The Changing HIV Drug resistance landscape: programmatic implications

Gert van Zyl -February 2026

Photo by Stefan Els

Outline

- Use-cases for HIV drug resistance testing
- Evolution of HIV drug resistance and viral fitness
- HIV drug resistance testing
- Drug resistance to second generation integrase strand transfer inhibitors (INSTIs)
- Adherence pattern, genetic barrier and drug resistance
- Clinical studies reporting HIV drug resistance
- Transmitted and pre-treatment drug resistance
- Resistance to long-acting ART
- Investigating cases with virological failure: principles and practice

Use cases for HIV drug resistance testing

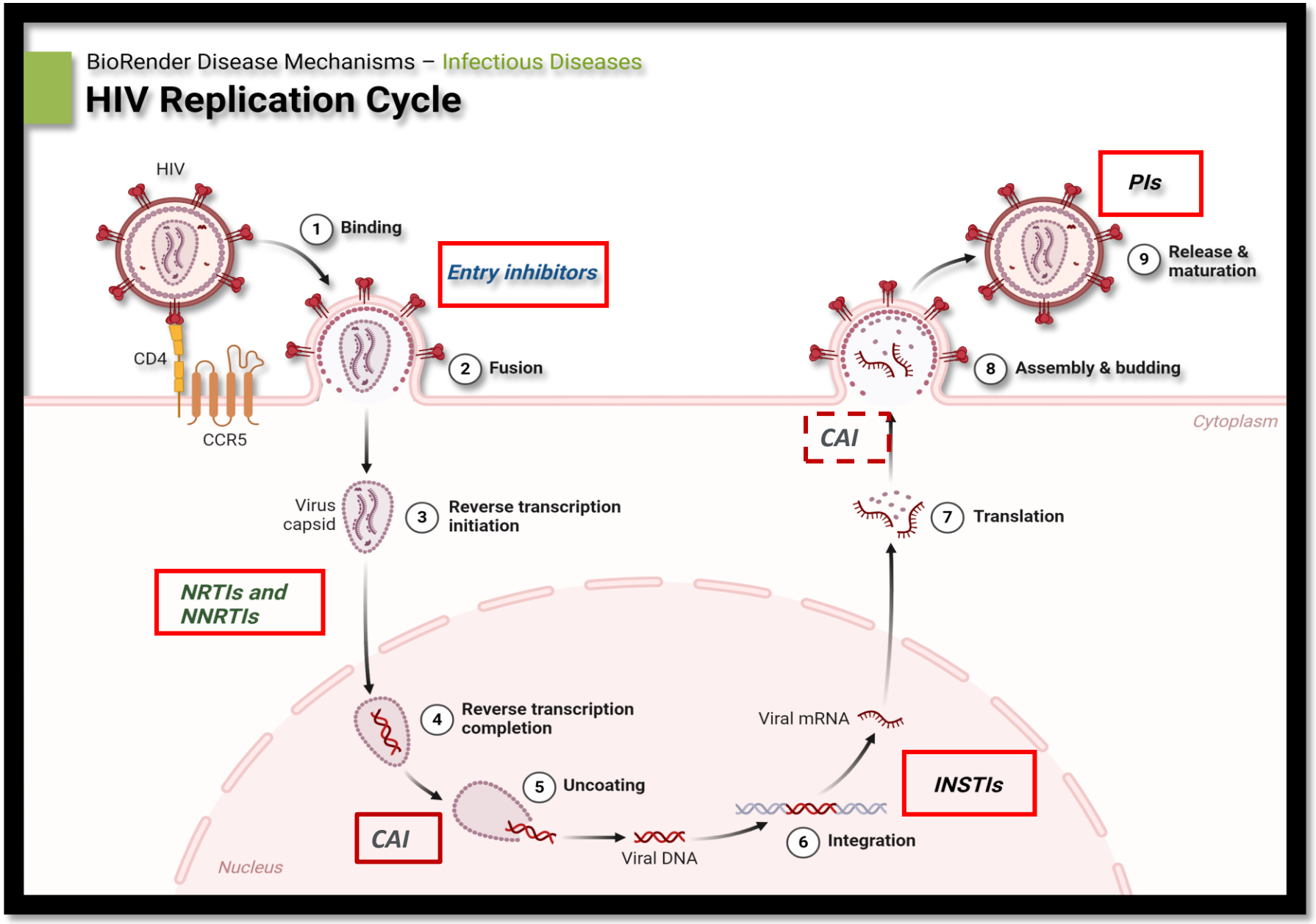
Surveillance

- Pre-treatment or transmitted drug resistance
- Acquired drug resistance after different therapy regimens or PrEP

Patient management

- Pre-treatment
- Determine if a regimen change is needed - relevant resistance to current regimen
- Assist with regimen selection

ART: mechanism of action


BioRender Disease Mechanisms – Infectious Diseases
HIV Replication Cycle
HIV
CD4
CCR5
1 Binding
Entry inhibitors
2 Fusion
PIs
9 Release & maturation
8 Assembly & budding
Cytoplasm
CAI
Virus capsid
3 Reverse transcription initiation
7 Translation
NRTIs and NNRTIs
4 Reverse transcription completion
Viral mRNA
5 Uncoating
INSTIs
CAI
Viral DNA
6 Integration
Nucleus

Evolution of HIV drug resistance (focus on INSTIs)

Conditions for INSTI resistance

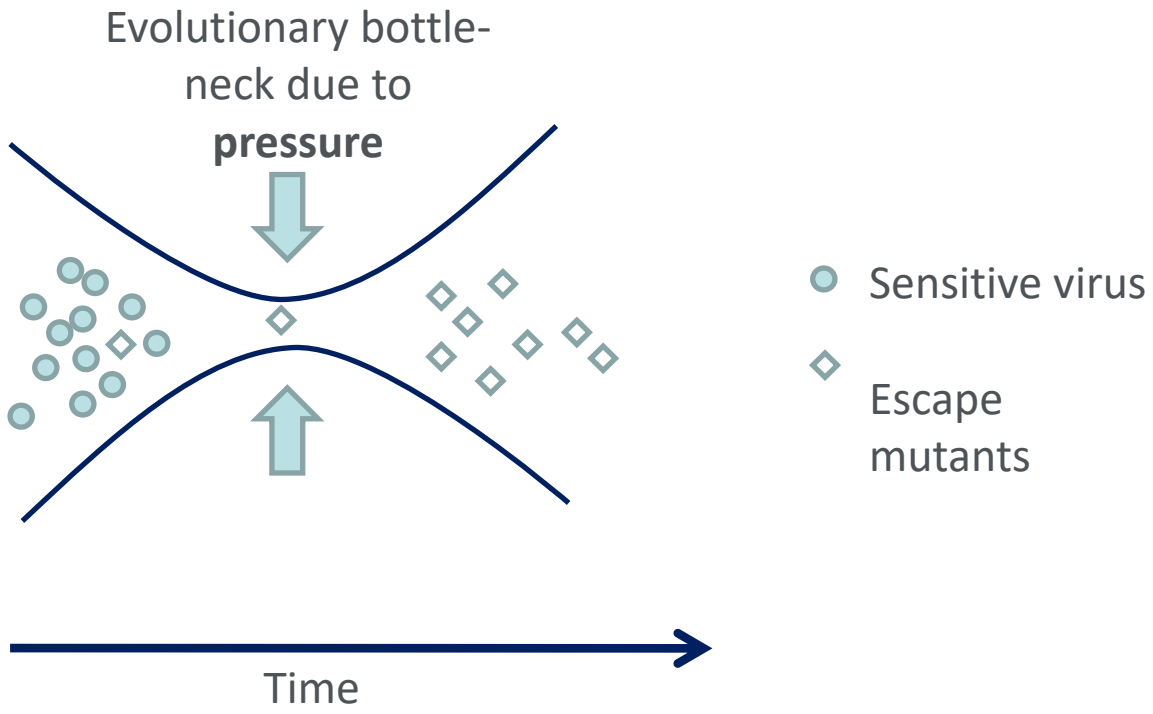
Viral replication – no evolution without replication

- Inadequate drug levels to suppress replication
- Too few active drugs to suppress replication

Conditions must select for variants that have drug resistance

- Resistant viruses must have a replication advantage despite major INSTI mutations having a fitness cost

Selection of escape mutants



Rapid mutation and pressure:

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

Virus will tend to escape pressures by evolution

Immune pressure

Drug pressure

Fitness and reproduction number

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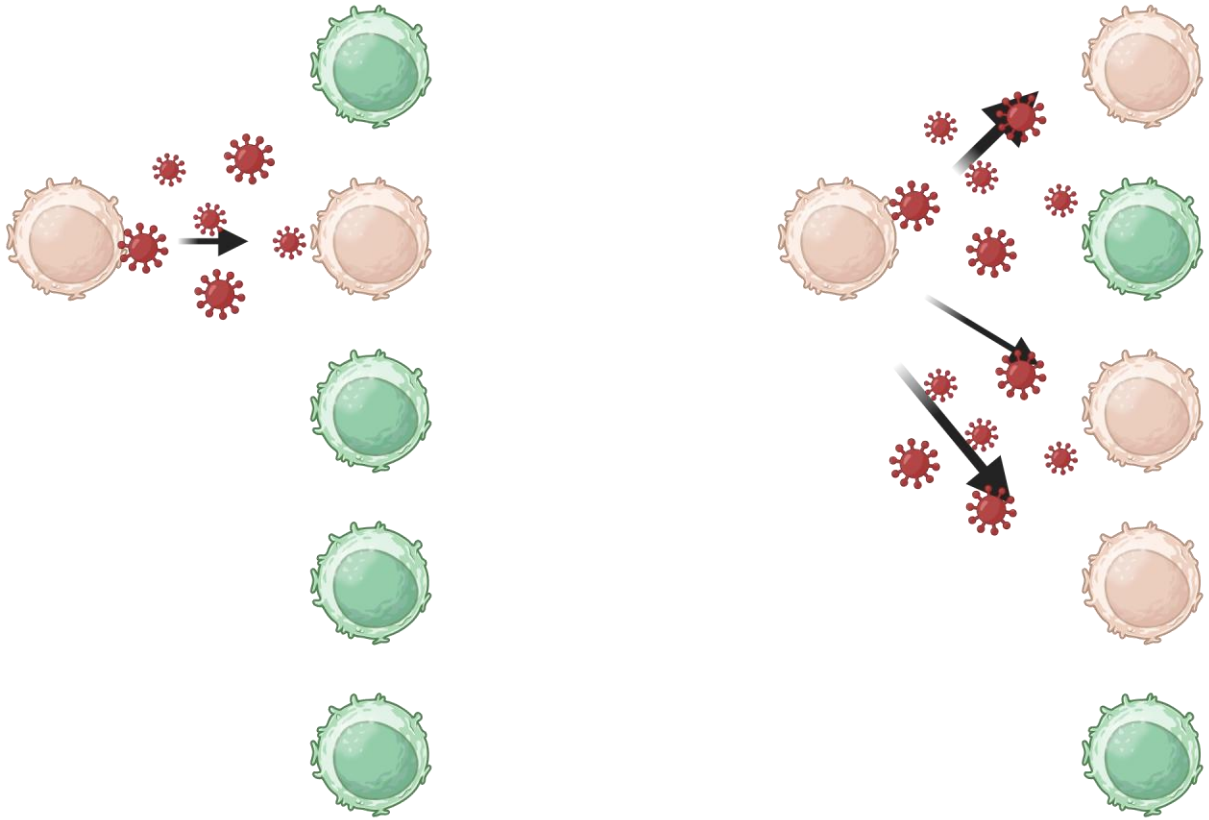


