of Confirmed Virological Failure on TLD" on page 23

Repeat VL at next scheduled routine VL
(i.e., in 6 months' time)
Intensify efforts to **resolve adherence issues** [2]

Virological Failure	• **Definition:** two or more VLs ≥ 1000 c/mL taken two or more years after starting a DTG/PI-containing regimen and adherence > 80% • **Focus on improved adherence:** Resistance to DTG is very uncommon. If other reasons for an unsuppressed VL (including drug interactions) have been addressed or excluded, the highest probability of improving adherence would be to remain on a once-daily, well-tolerated, fixed-dose combination regimen (TLD) while identifying and addressing the underlying root causes of non-adherence. • **No regimen changes without a resistance test:** Switching off a DTG-containing regimen should only happen if InSTI resistance has been confirmed by a resistance test • Resistance testing can only be authorised by a member of the National Third-line committee, one of the helpline consultants, or a nominated provincial expert

Management of Confirmed Virological Failure on TLD

(also applicable to ALD and other DTG-containing regimens)



Current and future changes ART algorithms

- TLD1 ≥ 2 years with confirmed VF: AZT/3TC and LPV/r

Current and future changes ART algorithms

- ~~TLD1 ≥ 2 years with confirmed VF: AZT/3TC and LPV/r~~
  - Consult expert – no switch away from TLD without HIV drug resistance test
  - Reason: low probability of TLD1 resistance; most studies suggest DTG superior to PI regimen

Current and future changes ART algorithms

- After TDF/XTC in first-line AZT/3TC in second line

Current and future changes ART algorithms

- ~~After TDF/XTC in first-line AZT/3TC in second line~~
  - retain TDF in second line
  - Reason: NADIA, ODYSSEY & ARTIST

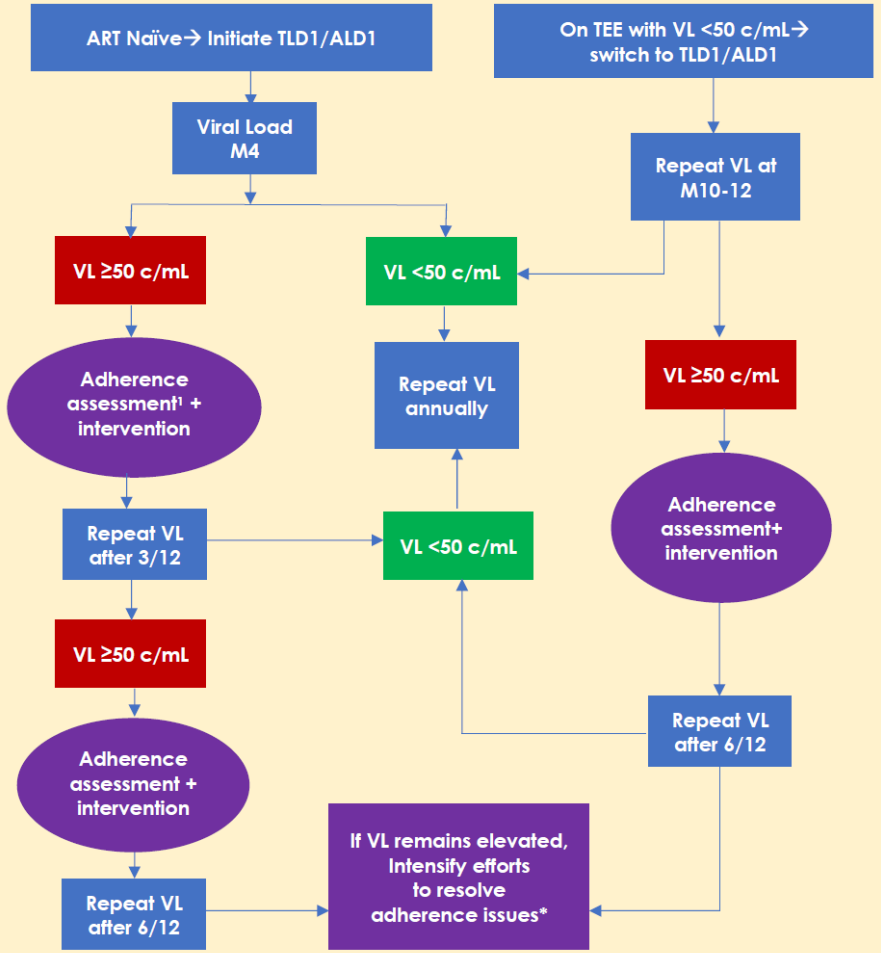
Current and future changes ART algorithms

