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GRT reflex testing: rationale and practical approach

Dr Richard Lessells

AWACC – 28 October 2026

Key takeaways

- Viral load monitoring and targeted genotypic resistance testing is designed to optimize individual and population health outcomes
- Identification of DTG resistance and timely switch to DRV/r-based therapy is important
- The GRT reflex testing strategy in the 2026 guidelines is evidence based, pragmatic and cost efficient
- We should all follow the guidelines

Importance of identifying DTG resistance

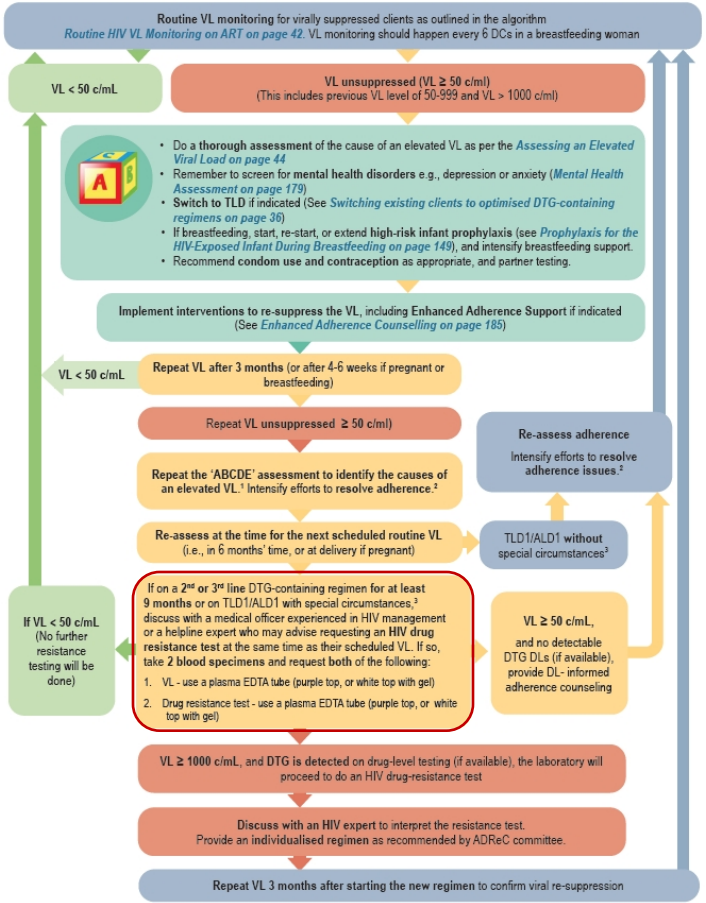
Ndovu RCT (Kenya, Lesotho)

72 participants with persistent viraemia (≥200 copies/mL) on DTG-containing regimen and ≥1 major INSTI DRM - randomized to continue DTG or switch to DRV/r-based regimen

	DTG	DRV/r
≥1 $\log_{10}$ ↓ in viral load at M1	7/37 (19%)	24/30 (80%)
VL <200 copies/mL at M3	3/23 (13%)	20/24 (83%)

Ombajo 26th AIDS 2026 [OAB2006LB]

Viral load monitoring and GRT algorithm



Eligibility criteria for GRT

TLD2, or TLD1 with special circumstances

Receiving DTG-containing regimen for at least 9 months

Two consecutive VL >1000 copies/mL

At least two adherence assessments and interventions

NDoH 2026 Guidelines

Reflex GRT with plasma DTG exposure testing

ITREMA-2 study (Gauteng, SA)



Plasma dolutegravir exposure testing to identify people with HIV at highest risk for dolutegravir resistance (ITREMA-2): a two-centre, prospective implementation study in South Africa

Kim Steegen, Jeremy Nel, Erin H Smeijsters, Chijioke N Umunnakwe, Karabo Mophiring, Sean Currin, Wouter MTief Groenestege, Matthijs van Luin, Lucas E Hermans, Hugo A Tempelman, Lucia Hans, Lise Jamieson, Siphamandla Gumede, Athini Nyatela, Willem D F Venter, Monique Nijhuis, Annemarie M J Wensing

Summary

Background Dolutegravir resistance is increasingly reported in treatment-experienced people with HIV in low-income and middle-income countries. Resistance testing resources are sparse, and viral rebound often reflects adherence lapses rather than resistance. Efficient strategies are needed to target testing to individuals at highest risk. We evaluated a reflex laboratory approach using plasma dolutegravir exposure to guide resistance testing in routine care.