Major INSTI mutations occur at a high fitness cost

Cell to cell reproduction number = viral fitness

HIV drug resistance testing

Drug resistance testing methods

Phenotypic testing:

- Expensive, time consuming
- Valuable when a drug is new or resistance pattern is complex or for explaining novel mechanisms of resistance
- In ZA: rare outside clinical trials

Genotypic HIV drug resistance testing

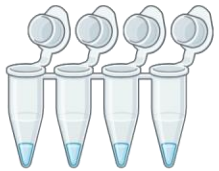
- Target genes are amplified by PCR
- Followed by sequencing (Sanger and recently more next generation sequencing) - > drug resistance interpretation

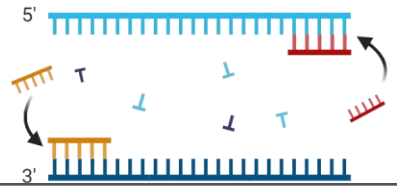
Genotypic drug resistance testing process

Plasma from EDTA blood;
DBS
Cells – proviral
CSF

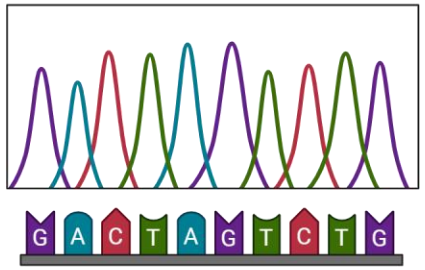
HIV-1 RNA isolation (or DNA 'archived')

Reverse transcription





DNA amplification by PCR
(often pre-nested and nested PCR)



Sequencing:
Traditionally – Automated Sanger Sequencing ;
NGS

Bioinformatics and Drug resistance interpretation algorithm

Report of any resistance detected to currently used drugs

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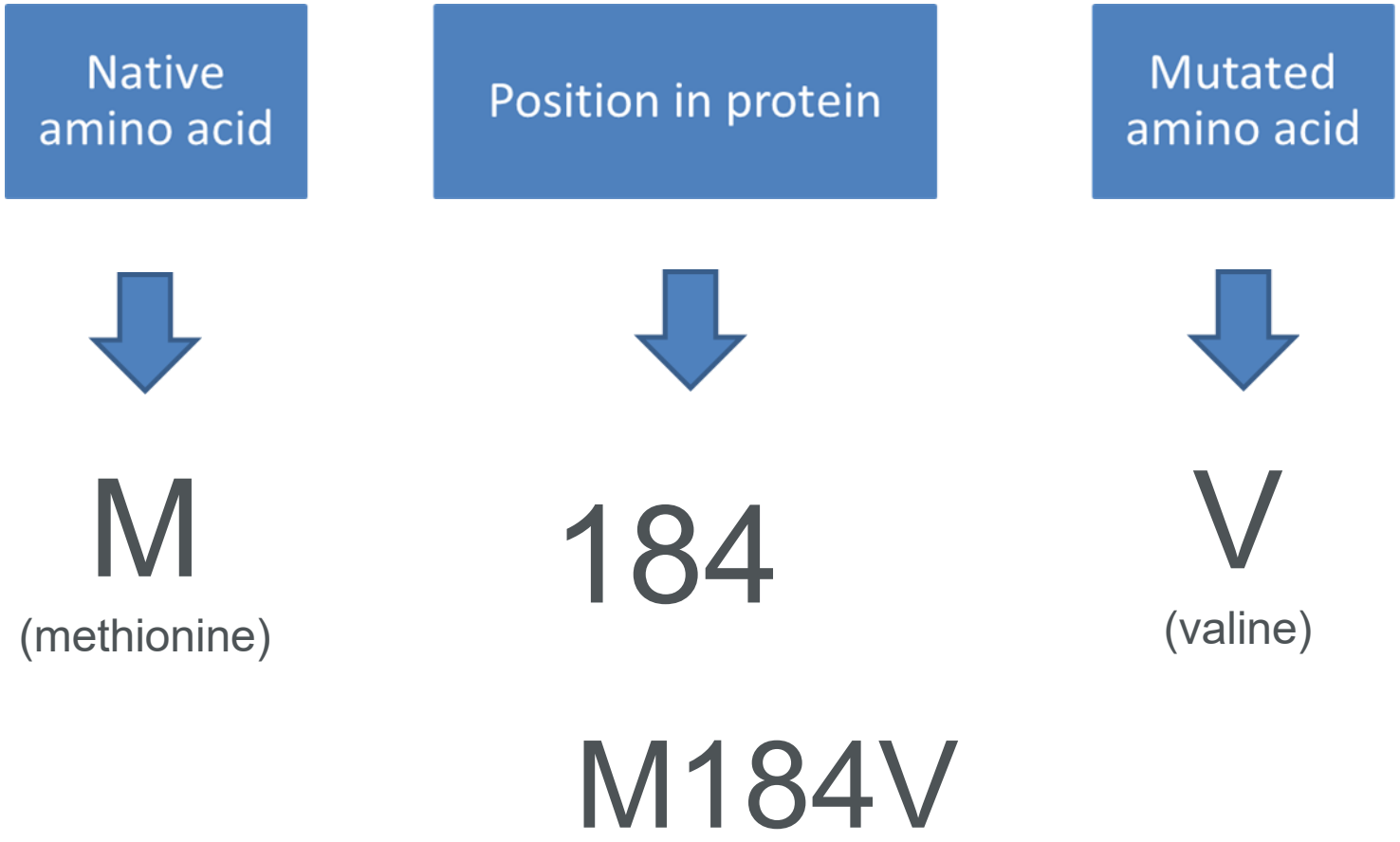
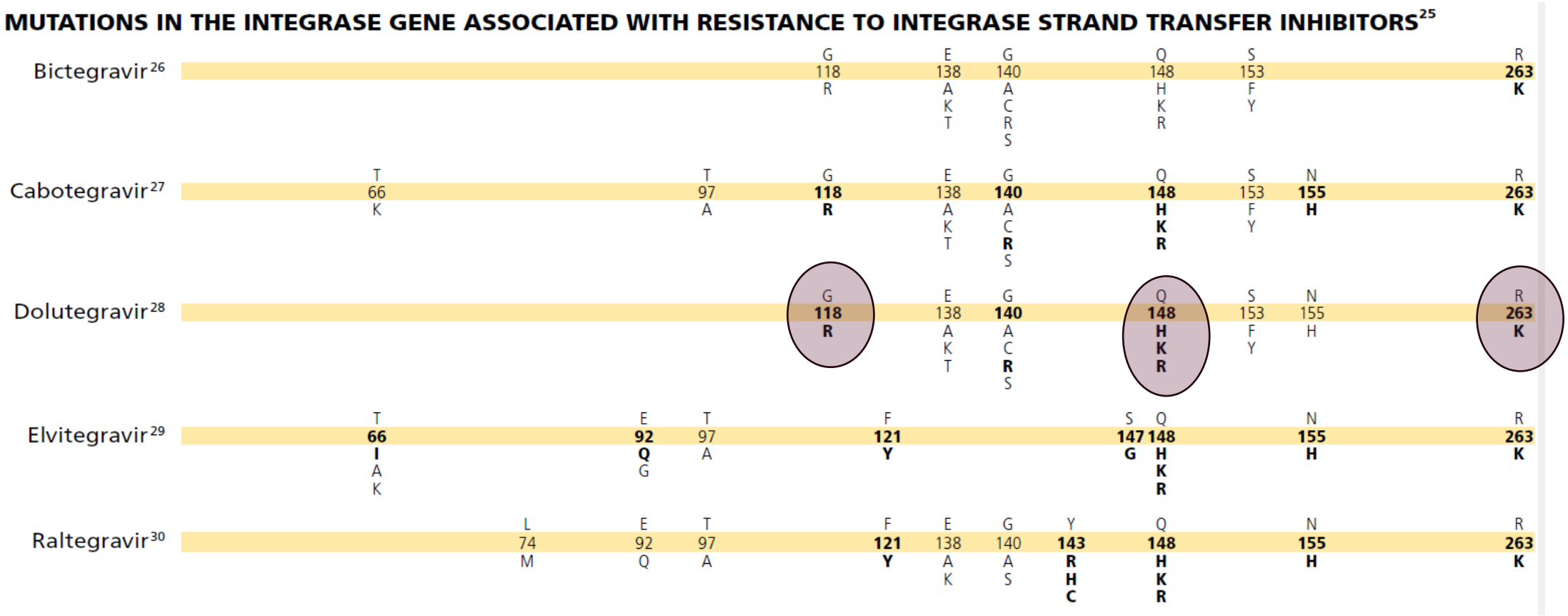
Mutation notation



HIV integrase inhibitors: major and accessory mutations

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]

Barriers to DTG resistance

- High potency
- High affinity for integrase and slow dissociation
- Fixed dose combination (FDC): TDF, 3TC, DTG – all have a long duration of intracellular activity
- Fitness cost of major INSTI mutations
  - R263K– maximal integration decreases by 60%
  - G118R– maximal integration decreases by 85%
  - R263K: 2-3 fold resistance
  - G118R: 2-10 fold resistance

Xiao et al 2023. Antimicrobial Agents and Chemotherapy 67, e01386-22.
Brenner et al. Journal of Antimicrobial Chemotherapy 71, 1948–1953
Mesplede et al. 2012. Journal of the International AIDS Society 15, 18113.
Wainberg et al. 2015. J Virus Erad 1, 13–16.
Quashie et al. 2015. Journal of Virology 89, 3163–3175.