- Delay resistance testing on TLD2 for ≥ 2 years

Current and future changes ART algorithms

- ~~Delay resistance testing on TLD2 for ≥ 2 years~~
  - WC Province – as soon as having 3 viral loads and still VF despite good adherence (currently considered to revise this nationally)
  - Reason: multiple studies showing high prevalence of drug resistance in patients on TLD2 with VF (20% or even as high as 60% in treatment experienced patients on TLD after 2 years of Rx)

ANNEXURE A: VIRAL LOAD TESTING & ELIGIBILITY FOR RESISTANCE TESTING IN PATIENTS ON FIRST LINE DOLUTEGRAVIR REGIMENS

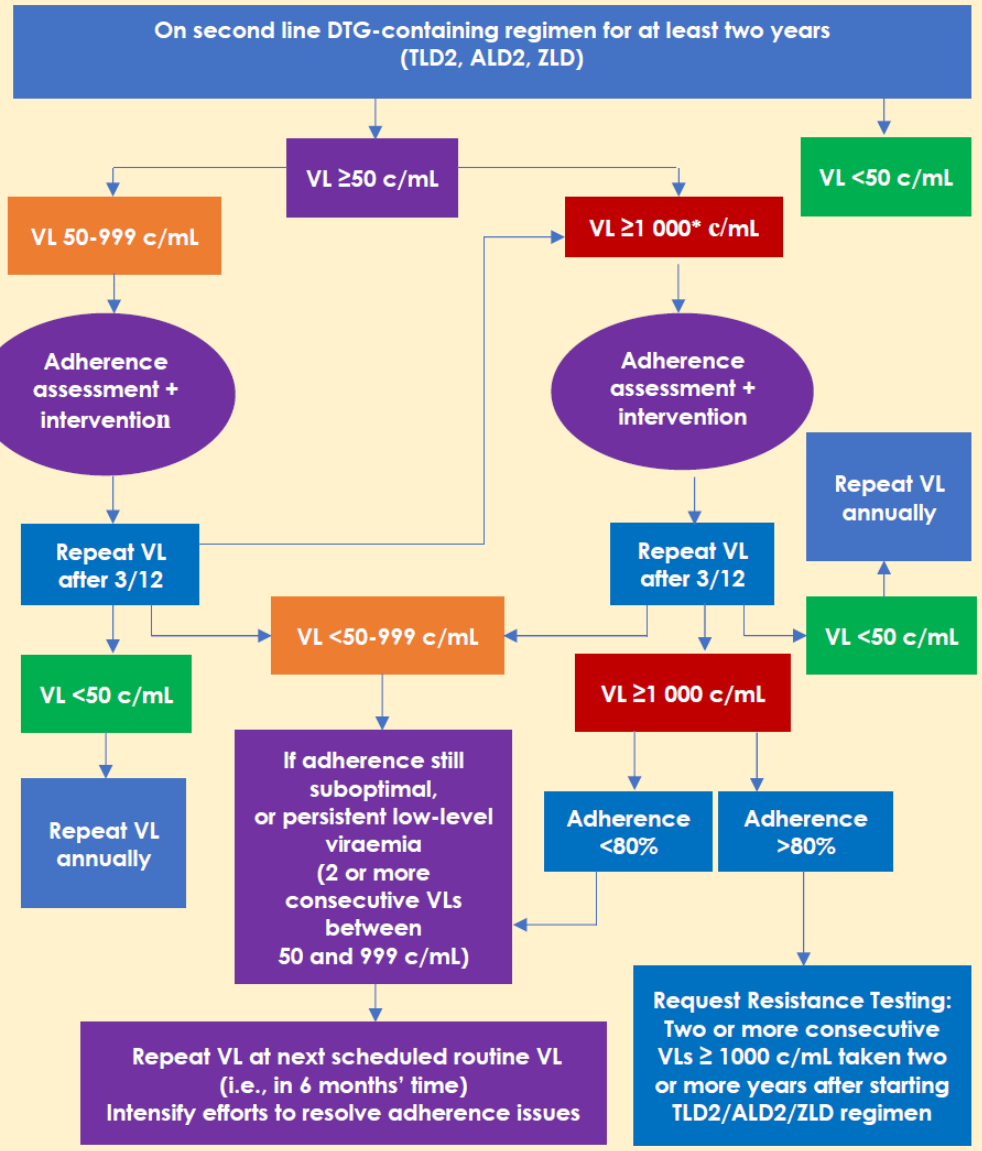


*If adherence assessed is >80% and VL remains ≥ 1000 c/mL discuss with expert.

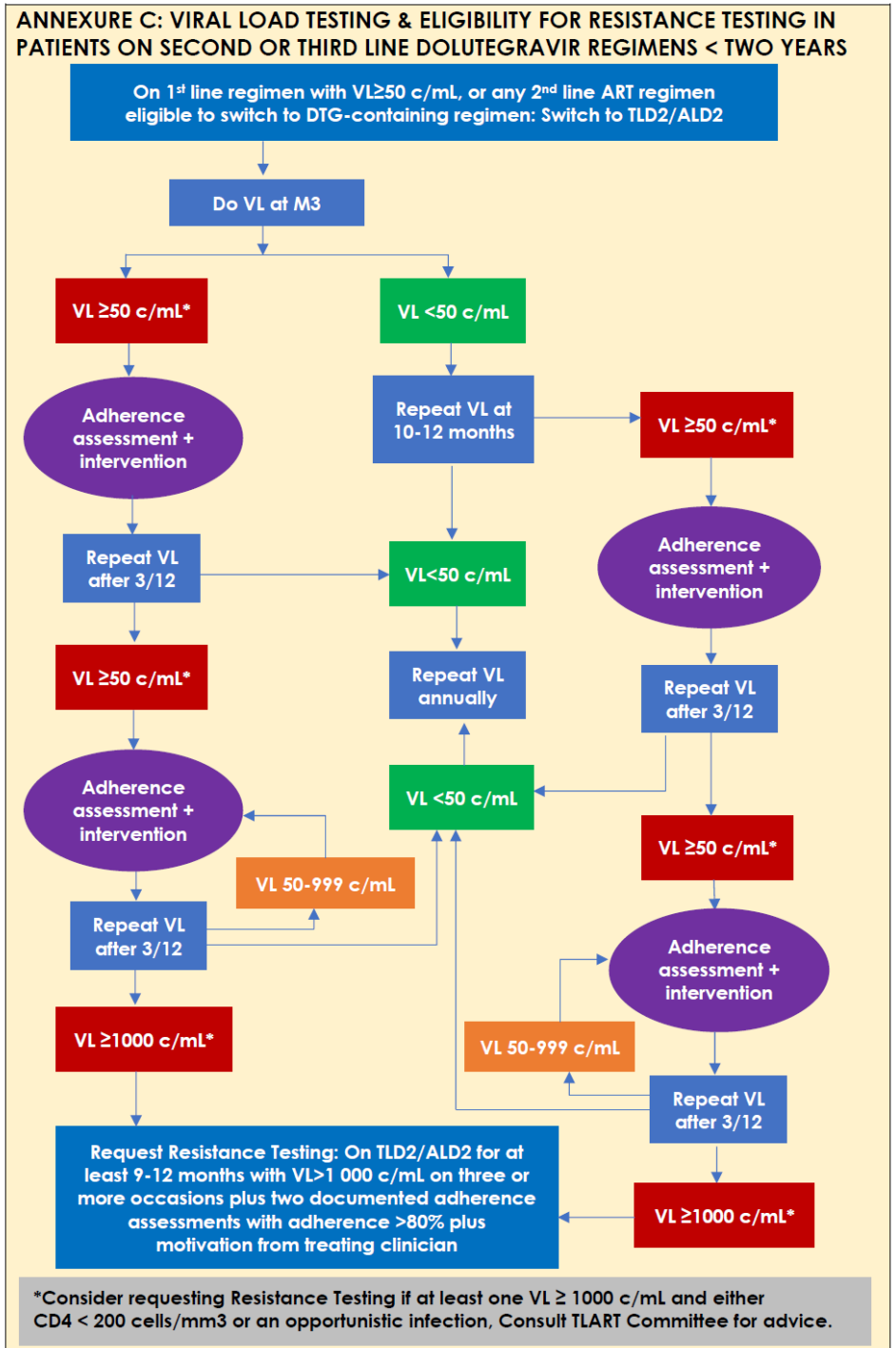
SPECIAL CIRCUMSTANCES THAT WARRANT A RESISTANCE TEST IF ON A FIRST LINE DTG REGIMEN