Methods In this prospective implementation study at two public-sector clinics in Johannesburg, South Africa, we analysed adults (aged ≥18 years) on dolutegravir-based antiretroviral therapy (ART) with viral rebound of 400 copies per mL or higher. From May 18, 2023, to Jan 10, 2025, we tested residual routine viral load samples for dolutegravir exposure using an enzyme immunoassay. If dolutegravir was detectable (≥20 ng/mL), we did reflex resistance testing on the same specimen; retrospective sequencing was done at study end for dolutegravir-undetectable samples. We modelled costs comparing the reflex approach with standard of care.

Findings We analysed 400 samples from 288 individuals; 160 (56%) were female and 128 (44%) male, the median age was 44 years (IQR 35–50), and 240 (83%) had previous non-dolutegravir ART exposure. Plasma dolutegravir was detectable in 108 (38%) participants. Among those with successful sequencing, dolutegravir resistance occurred in 13 (13%) of 102 participants with detectable dolutegravir and three (2%) of 138 with undetectable dolutegravir, yielding an overall prevalence of 6·7% dolutegravir resistance and a negative predictive value for absence of dolutegravir resistance of 97·8% (95% CI 93·5–99·5). Dolutegravir resistance was associated with detectable dolutegravir (odds ratio [OR] 3 [95% CI 1–9], p=0·031), nucleoside reverse transcriptase inhibitor mutations (OR 33 [4–264], p=0·0009), non-nucleoside reverse transcriptase inhibitor mutations (OR 17 [2–135], p=0·0068), or M184V (OR 20 [4–92], p=0·0002). Cost modelling showed a 23% reduction in monitoring cost per person using the reflex strategy after confirmed viraemia versus current national guidelines.

Interpretation Laboratory-initiated reflex plasma dolutegravir exposure testing provides an objective, cost-efficient strategy to predict the absence of dolutegravir resistance and supports adherence management, enabling timely, individualised treatment decisions. Reflex dolutegravir exposure testing could enhance clinical decision making, improve treatment outcomes, and strengthen HIV treatment and resistance monitoring algorithms in programmatic settings.

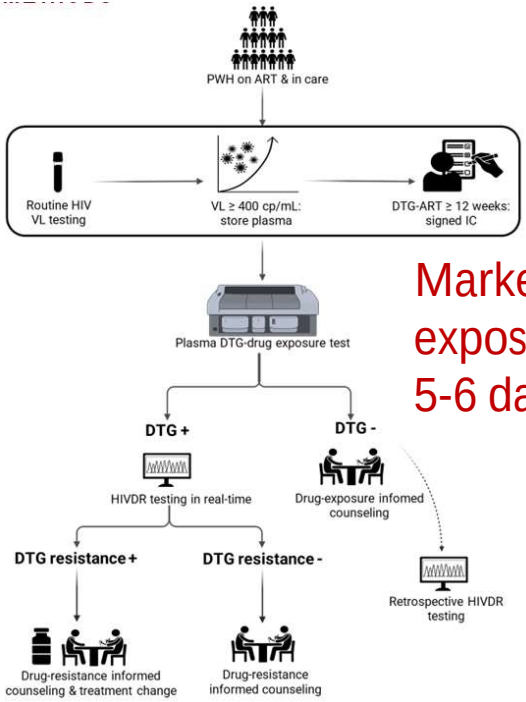
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ITREMA-2 laboratory-based reflex testing algorithm (generated in BioRender.com)

VL=viral load, DTG=dolutegravir, ART=antiretroviral treatment, IC=informed consent, HIVDR=HIV drug resistance