Multiple choice questions (1)

1. Considering the impact of viral fitness cost of mutations - what would be the impact of the high fitness cost on interpreting a drug resistance test result?

a) Unless a patient is currently adherent to a regimen that selects for these mutations, drug resistance mutations may not be detectable

b) It would make phenotypic drug resistance testing preferable to genotypic drug resistance testing

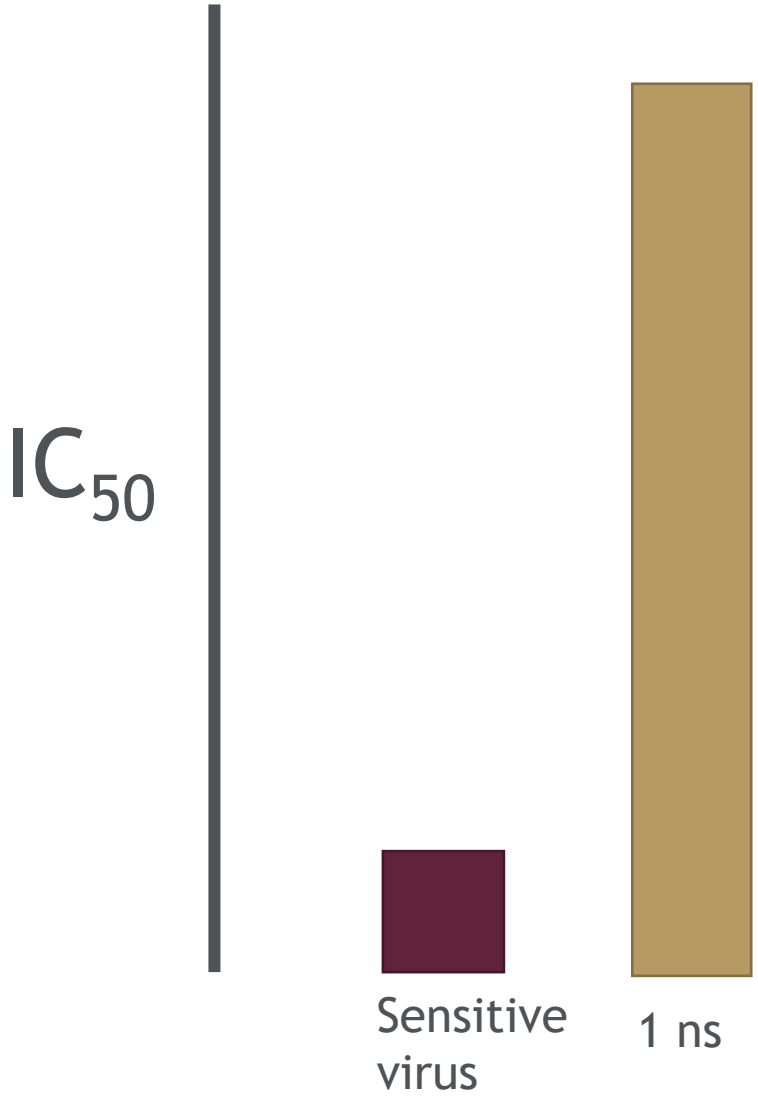
c) Patients with drug resistance are likely to have very high viral loads

d) Drug resistance testing should be performed before treatment starts, to have a baseline

Adherence patterns and drug resistance

Low genetic barrier drugs

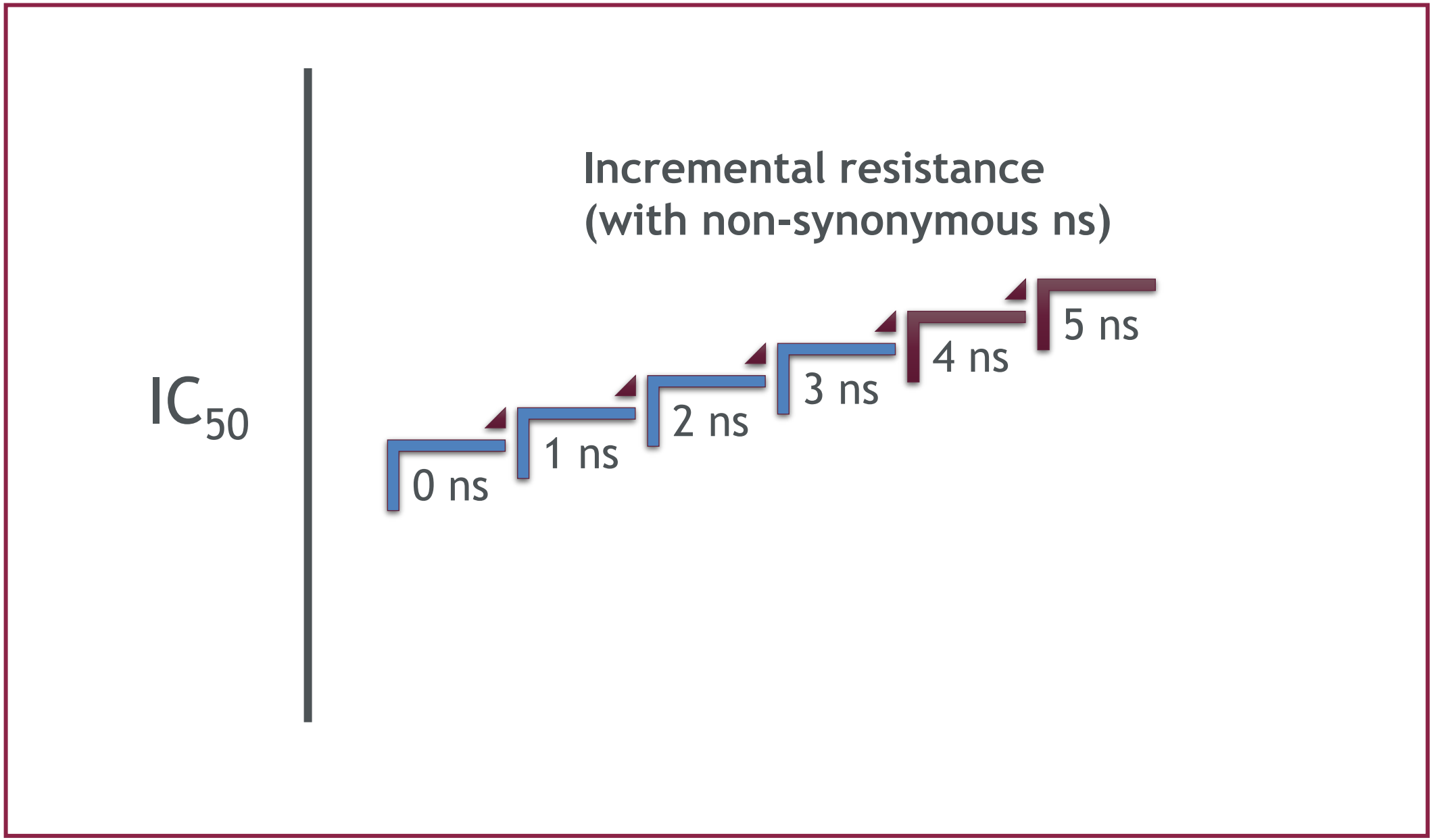
Single mutation results in large “fold change”