- As a rule, resistance testing is not indicated for clients on TLD1 [2]
- Special circumstances[3] e.g., incorrect classification as TLD1 (including perinatally infected adolescents), drug interactions
- Discuss with an HIV expert[4] to authorise and interpret a resistance test

ANNEXURE B: VIRAL LOAD TESTING & ELIGIBILITY FOR RESISTANCE TESTING IN PATIENTS ON SECOND LINE DOLUTEGRAVIR REGIMENS ≥ TWO YEARS



*Consider requesting Resistance Testing if at least one VL ≥ 1000 c/mL and either CD4 < 200 cells/mm3 or an opportunistic infection, Consult TLART Committee for advice.



Patients on TLD2/3 eligible for earlier drug resistance testing
(important to know who is on TLD1 vs TLD2/3)

Change based on high prevalence of DTG resistance when delaying drug resistance testing until 2 years on TLD2/3

Western Cape: new guideline

Management of patient switching to second or third line DTG regimen	
Viral Load Testing	Do first VL 3 months after starting DTG regimen. Repeat VL annually if VL <50c/ml
Response to Viral Load ≥ 50 c/mL	ABCDE assessment (Annexure D) of the cause of an elevated VL. Address any concerns. Repeat VL after 3 months. If VL ≥50 c/ml, repeat ABCDE assessment and address concerns. Repeat VL again after 3 months.
Eligibility for Resistance Testing	If on regimen for less than 2 years: Eligible for resistance testing if on regimen for at least 9 months and if: **three or more consecutive VLs ≥ 1000 c/mL** plus **two documented adherence assessments with adherence >80%** plus **motivation from treating clinician**
	If on regimen for more than 2 years: Eligible for resistance testing if: **two or more consecutive VLs ≥1000 c/mL taken two or more years after starting/ switching to DTG regimen** and **assessed adherence > 80%** **or at least one VL≥1000 c/mL and either CD4 < 200 cells/mm^3 or opportunistic Infection.**

Using drug resistance tests to select regimens

Confirmed VF and meeting criteria for resistance testing

Considerations

Current regimen	Treatment history	Renal function	Hepatitis B status

PI resistant cases

Patient is on 2nd line PI regimen and has developed LPV/r or ATV/r resistance (score ≥15) but DRV/r score <10 and no prior integrase inhibitor exposure

a) TLD

b) If not eligible for TDF (<10 years of age or <30 kg or inadequate renal function or prior TDF nephrotoxicity), replace with ABC, or consider TAFED (>25kg, adequate renal function, if available)

c) In children/adolescents/young adults with unknown prior PI exposure/ resistance: individualised regimen.

https://knowledgehub.health.gov.za/system/files/elibdownloads/2024-05/FINAL%20TLART%20Regimens%20APRIL%202024_V3.1.pdf

PI resistant cases (2)

Patient (possibly previously on NNRTI-based regimen) is on 2nd line PI regimen and has developed LPV/r or ATV/r resistance (score ≥15) and DRV/r score 10-59 and no prior integrase inhibitor exposure

a) TLD + DRV/r dosed twice daily (adults/>35 kg: 600 mg/100 mg twice daily, <35 kg: refer to weight band dosing)

b) If not eligible for TDF (<10 years of age or <30 kg or inadequate renal function,- or prior TDF nephrotoxicity), replace TE with ABC/3TC

c) Discretion may be applied if there are adherence concerns and DRV/r score <30. In these cases, can consider using TLD alone (after discussion with an expert/the TLART Committee).