Marker of drug exposure in past 5-6 days

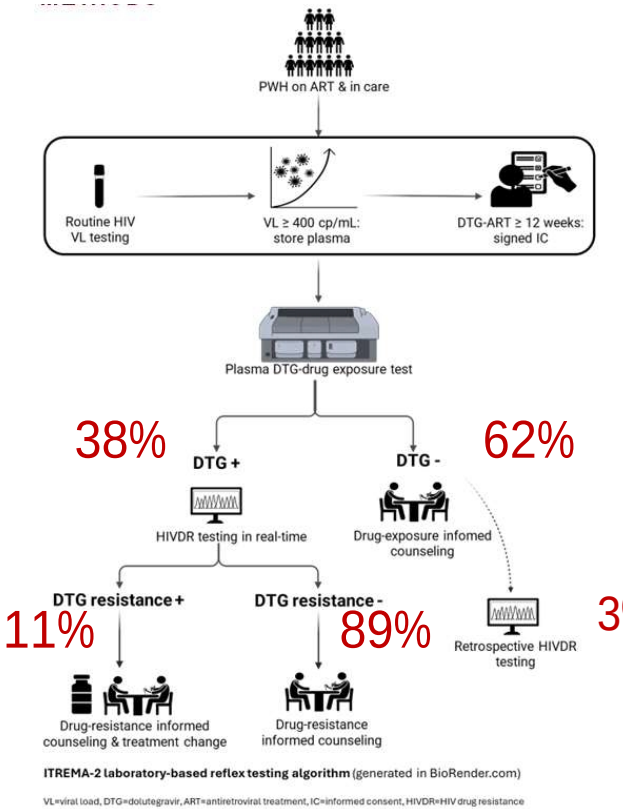
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ITREMA-2

- 288 adult participants (400 samples) with VL >400 copies/mL
- 222/288 (77%) had VL ≥1000 copies/mL
- 84% on TLD
- 83% treatment experienced (≥1 regimen prior to DTG)
- Median time on DTG 13 months (IQR 6-28)

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ITREMA-2



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Diagnostic performance of DTG exposure testing for detection of DTG resistance

	n/N	% (95% CI)
Sensitivity	10/15	66.7 (41.5 - 85.0)
Specificity	148/225	65.8 (59.4 - 71.7)
Positive predictive value	10/87	11.5 (6.2 - 20.1)
Negative predictive value	148/153	96.7 (92.4 - 98.8)

Analysis based on first available sample for participants

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Diagnostic performance of DTG exposure testing