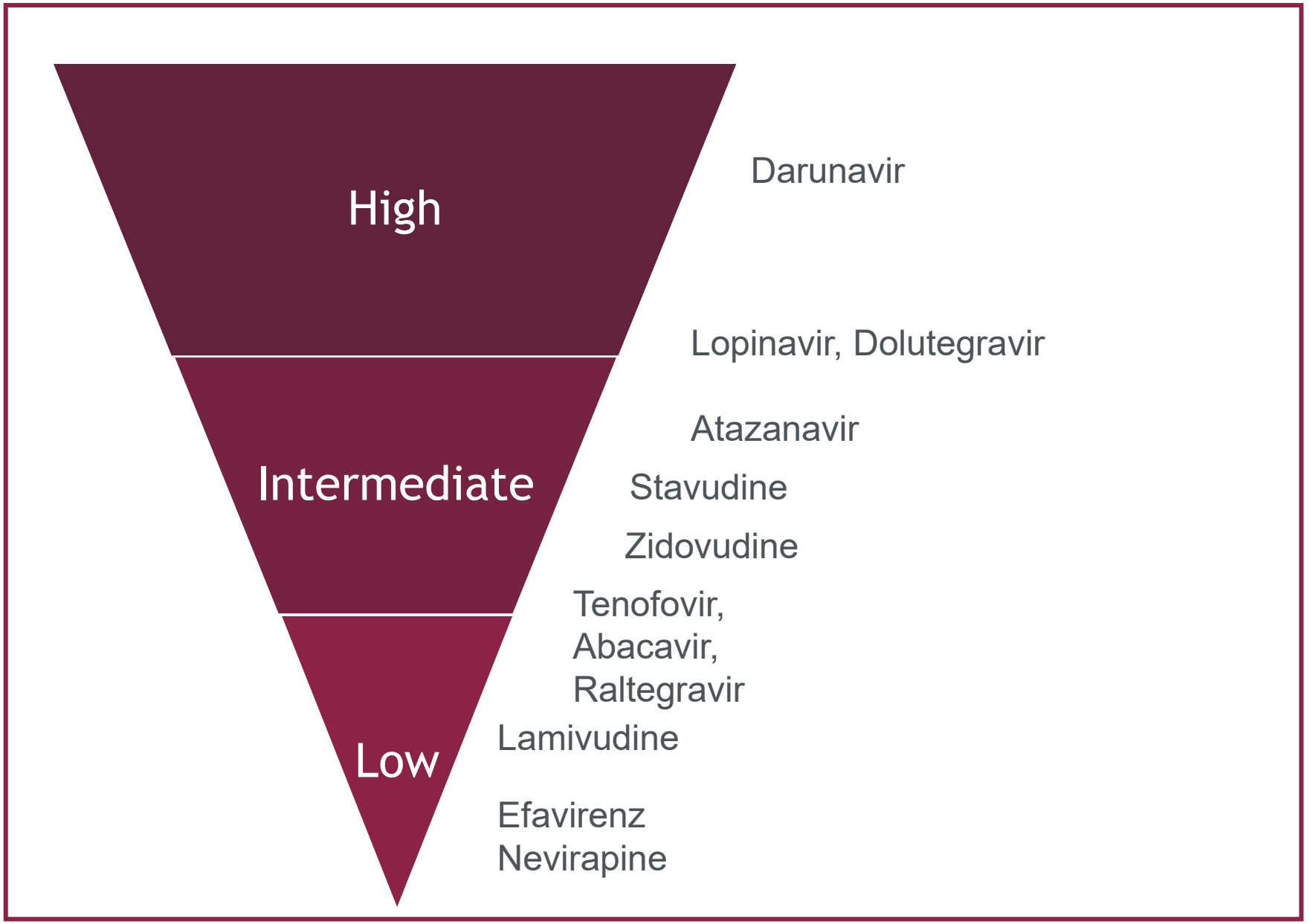
ns= nucleotide substitution

Examples:
K103N – EFV /NVP
M184V – 3TC/FTC

High genetic barrier drugs

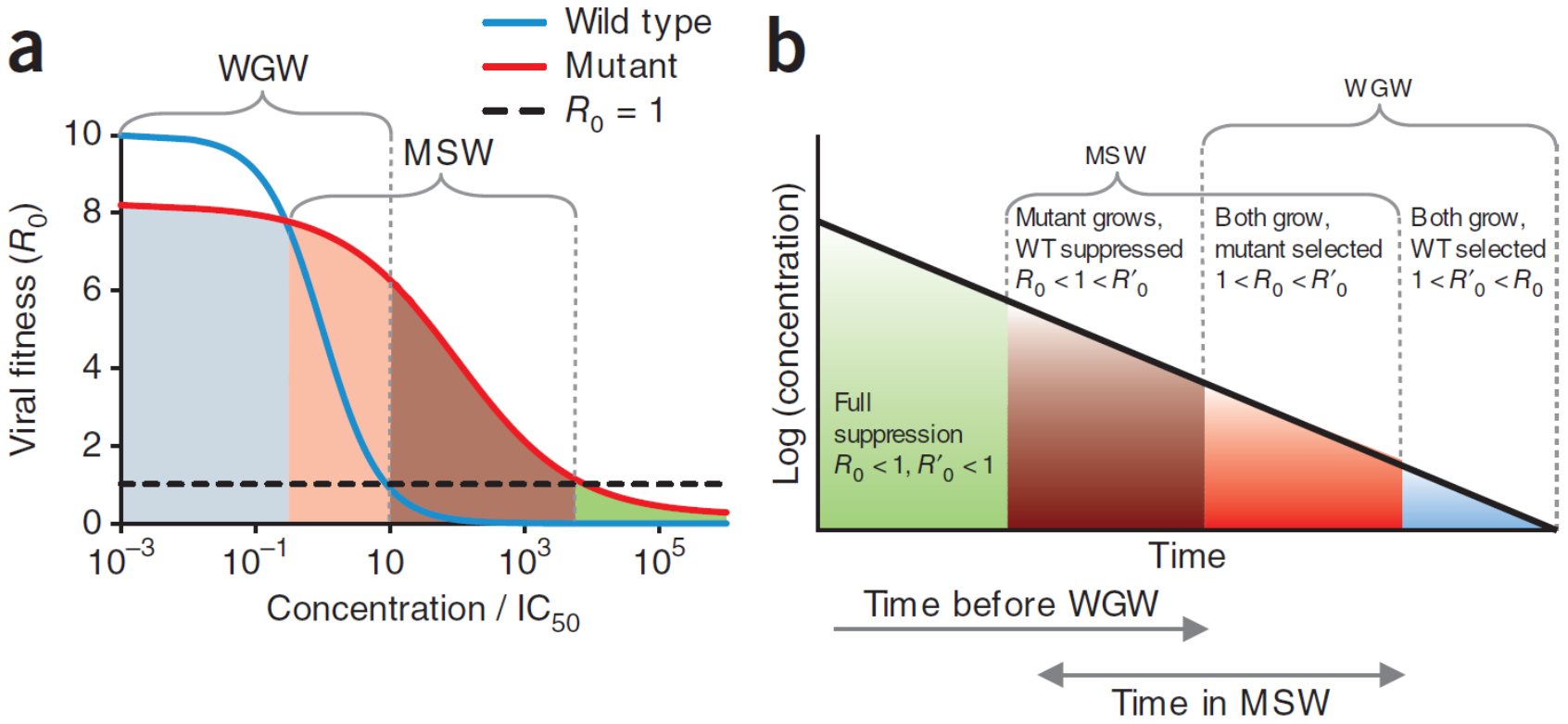


Arbitrary genetic barrier comparison



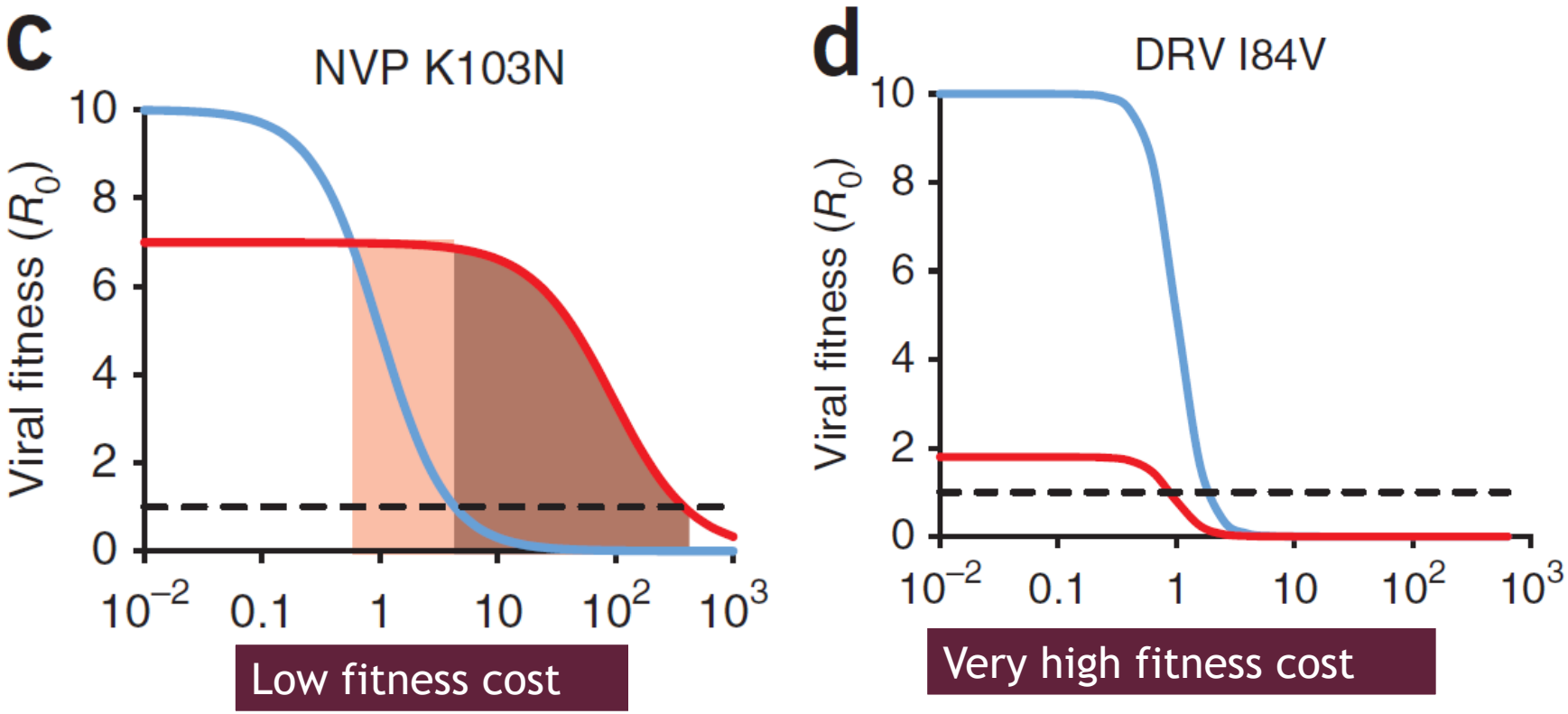
Number of mutations required, the difficulty of their evolution, and their fitness cost

Combined model(2)



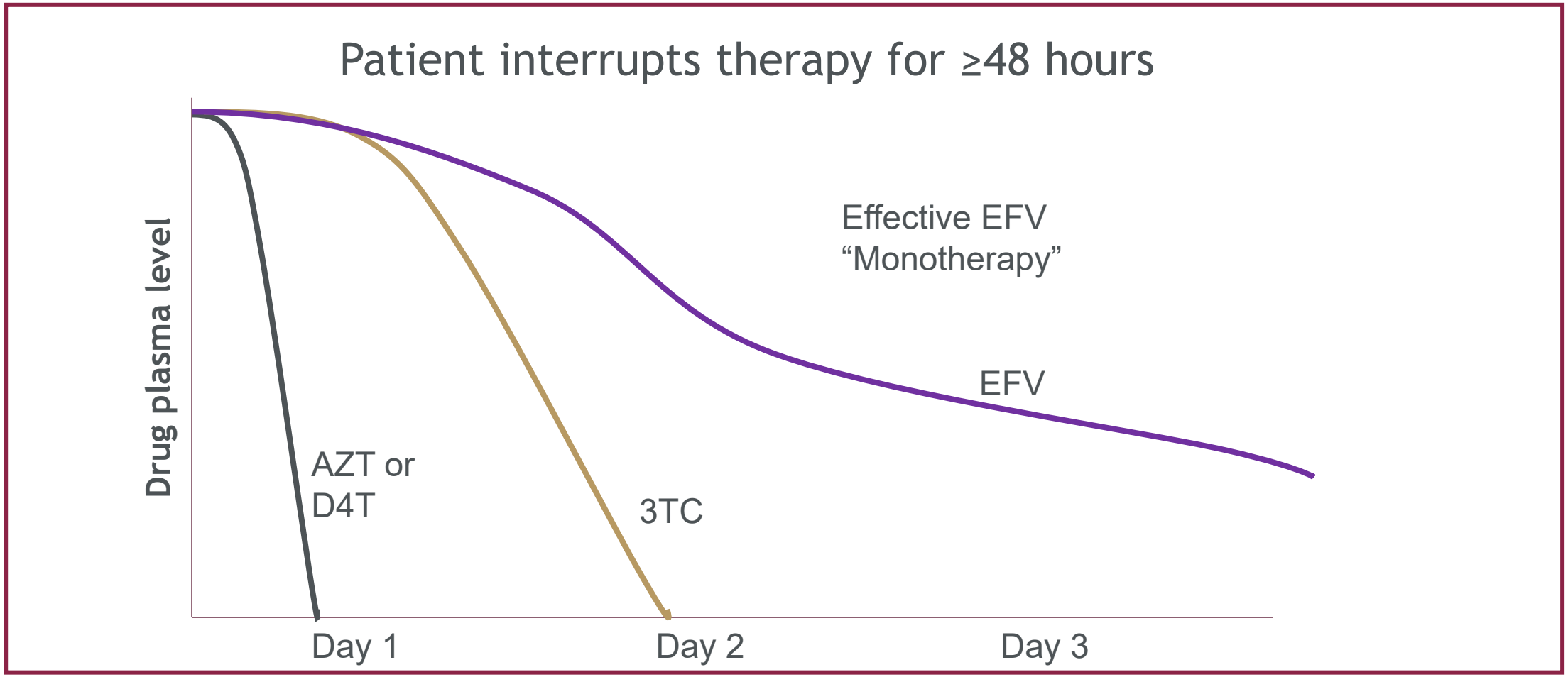
Rosenbloom DIS, Hill AL, Rabi SA, Siliciano RF, Nowak MA. Antiretroviral dynamics determines HIV evolution and predicts therapy outcome. Nat Med 2012; 18:1378–85.