https://knowledgehub.health.gov.za/system/files/elibdownloads/2024-05/FINAL%20TLART%20Regimens%20APRIL%202024_V3.1.pdf

PI resistant cases(3)

Patient is on 2nd line PI regimen and has developed LPV/r or ATV/r resistance (score ≥15) and DRV/r score ≥60 and no prior integrase inhibitor exposure

a) Discretion may be applied if there are adherence concerns can consider using TLD alone (after discussion with an expert/the TLART Committee).

b) Individualised regimen based on genotype and clinical history; consider inclusion of etravirine (ETR) in regimen.

https://knowledgehub.health.gov.za/system/files/elibdownloads/2024-05/FINAL%20TLART%20Regimens%20APRIL%202024_V3.1.pdf

DTG resistant cases

Patient is on 1st line DTG regimen and has developed DTG resistance

a) TE + DRV/r dosed once daily (adults/>35 kg: 800 mg/100 mg once daily; <35 kg: weight band dosing).

b) If not eligible for TDF (<10 years of age or <30 kg or inadequate renal function or prior TDF nephrotoxicity), replace TE with ABC/3TC

Patient is on 2nd line DTG regimen (i.e., AZT + 3TC + DTG or TLD), is PI naïve and has developed DTG resistance

a) TE + DRV/r dosed once daily (adults/>35 kg: 800 mg/100 mg once daily; <35 kg: weight band dosing).

b) If not eligible for TDF (<10 years of age or <30 kg or inadequate renal function- or prior TDF nephrotoxicity), replace TE with ABC/3TC

https://knowledgehub.health.gov.za/system/files/elibdownloads/2024-05/FINAL%20TLART%20Regimens%20APRIL%202024_V3.1.pdf

DTG resistant cases (2)

Patient has developed DTG resistance and has prior ATV/r or LPV/r exposure, but no resistance test was done at time of switch to DTG regimen

a) TE + DRV/r dosed once daily (adults/>35 kg: 800 mg/100 mg once daily; <35 kg: weight band dosing).

- If history suggests possible DRV/r cross-resistance (e.g. prolonged non-suppression whilst on ATV/r or LPV/r), then adjust dosing to DRV/r twice daily (adults/>35 kg: 600 mg/100 mg twice daily, <35 kg: refer to weight band dosing).
- Do a viral load in 3 months' time and another genotype if the patient is still not suppressed (to pick up any possible DRV resistance).

b) If not eligible for TDF (<10 years of age or <30 kg or inadequate renal function- see below – or prior TDF nephrotoxicity), replace TE with ABC/3TC

https://knowledgehub.health.gov.za/system/files/elibdownloads/2024-05/FINAL%20TLART%20Regimens%20APRIL%202024_V3.1.pdf

Third-line/ complex cases

Failing 3rd line/treatment that includes DTG or DRV/r, or both DTG and DRV/r

a) Individualised regimen based on genotype and clinical history; (i.e., refer to DR HIV Committee).

https://knowledgehub.health.gov.za/system/files/elibdownloads/2024-05/FINAL%20TLART%20Regimens%20APRIL%202024_V3.1.pdf

Advanced HIV disease

Definition: CD4 count < 200 copies/mL

Up to a third of patients present late

Low CD4 count and often high viral load – not tested at baseline

The challenges with patients with advanced disease

- Risk of opportunistic infection
- Unmasking IRIS
- Concomitant medications and drug interactions
- Complex treatment histories – some with multiple treatment experience and high levels of drug resistance
- Role of immune system in controlling viral replication is limited
- Require rapid definitive therapy
- Higher risk of hospitalization and death

Advanced disease and HIV drug resistance

- High viral loads and advanced disease are risk factors for HIV drug resistance
    - Review articles
    - Case reports: paediatric cases with high viral loads who developed drug resistance fast despite receiving TLD1
- Limited time to provide definitive regimen
- Drug interactions may lower drug exposure
- Complex treatment history and adherence challenges
- High pill burden

Cevik M, Orkin C, Sax PE. Emergent Resistance to Dolutegravir Among INSTI-Naïve Patients on First-line or Second-line Antiretroviral Therapy: A Review of Published Cases. Open Forum Infect Dis 2020; 7:ofaa202.