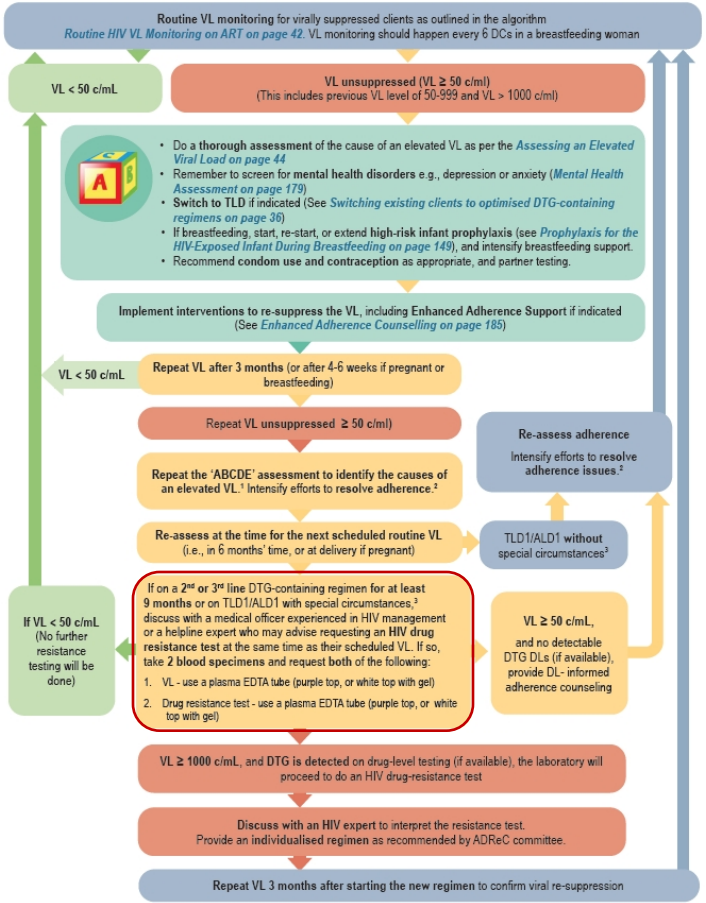
Patient ID	VL (copies/mL)	Plasma DTG level	ART at time of testing	Time on DTG	Total time on ART	INSTI DRM	PI DRM	NRTI DRM	NNRTI DRM
P017	52 500	Not detected	AZT-3TC-DTG	31m	42m	E138K, S147G, N155H, *S230R*	None	M184V	K103N, E138K
	45 900	Detected		36m	47m	E138K, S147G, **Q148QR**, N155H, *S230R*	None	M184V	K103N, E138K
P067	1 470	Not detected	TDF-3TC-DTG	**14m**	165m	G140A, Q148R, *L74M*	None	A62V, K65R, M184V	K101E, V106M, G190A
	5 550	Detected		17m	168m	**E138K,** G140A, Q148R, *L74M*	None	A62V, K65R, M184V	K101E, V106M, G190A
	4 210	Detected		19m	170m	E138K, G140A, Q148R, *L74M*	None	A62V, K65R, M184V	K101E, V106M, G190A
P071	6 850	Detected	TDF-3TC-DTG	36m	50m	E138A, G140A, Q148R	None	M184V	K103N, P225H
	3 800	Detected		37m	51m	E138A, G140A, Q148R	N/A	N/A	N/A
	10 700	Detected		38m	52m	E138A, G140A, Q148R	None	M184V	K103N
	10 500	Not detected		47m	61m	E138A, G140A, Q148R	N/A	N/A	N/A
	6 541	Detected		50m	64m	E138A, G140A, Q148R	None	M184V	K103KN, P225PH
P091	278 000	Not detected	TDF-3TC-DTG	**8m**	30m	Q146QR	None	M184V	K103N, P225H
	7 990	Detected		11m	33m	N155H, *H51HY*	None	M184V	K103N, P225H
	46 600	Not detected		18m	40m	*H51HY*	None	M184V	K103N, P225H
	1 216	Not detected		22m	44m	*H51HY*	None	M184V	K103N, P225H
P105	875	Detected	TDF-3TC-DTG	**10m**	57m	G118R	N/A	N/A	N/A
	703	Detected		13m	60m	**T66A**, G118R, **E138K**	N/A	N/A	N/A
P121	8 220	Detected	TDF-3TC-DTG	**4m**	54m	G118R	M46I, I50L, V82A, *L33F, Q58E, T74P*	D67N, K70R, M184V, L210W, T215F, K219E	K103N, P225H