Combined model(3)



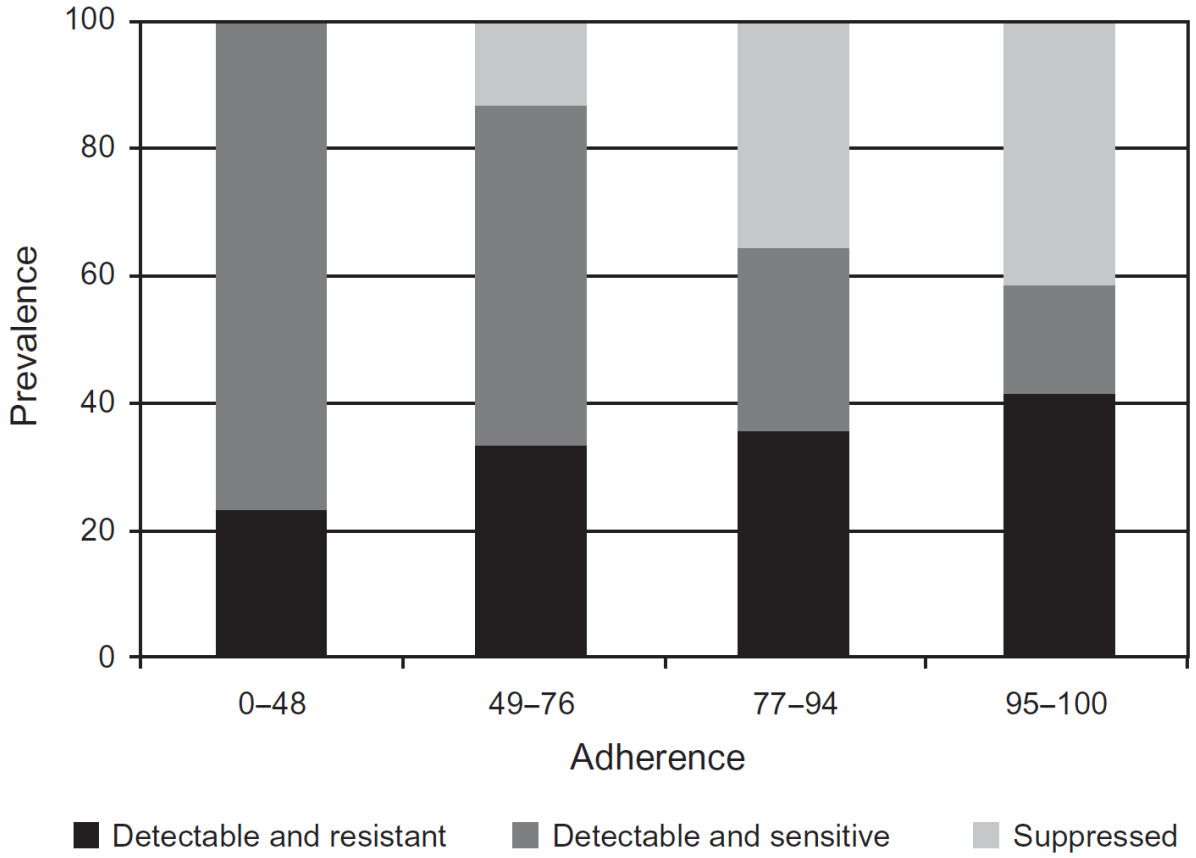
Rosenbloom DIS, Hill AL, Rabi SA, Siliciano RF, Nowak MA. Antiretroviral dynamics determines HIV evolution and predicts therapy outcome. Nat Med 2012; 18:1378–85.

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

Patients with viraemia but good levels of adherence are more likely to have PI resistance



Gardner et al. AIDS, 2009

Integrase inhibitors: adherence patterns

- Raltegravir virologic failure occurs with interruptions or low average adherence
- Dolutegravir has a high forgiveness and high genetic barrier
  - Resistance is rare and therefore the patterns associated with it are difficult to model

Parienti, J.-J. et al. Forgiveness of Dolutegravir-Based Triple Therapy Compared With Older Antiretroviral Regimens: A Prospective Multicenter Cohort of Adherence Patterns and HIV-RNA Replication. Open Forum Infect Dis 8, ofab316 (2021).
Gras, G. et al. Patterns of adherence to raltegravir-based regimens and the risk of virological failure among HIV-infected patients: the RALTECAPS cohort study. J Acquir Immune Defic Syndr 61, 265–269 (2012).

Multiple choice questions (2)

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2. Dolutegravir drug resistance is most likely with which adherence pattern?

a) Patients who leave out TLD on weekends

b) Patients who stop taking TLD for a week every 3 months

c) The pattern of adherence that selects for drug resistance on TLD is not clear

d) Patients who take TLD at different times of the day

Clinical study evidence for DTG first-line and treatment experienced - drug resistance

Studies of acquired HIV drug resistance

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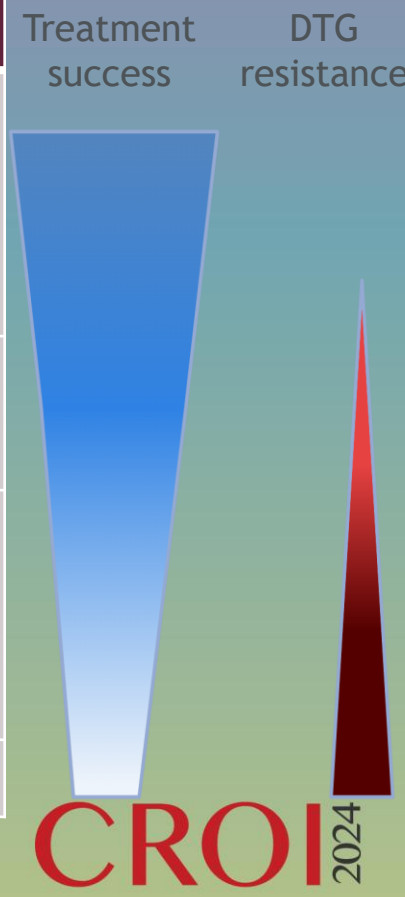
Randomized trials	Population based observational studies	Laboratory based studies
• Allocation is unbiased • **Strick entry criteria (excluding patients)** • **Relative short follow-up - drug resistance may take long**	• Representative or **convenience** samples • **Regimen allocation not random** •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

Virologic success and drug resistance with different DTG treatment scenarios

Treatment Scenario	Viral load	Studies
Treatment naive	BL VL < 100 000 copies/mL	SINGLE, SPRING-1&2, FLAMINGO, ADVANCE, NAMSAL
	BL VL ≥ 100 000 copies/mL	
Transition from current first-line	Viral load suppressed	Schramm et al. 2022 (Malawi)
	Viremic	
Treatment experienced: INSTI naïve	BL VL < 100 000 copies/mL	DAWNING, NADIA, awaiting data: VISEND, 2SD, ARTIST (96w), ODESSEY, others
	BL VL ≥ 100 000 copies/mL	
INSTI experienced		VIKING



CROI 2024

Second generation INSTIs: treatment naïve individuals

- Highly effective and tolerable
  - Few cases of virologic non-suppression (V-NS)
  - Many resuppress – suggesting that V-NS is often due to poor adherence
- When DTG is used in initial antiretroviral combination therapy, major drug resistance mutations in *integrase gene* are rare
  - RCTs < 1% of cases with V-NS
  - Likely somewhat higher in real-world settings

Keene et al. 2023. J Acquir Immune Defic Syndr 92, 422–429.
Chu et al. 2024. Viruses 16, 399.

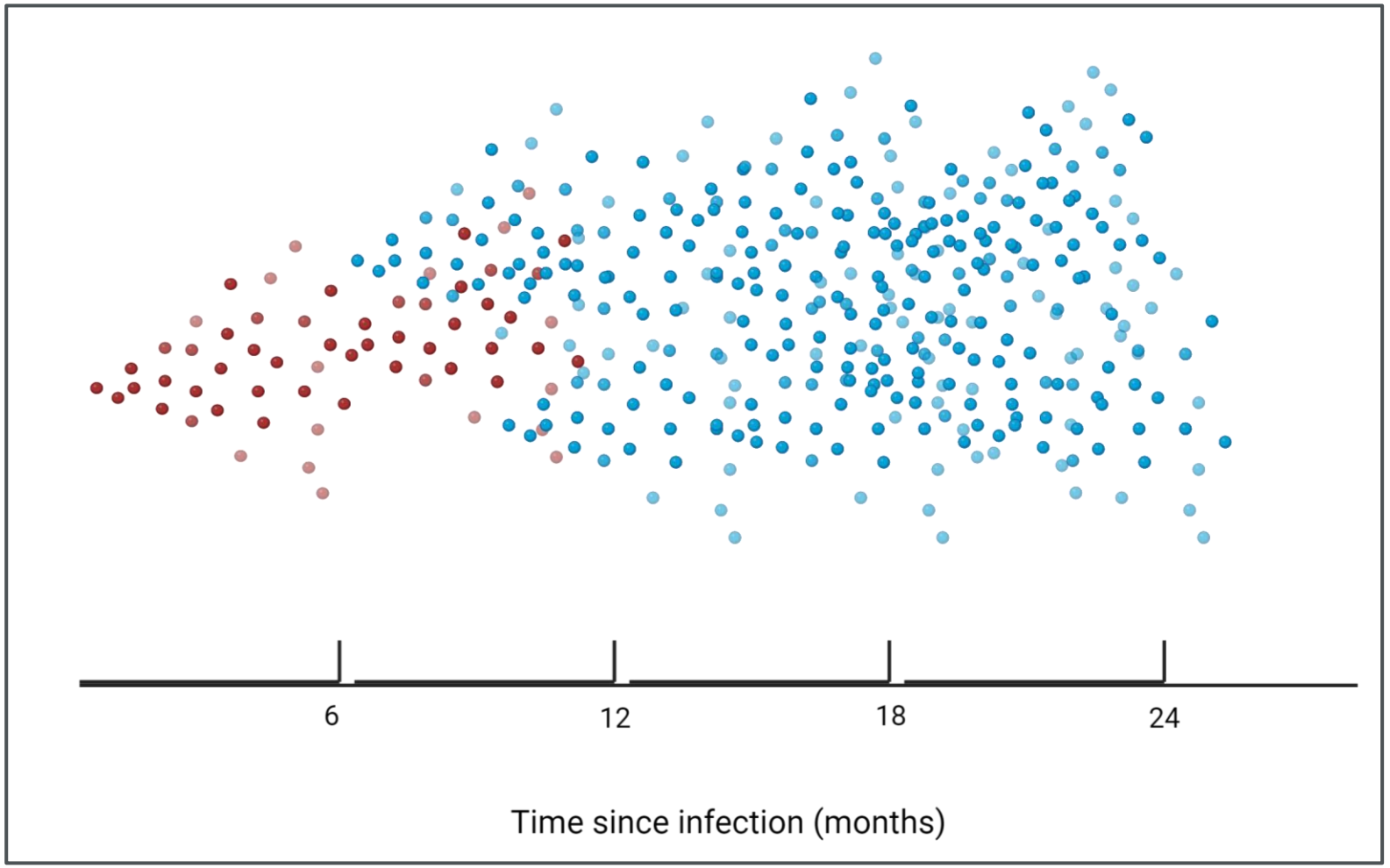
Second generation INSTIs: treatment experienced cases

- DTG triple combination regimens in individuals with previous V-NS on another regimen ~ DTG resistance in 20% of those with subsequent V-NS have DTG- associated mutations
- Long duration of V-NS: higher prevalence of drug resistance
- Zhao et al. ~DTG resistance in 57% with stringent guidelines for testing