Case of unexpected drug resistance

Mother diagnosed with HIV when child was 5/12 old and child presented with advanced HIV disease; mother VL suppressed on TLD

Baby HIV viral load > 1 M copies/mL; CMV pneumonitis

Baby initiated on ABC, 3TC, DTG at age 5/12

3 months later VF with VL 13 000 copies/mL

Drug resistance interpretation: RT — HIVDB 9.6 (2024-03-09)

NRTI Mutations: M184MV
NNRTI Mutations: None
RT Other Mutations: None

Nucleoside Reverse Transcriptase Inhibitors	
abacavir (ABC)	Low-Level Resistance
zidovudine (AZT)	Susceptible
emtricitabine (FTC)	High-Level Resistance
lamivudine (3TC)	High-Level Resistance
tenofovir (TDF)	Susceptible

Non-nucleoside Reverse Transcriptase Inhibitors	
doravirine (DOR)	Susceptible
efavirenz (EFV)	Susceptible
etravirine (ETR)	Susceptible
nevirapine (NVP)	Susceptible
rilpivirine (RPV)	Susceptible

No drug resistance mutations were found for NNRTI.

Drug resistance interpretation: IN — HIVDB 9.6 (2024-03-09)

INSTI Major Mutations: G118GR • E138EK
INSTI Accessory Mutations: None
IN Other Mutations: L74I

Integrase Strand Transfer Inhibitors	
bictegravir (BIC)	High-Level Resistance
cabotegravir (CAB)	High-Level Resistance
dolutegravir (DTG)	High-Level Resistance
elvitegravir (EVG)	High-Level Resistance
raltegravir (RAL)	High-Level Resistance

https://hivdb.stanford.edu/hivdb/by-patterns/

How could advanced disease have contributed to VF in this case?

- High baseline viral load
- Limited role of immune system in controlling infection
- Child was sick, concomitant medication: adherence challenges

MCQ questions

1) **Which best explains why combination antiretroviral therapy is more successful than monotherapy?**

- A) Combination therapy provides better viral load suppression than monotherapy
- B) There is a low joint probability of a virus being resistant to all drugs
- C) Current regimens include high genetic barrier drugs
- D) Mutations towards one drug may reduce the risk of resistance developing towards other drugs due to fitness interactions
- E) All of the above

Correct answer: E) All of the above

MCQ questions continue

2) Increased global prevalence of pre-treatment resistance towards which drug class contributed to the introduction of dolutegravir regimens?

- A) NNRTIs
- B) PIs
- C) INSTIs
- D) NRTIs

Correct answer: A) NNRTIs

MCQ questions continue

3) Which treatment category that includes dolutegravir has the highest risk of virologic failure and drug resistance towards dolutegravir?

- A) Dolutegravir in previously treatment naïve patients
- B) Dolutegravir in patients who previously used NNRTIs
- C) Dolutegravir in patients who previously used PIs
- D) Dolutegravir in patients who previously used other INSTIs

Correct answer D)

MCQ Questions Continue

4) A patient is on 2nd line TDF/FTC and ATV regimen and has ATV/r resistance (score ≥15) but DRV/r score <10 and no prior integrase inhibitor exposure

What is the recommended third line regimen?

a) AZT, 3TC, DRV/r
b) TDF, FTC and LPV/r
c) AZT, 3TC and DTG
d) TDF, 3TC and DTG
e) TDF, 3TC, DTG and DRV/r

Correct answer: d)

MCQ Questions Continue

5. What is influencing possible programmatic earlier access (than after 2 years) to drug resistance testing for treatment experienced patients on TLD ?

a) The patients with virologic failure cannot tolerate TLD

b) There is an increase in transmitted integrase resistance

c) The prevalence of drug resistance is already high at 2 years on TLD in patients with ongoing VF

d) Drug resistance testing is cheaper than performing 3 more viral load tests.

Correct answer: c)