	21 200	Detected		5m	56m	G118R	M46MI, I50IL, V82A, *L33LF, Q58QE, T74TP*	D67N, K70R, M184V, L210W, T215F, K219E	K103N, P225H
	109 000	Not detected		8m	59m	**T66I,** G118R, **E138EAKT**	M46I, I50L, V82A, *L33F, Q58E, T74P*	D67N, K70R, M184V, L210W, T215F, K219E	K103N, P225H
	254 000	Detected		10m	61m	T66TI, G118R, E138K	M46I, I50L, V82A, *L33F, Q58E, T74P*	D67N, K70R, M184V, L210W, T215F, K219E	K103N, P225H
P152	15 100	Detected	TDF-3TC-DTG	38m	202m	E138K, G140A, S147SG, Q148K	None	D67N, K70R, M184V, K219Q	K103KN, P225H
	9 500	Not detected		46m	210m	E138K, G140A, S147G, Q148K	None	D67N. K70R, M184V, K219Q	K103N, P225H
P157	129 000	Detected	AZT-3TC-DTG	**9m**	101m	E138EK, S147G, N155H, *H51HY, T79TA*	None	D67DN, K70KR, M184V	K103N, V108I
	55 700	Detected		12m	104m	E138K, **G140A,** S147G, **Q148R,** N155H	None	D67N, K70R, M184V	K103N, V108I
	27 700	Detected		15m	107m	E138K, G140A, S147G, Q148R, N155H	None	D67N, K70R, M184V	A98G, K103N
P258	780	Detected	TDF-3TC-DTG	**4m**	176m	R263K	None	D68G, M184V	None
P413	328 000	Detected	TDF-3TC-DTG	**13m**	Unknown	R263K	None	K65R, S68G	A98G, E138A, G190E
P486	1 486	Detected	TDF-3TC-DTG	**15m**	102m	R263K	None	None	E138EG, G190A
P2-045	869	Detected	TDF-3TC-DTG	**5m**	104m	T66I, G118R, E138A	N/A	N/A	N/A
P2-302	34 497	Detected	TDF-3TC-DTG	**18m**	47m	T66I, G118R, E138K, *E157Q*	None	D67E, S68R, T69G, K70R, M184V, T215I, K219KE	K103N, Y188L
P026	1 100	Not Detected	TDF-3TC-DTG	**23m**	111m	R263KR	None	M184V	K101PS, K103N
P104	706	Not Detected	ABC-3TC-DTG	43m	48m	R263K	N/A	N/A	N/A
P2-019	123 000	Not Detected	ABC-3TC-DTG	**15m**	211m	R263K	None	M184V	E138A