Zhao et al. 2025. J Acquir Immune Defic Syndr 99, 283–287.
Chu et al. 2024. Viruses 16, 399

Transmitted and pre-treatment HIV drug resistance

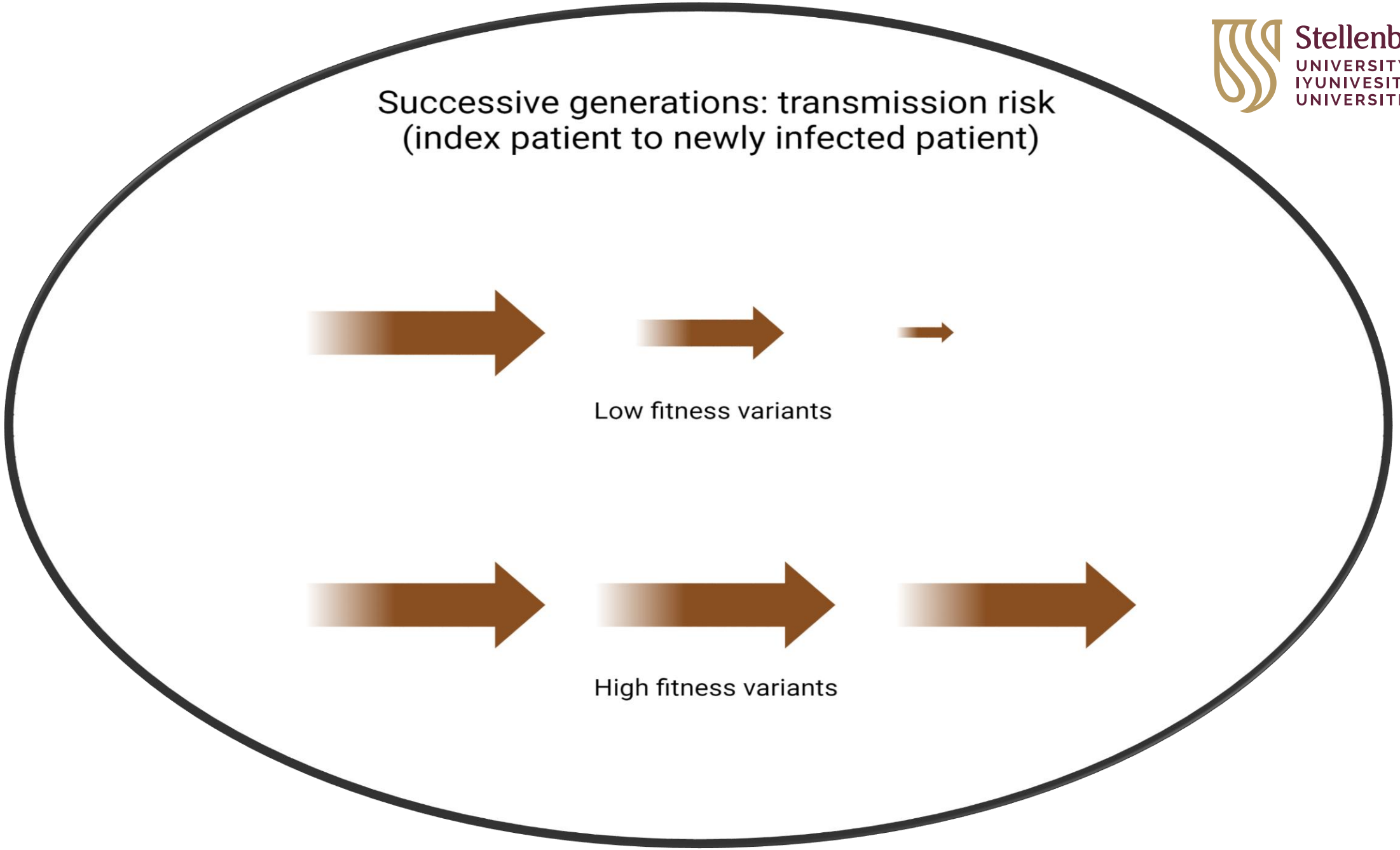
Drug resistance reversion



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

Fitness and transmission

- Fit variants may not revert before the next transmission generation
  - Some NNRTI mutations have similar fitness to wildtype
- Acute infection is associated with a high viral load and high risk of transmission
  - these individuals more likely to transmit drug resistance variants, even if less fit (not enough time for reversion)
- High-risk individuals may therefore fuel transmitted resistance
- Little is known about fitness of various accessory INSTI mutations selected by DTG across HIV-1 subtypes
- Further research is required to establish transmission risk of INSTI resistant variants

Wagner BG et al. "Factors limiting the transmission of HIV mutations conferring drug resistance: fitness costs and genetic bottlenecks" (2012) *Scientific Reports* 2: 320

Data on pre-treatment INSTI resistance

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INSTI drug resistance mutations from studies 2010-2020 – 5 continents*

No evidence of increase in INSTI non-polymorphic mutations*

Levels ≤ 0.5%*

Many other studies confirm that there is no evidence of a rapid increase in INSTI resistance#

This despite the initial use of low genetic barrier first generation INSTIs

*Bailey, A.J., Rhee, S.-Y. and Shafer, R.W. (2021) 'Integrase Strand Transfer Inhibitor Resistance in Integrase Strand Transfer Inhibitor-Naive Persons', AIDS Research and Human Retroviruses, 37(10), pp. 736–743. Available at: https://doi.org/10.1089/aid.2020.0261

#Alvarez, M. et al. (2019) 'Surveillance of transmitted drug resistance to integrase inhibitors in Spain: implications for clinical practice', Journal of Antimicrobial Chemotherapy, 74(6), pp. 1693–1700

#Viñuela, L. et al. (2023) 'Transmitted drug resistance to antiretroviral drugs in Spain during the period 2019–2021', Journal of Medical Virology, 95(12), p. e29287. Available at: https://doi.org/10.1002/jmv.29287.

Multiple choice questions (3)

3. Which of the following is the best evidence-based association, with an increase in dolutegravir (DTG) resistance risk, in an individual?

a) A high proportion of the population receiving DTG, since that would result in transmitted DTG resistance

b) Multiple prior regimens, especially previous INSTI use

c) Rifampicin use in combination with TLD

d) Unprotected sex

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Factors influencing drug resistance risk

Drug resistance: probability and impact determines importance of testing

- Probability of drug resistance
  - Treatment experienced
  - High viral load
  - Adherence challenges
  - Inadequate regimen

- Impact of drug resistance
  - Little time to achieve optimal therapy –
    - Pregnancy
    - Advanced disease

Case report: rapid emergence of drug resistance

- Child perinatally infected with a wildtype virus (sequenced from DBS)
- Started ABC, 3TC, DTG at 4-months-of-age
- 7-months-of-age (3 months after ART initiation) she was re-admitted with septic shock resulting from Pseudomonas aeruginosa bacteraemia.
- Her HIV VL at that time was > 10 million copies/mL (> 7 log10) and CD4 count 41 cells/µL (17%)
- *Developed DTG drug resistance G118R and E138K, within 97 days of treatment initiation*
- *Risk factors: Advanced disease, sick child receiving therapy*
- *Concurrent valganciclovir*
- *Poor feed and medication tolerance*

O'Connell, N. L., von Mollendorff, T.-L., van Zyl, G., Korsman, S. & Nuttall, J. Rapid development of drug resistance during initial dolutegravir-based antiretroviral therapy of an infant with HIV. South Afr J HIV Med 26, 1750 (2025).

Long-acting ART and drug resistance

Long-acting treatment – special considerations

- On time injections- easy to ascertain adherence
- CAB/RPV: IM injections importance of correct procedure – impact of injection and BMI on drug exposure
- LEN: subcutaneous injection
- Long pharmacokinetic tail when interrupting treatment
  - incident cases during this period may have a high risk of drug resistance

CAB/RPV - VF and drug resistance

Setting	Induction maintenance	Switch-suppressed	Switch-viremic
Virologic failure	6/513 (1%)	92/7801 (1%)	37/910 (5%)
INSTI resistance	4/5 (71%)	23/37 (61%)	7/17 (41%)

(19 studies)

Perez Navarro et al. 2024. “Virologic Failure and Emergent Integrase Strand Transfer Inhibitor Drug Resistance With Long-Acting Cabotegravir for HIV Treatment: A Meta-Analysis.” Clinical Infectious Diseases, December 26, ciae631.

CAB/RPV: Pre-existing resistance – clinical relevance

- Sub-Saharan Africa has a high level of NNRTI exposure – it is uncertain how this would impact on CAB/PRV should this be rolled out more widely for treatment
- However South African participants in FLAIR and ATLAS-2M had excellent outcomes
  - Only 1/ 49 receiving CAB/RPV had confirmed virologic failure by 96 weeks (this participant had pre-therapy drug resistance to RPV and also G140R, conferring CAB resistance)
  - Drug resistance genotypic testing at week 16 revealed NNRTI mutation (Y188L) and integrase resistance associated mutations (**N155N/H, Q148Q/R**), along with an integrase polymorphism (**L74L/I**).
- Possible association with 2 or more RPV RAMS and subtype A1/A6 and increased risk of VF on CAB/RPV; however good response in African A1 regions.

Steegen et al. 2023. "Impact of Rilpivirine Cross-Resistance on Long-Acting Cabotegravir-Rilpivirine in Low and Middle-Income Countries." AIDS 37 (6): 1009.
Mngqibisa et al. 2025. "The 96-Week Outcomes and Pharmacokinetics of Long-Acting Cabotegravir plus Rilpivirine in South Africans." *Southern African Journal of HIV Medicine* 26 (1): 7
Cutrell et al. 2021. "Exploring Predictors of HIV-1 Virologic Failure to Long-Acting Cabotegravir and Rilpivirine: A Multivariable Analysis." AIDS 35 (9): 1333.
Geretti et al. 2025. "Optimizing the Use of Cabotegravir Plus Rilpivirine Long-Acting Therapy in HIV Care: Evidence, Implementation, and Unanswered Questions." Open Forum Infectious Diseases 12 (7): ofaf368.

Should one use the same class for PrEP and treatment? INSTI mutation overlap

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Resistance pathways very similar

Major Integrase Inhibitor (INSTI) Resistance Mutations

	66	92	118	138	140	143	147	148	155	263
Consensus	**T**	**E**	**G**	**E**	**G**	**Y**	**S**	**Q**	**N**	**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)	AIK	**Q**	R	**KAT**	SAC	RCH		HRK	H	K

Stanford HIV drug resistance database: https://hivdb.stanford.edu/dr-summary/resistance-notes/INSTI/

Drug resistance when receiving LEN as part of treatment

- Capella study:
  - RCT of LEN (SC, 26 weekly) with optimized background regimen (OBR) in heavily treatment experienced participants with multi-drug resistant (MDR) HIV-1 (drug resistance to ≥ 2 of 4 main classes)
  - 72 participants were enrolled
  - 27 participants did not achieve VL < 50 copies/mL by week 104
  - 14/27 (52%) had capsid inhibitor associated mutations
    - 4 had no active drugs in their OBR
    - 10 had inadequate plasma drug concentrations in their OBR
  - 7 resuppressed with changes in (n=2) or improved adherence (n=5) in the OBR

Segal-Maurer et al. 2022. “Capsid Inhibition with Lenacapavir in Multidrug-Resistant HIV-1 Infection.” The New England Journal of Medicine 386 (19): 1793–803.

Capella study mutations (14 participants):

Mutation	Number
M66I	6
Q67H/K/N	8
K70H/N/R/S	7
N74D/H/K	5
A105S/T	5
T105A/C/N	6

Segal-Maurer et al. 2022. “Capsid Inhibition with Lenacapavir in Multidrug-Resistant HIV-1 Infection.” The New England Journal of Medicine 386 (19): 1793–803.

Level	DRM Pattern[1]	Fold Reduced Susceptibility	Replication Capacity (%)
Low	**Q67H**	6_2	78_2
	K70R	1	10
	T107N	4	32
Intermediate	**N74D**	17_3	49_3
	Q67H, K70R	18_2	-
	K70N	24	7
	Q67H, N74S	32	34
High	**K70H**	70_2	24_2
	Q67H, T107N	62	41
	Q67H, K70R, T107S	66	109
Very High	**M66I**[3]	$>1000_4$	4_4
	Q67H, N74D	>1000	30

Footnote: [1]All isolates shown were site-directed mutants tested using the Monogram BioSciences Assay except for the two clinical isolates containing Q67H/K70R. [2]The subscript indicates the number of isolates tested. L56I, which was reported only during in vitro selection experiments, had a fold reduced susceptibility of 204 and an RC of 4%. [4]Isolates with M66I plus A105T, T107S, Q67H, and Q67H/K70R are not shown. Each had a fold reduced susceptibility >1000 and RC values of between 1% and 24%.

Van Zyl, Shafer et al. “Lenacapavir-Associated Drug Resistance: Implications for Scaling up Long-Acting HIV Pre-Exposure Prophylaxis.” The Lancet HIV.

Calibrate study

- Randomized open label study - primary endpoint week 54
- Treatment naïve individuals, received 2 weeks oral LEN lead-in with FTC/TAF followed by:
  - SC-LEN 26 weekly with oral FTC/TAF (group 1; n=52)
  - SC-LEN 26 weekly + BIC (group 2; n=53)
  - oral LEN, FTC/TAF (group 3; n=52)
  - and BIC, FTC/TAF (group 4; n=25)
- 2 cases of LEN drug resistance:
  - 1 in group 2 (Q67H and K70R)
  - 1 in group 3 (Q67H)

Gupta et al. 2023. “Lenacapavir Administered Every 26 Weeks or Daily in Combination with Oral Daily Antiretroviral Therapy for Initial Treatment of HIV: A Randomised, Open-Label, Active-Controlled, Phase 2 Trial.” *The Lancet HIV* 10 (1): e15–23.

Understanding virologic failure on injectable regimens

Drug exposure

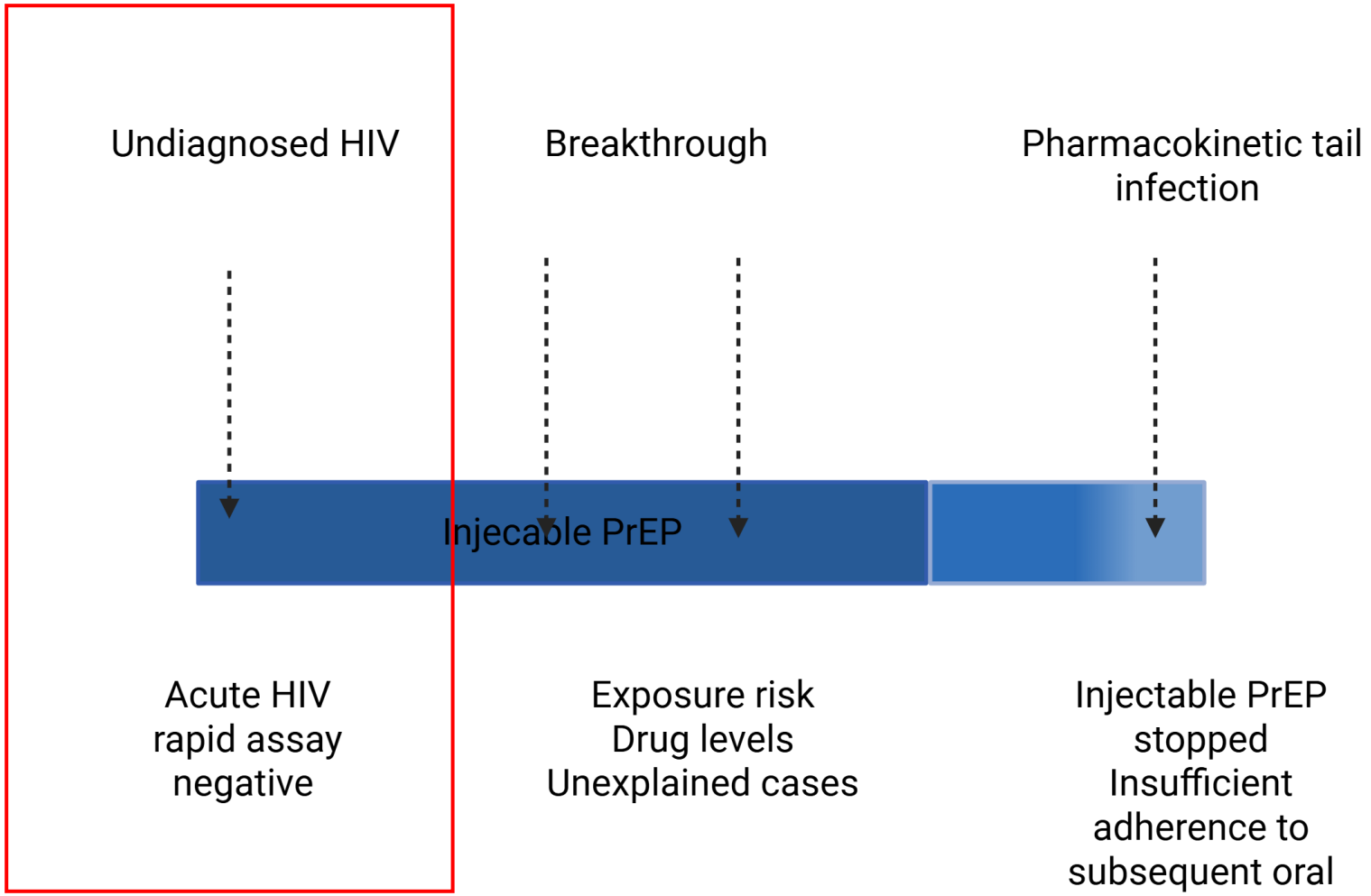
- On-time injections - objective evidence of adherence
- BMI –possible factor; no convincing data
- Pregnancy – limited data
- Drug interactions - over-the-counter/ traditional medicine; concomitant medication

Rare cases with virologic failure despite on-time injections and sufficient drug levels

- Poorly understood
- CAB/RPV:
  - Role of HIV-1 subtype (subtype A1 and A6 – higher prevalence of L74I)
  - INSTI mutations/ other mechanisms ?

Cutrell et al. 2021. "Exploring Predictors of HIV-1 Virologic Failure to Long-Acting Cabotegravir and Rilpivirine: A Multivariable Analysis." AIDS 35 (9): 1333.

Drug resistance during long-acting PrEP



CAB-PrEP drug resistance

- HPTN-083 – **4 566** cisgender men and transgender women:
  - **35** HIV infections
  - 25 during primary blinded study and one-year unblinded:
    - 3 - oral lead-in
    - 12 – after lapses in injections > 6 months
    - 3 - variable injection delays
    - 7 – on-time injections
  - 10
    - 4 undetected early infections
    - 6 seroconverted 1 year after switched to oral TFV/FTC
  - **Drug resistance testing in 16 with CAB exposure**
  - **7/16 (44%) had INSTI resistance**
- HPTN-084 - 3 223 cisgender women in sub-Saharan Africa
  - 4 breakthrough infections – **no INSTI drug resistance**

Parikh et al. 2022. "Long-Acting Injectable Cabotegravir for HIV Prevention: What Do We Know and Need to Know about the Risks and Consequences of Cabotegravir Resistance?" *Current HIV/AIDS Reports* 19 (5): 384–93

LEN PrEP Breakthrough Cases

PURPOSE-1: No breakthrough cases amongst 2134 cisgender women

PURPOSE-2: Two breakthrough cases amongst 2179 gender-diverse men

- Participant A was diagnosed at 13 weeks, concurrent HIV-1 viral load of 934,000 copies/mL (retrospective 8 weeks load of 4.8 copies/mL); mutation N74D
- Participant B was diagnosed at 26 weeks, concurrent HIV-1 viral load of 14,100 copies/mL; mutation N74D

Bekker, LG, et al. Twice-Yearly Lenacapavir or Daily F/TAF for HIV Prevention in Cisgender Women. NEJM 2024

Kelley, C. F. et al. Twice-Yearly Lenacapavir for HIV Prevention in Men and Gender-Diverse Persons. New England Journal of Medicine (epublished before print 2024)

Other long acting regimens

- Islatravir – oral weekly regimen with LEN
  - Islatravir has a high genetic barrier to drug resistance
- This may offer a robust regimen considering the lack of pre-therapy resistance to LEN and Islatravir' s high genetic barrier
- bNAbs
  - breakthrough risk with resistant minor variants
    - Requiring combinations of bNAbs
    - Most suitable for treating early, less diverse infections
    - Assays to screen for susceptibility are costly – better solutions are needed
  - LS – mutations in FC for longer t ½
  - Additional advantages – vaccinal effect and possible reservoir reduction

Diamond, Tracy L., Winnie Ngo, Min Xu, et al. 2022. "Islatravir Has a High Barrier to Resistance and Exhibits a Differentiated Resistance Profile from Approved Nucleoside Reverse Transcriptase Inhibitors (NRTIs)." Antimicrobial Agents and Chemotherapy 66 (6): e00133-22.