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Word of caution

- No screening test/triage tool is perfect. In implementing the algorithm, we will miss cases with DTG resistance who have no recent DTG exposure
- Clinical judgement remains important
  - Timing of GRT sampling
  - Thorough adherence evaluation
  - Consideration of clinical presentation: acutely unwell, nausea/vomiting, etc.
- Do not be afraid to call Virology and/or Infectious Diseases to discuss individual cases - consider GRT without drug level testing (or testing regardless of DTG drug level)

Viral load monitoring and GRT algorithm



Eligibility criteria for GRT

TLD2, or TLD1 with special circumstances

Receiving DTG-containing regimen for at least 9 months

Two consecutive VL >1000 copies/mL

At least two adherence assessments and interventions

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Definitions of DTG-containing regimens

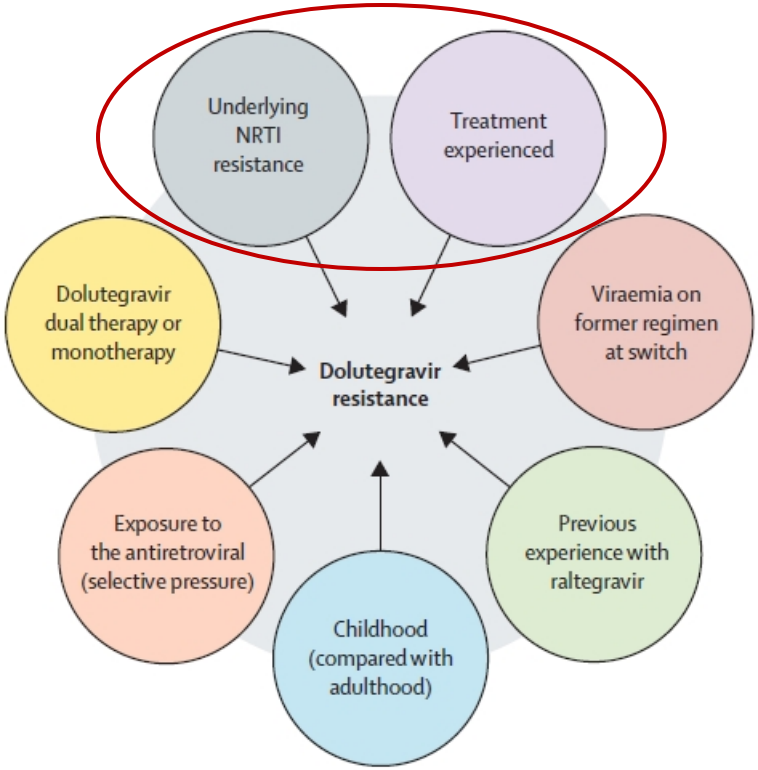
	Previous ART exposure	Regimen
First-line DTG-containing regimens	• ART-naïve patients who initiated ART on a DTG-containing regimen • Patients who were switched to DTG from a first-line non-DTG-based regimen (e.g., TEE) with a VL < 50 c/mL in the last 12 months	**Tenofovir/lamivudine/dolutegravir [TLD 1]** **Abacavir/lamivudine/dolutegravir [ALD 1]**
Second-line DTG-containing regimens	• Patients who were switched to DTG from a first-line ART regimen (NNRTI or PI-based) with a VL ≥ 50 c/mL • Patients who were switched to DTG from a second-line PI-based ART regimen with a VL < 50 c/mL in the last 12 months • Patients who were switched to DTG from a PI-based regimen with a VL ≥ 50 c/mL without a genotypic resistance test	**Tenofovir/lamivudine/dolutegravir [TLD 2]** **Abacavir/lamivudine/dolutegravir [ALD 2]**
Third-line DTG-containing 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 a previous second-line regimen	**Individualised DTG-based regimen**
If clients are not eligible to use TDF and they had an ABC hypersensitivity reaction, use AZT/3TC/DTG		