Long-acting regimens conclusive comments

- CAB, DTG and BIC share resistance pathways – consideration for guidelines
- LEN – current usage is low – no impact on current recommended regimens
- RPV has a low genetic barrier
- Clinical studies show low risk of VF with injectable treatment – but high probability of drug resistance ?
- Real-world settings – VF rate may be higher
- CAB + LEN injectable or LEN + islatravir (oral) may have higher genetic barrier

Long-acting regimens conclusive comments(2)

- Emerging pipeline
- CAB/RPV
  - VF is rare, but when it occurs there is a high risk of drug resistance
- LEN for treatment
  - Salvage regimens
    - Risks of LEN VF and drug resistance: inadequate backbone
  - Future – other indications
  - Combination LEN with CAB
    - may have lower risk that CAB/RPV: no pre-existing LEN resistance (unlike RPV)
- Patients with VF on injectables or PrEP breakthrough infections, require HIV drug resistance testing (polymerase gene +/- gag ? additional regions)

Multiple choice questions (4)

4. Which of the following is true regarding drug resistance associated with long-acting regimens?

a) The high levels of NNRTI resistance in the community would make CAB/RPV an unviable treatment option

b) LEN should be avoided in salvage therapy as that would preclude its use for PrEP

c) A high prevalence of transmitted capsid inhibitor resistance is likely to follow LEN rollout for PrEP

d) The biggest drug resistance concern with PrEP is when patients are already HIV infected when PrEP is initiated

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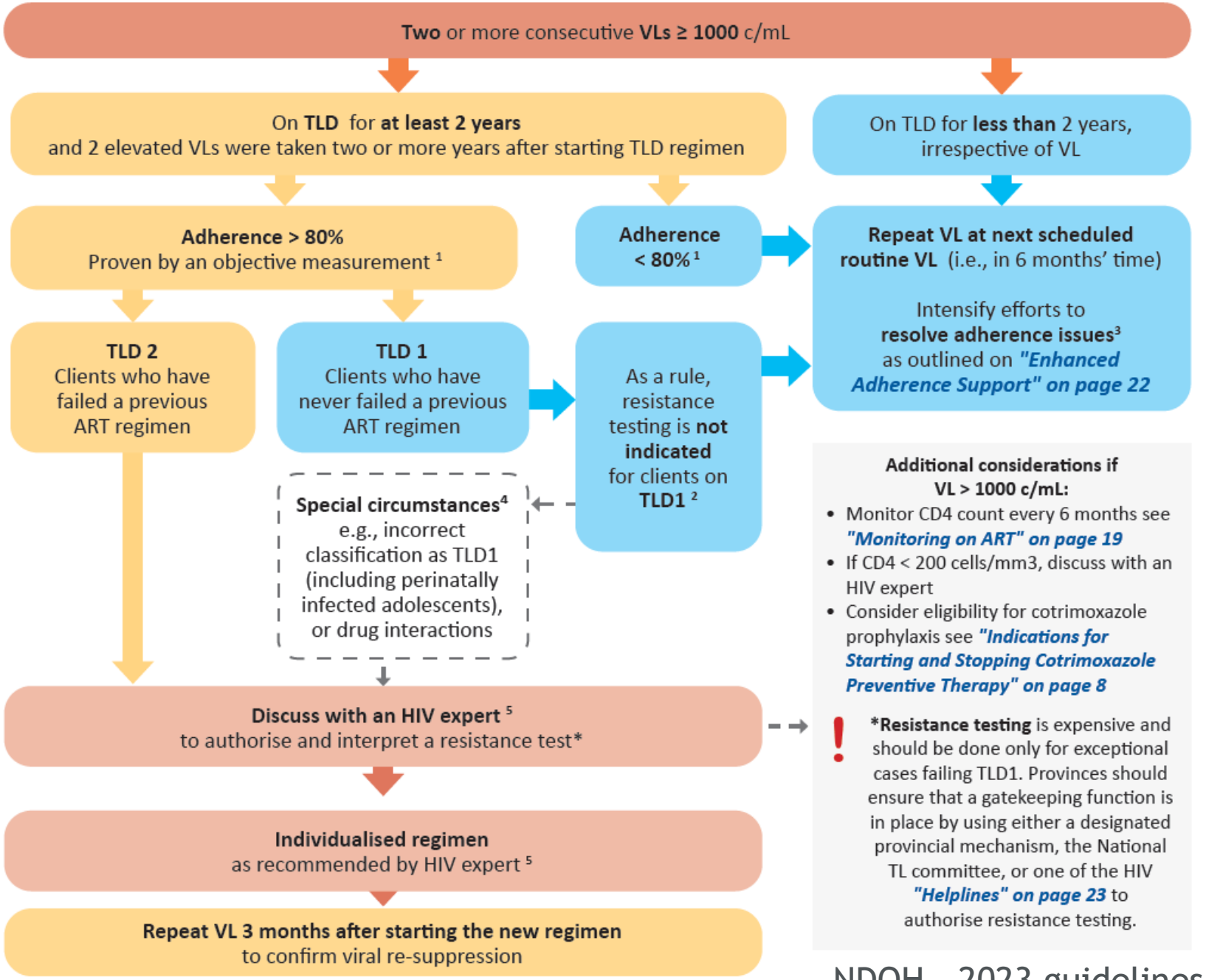
Investigating cases with virological failure: principles and practice

Management of Confirmed Virological Failure on TLD

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



NDOH – 2023 guidelines

Western Cape update (DTG in second or third-line regimen):

<u>If on regimen for < 2 years:</u> Eligible for resistance testing on regimen ≥ 9 months and if:

- *three or more consecutive VLs ≥ 1000 c/mL*
- *AND two documented adherence assessments with adherence >80%*
- *AND motivation from treating clinician*

If on regimen ≥ 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%
- **<u>or</u>** at least one VL ≥ 1000 c/mL AND either CD4 < 200 cells/mm³ or opportunistic infection.

Causes of viral load non-suppression

- Insufficient time elapsed to suppress viral load
  - very rapid with INSTIs
- Inadequate adherence
- Drug resistance in target genes
- Non-canonical drug resistance (mutations outside of target genes)
  - detected in some patients but their role in explaining clinical virologic failure is currently unknown
  - in-vitro evidence for mutations in envelope and in-vitro and clinical study evidence for mutations in gag nucleocapsid
  - mutations in envelope difficult to study as it varies much between individuals

Hikichi et al. High-Level Resistance to Integrase Inhibitors Conferred by Mutations Outside Integrase. in Conference on Retroviruses and Opportunistic Infections: CROI 2024, March 3-6 (Denver, Colorado, USA, 2024).

Hikichi et al. Epistatic pathways can drive HIV-1 escape from integrase strand transfer inhibitors. Sci Adv 10, eadn0042 (2024).

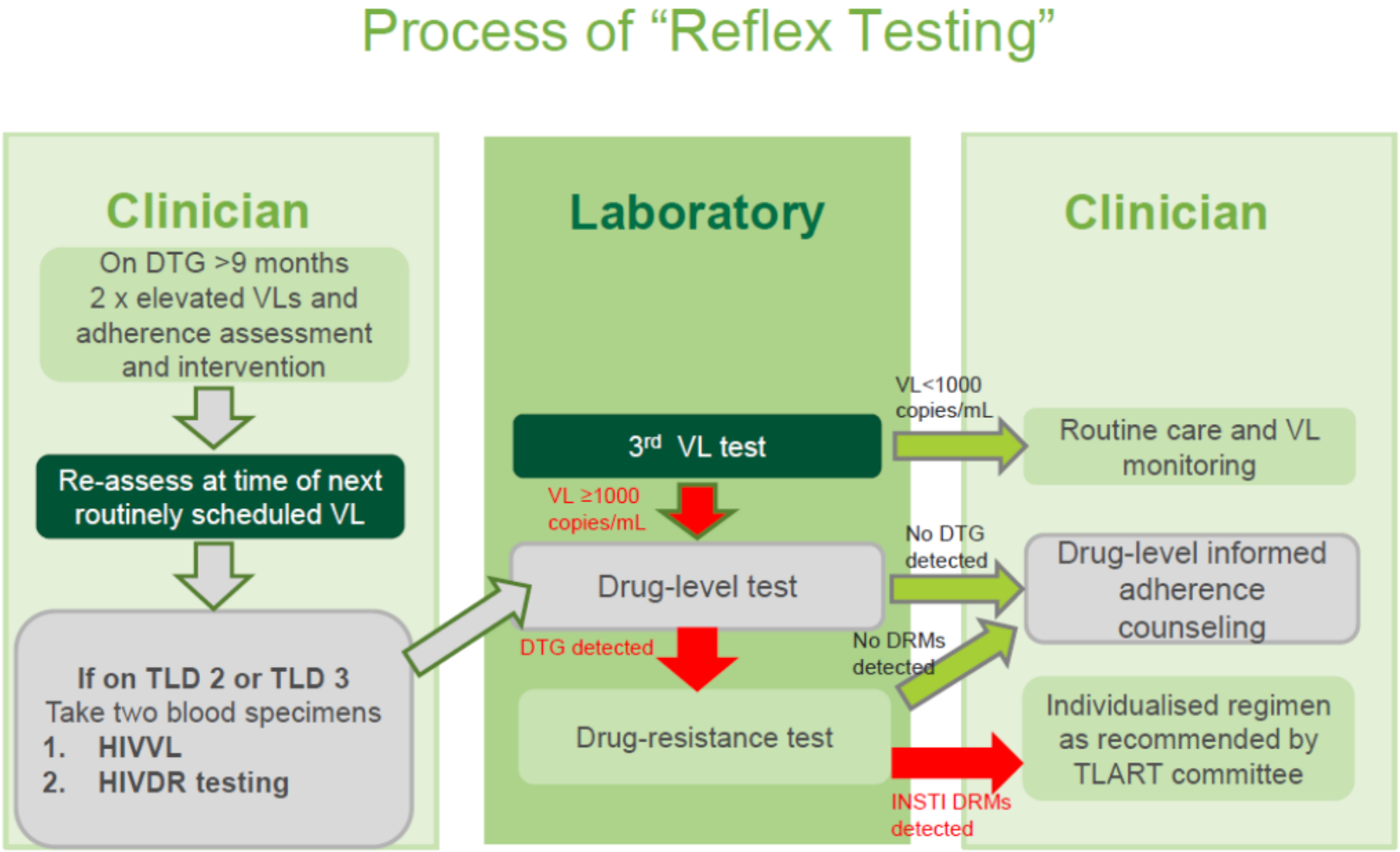
Limitations of adherence measures

- Self report – desirability bias
- Electronic monitoring costly devices
- Drug exposure tests – different adherence windows and variable costs

Determine adherence first: Drug exposure

Assay	Adherence window	Cost
Urine lateral flow test for Tenofovir (TFV)	Up to 14 days after the last dose	Lowest
TFV in plasma	Up to 5 days after the last dose	Intermediate
TFV diphosphate in dried blood spots	Up to 6 weeks after the last dose	High (current versions)

Proposed algorithm



Source : Dr Kim Steegan, NHLS, September 2025

Objective drug exposure measurement

- Considerations
  - Cost
  - Ease of use / procedural
  - Acceptability
  - Diagnostic window and accuracy

Multiple choice questions (5)

5. Plasma testing for DTG before drug resistance testing has the following implication:

a) Patients with detectable DTG have proven long-term good adherence

b) In the absence of detectable DTG one can be sure that there is no DTG-associated drug resistance

c) Patient samples with undetectable DTG do not warrant a drug resistance test and the patient should first have adherence reinforcement until DTG is detectable

d) DTG level testing should be done in patients with HIV viral loads < 500 copies/mL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Thank you
Enkosi
Dankie
Photo by Stefan Els