! At certain times, the distinction between a TLD1 and TLD2 classification may not be clear. This is especially true for clients re-engaging in care after a treatment interuption. Many clients initiating ART as TLD1 may well be TLD2, but are not disclosing their earlier ART exposure. If in doubt, discuss with an expert, or err on the side of caution and classify as TLD2, as misclassification may affect their eligibility for resistance testing.

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Prioritization of TLD2

- Evidence continues to mount that almost all cases of DTG resistance are occurring in treatment-experienced individuals – with the main driver being <u>underlying NRTI resistance</u>

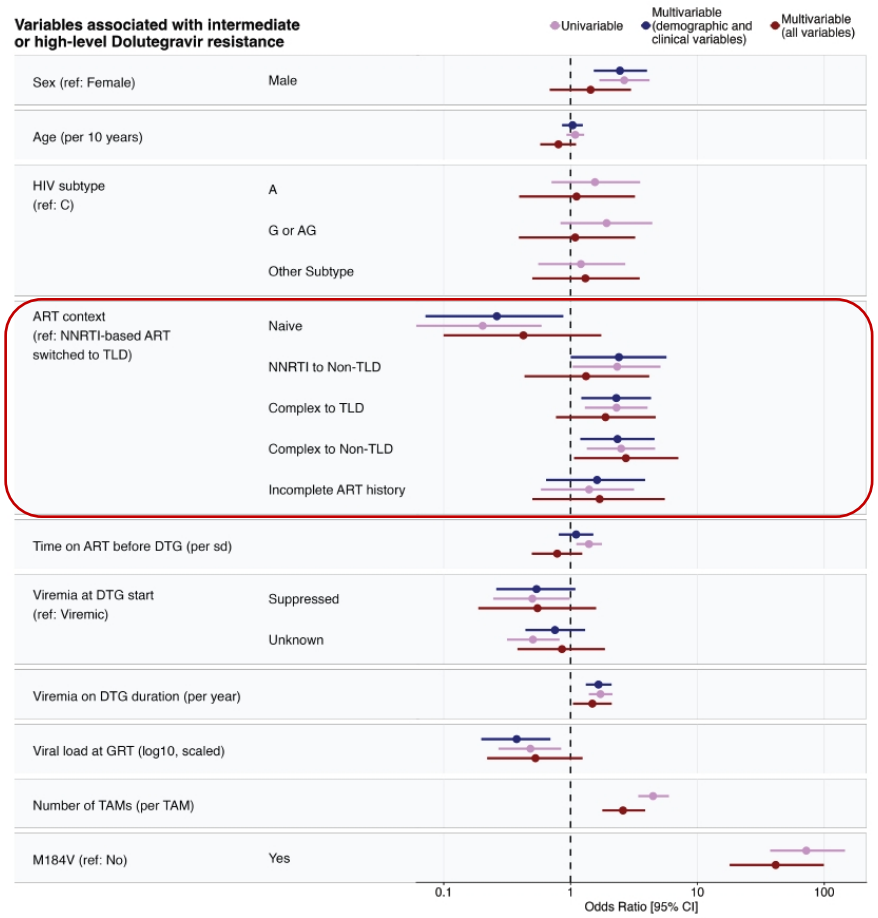


McCluskey Lancet HIV 2025

DTG RESIST study

Multicountry

- 450 sequences from adults and adolescents with at least one VL ≥1000 copies/mL on DTG-containing ART
- Of 90 cases with intermediate/high-level DTG resistance, only one was ART naïve prior to DTG

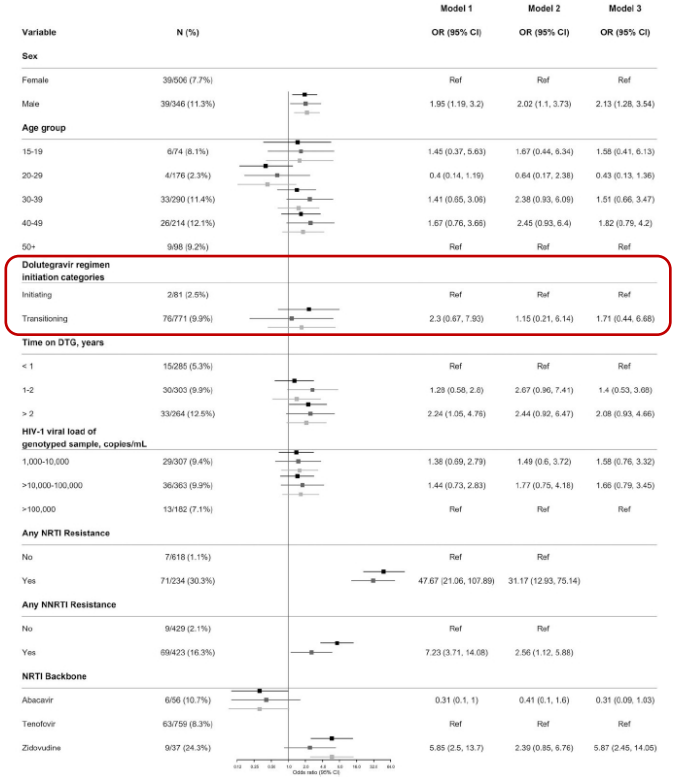


Loosli 26th AIDS 2026 [LB28]

CADRE surveillance program

Malawi, Mozambique, Uganda, Ukraine

- 965 sequences from adults and adolescents with at least one VL ≥1000 copies/mL on DTG-containing ART
- Of 83 cases with DTG resistance, <u>only two were ART naïve prior to DTG</u>



Variable	N (%)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Sex				
Female	39/506 (7.7%)	Ref	Ref	Ref
Male	39/346 (11.3%)	1.95 (1.19, 3.2)	2.02 (1.1, 3.73)	2.13 (1.28, 3.54)
Age group				
15-19	6/74 (8.1%)	1.45 (0.37, 5.63)	1.67 (0.44, 6.34)	1.58 (0.41, 6.13)
20-29	4/176 (2.3%)	0.4 (0.14, 1.19)	0.64 (0.17, 2.38)	0.43 (0.13, 1.36)
30-39	33/290 (11.4%)	1.41 (0.65, 3.06)	2.38 (0.93, 6.09)	1.51 (0.66, 3.47)
40-49	26/214 (12.1%)	1.67 (0.76, 3.66)	2.45 (0.93, 6.4)	1.82 (0.79, 4.2)
50+	9/98 (9.2%)	Ref	Ref	Ref
Dolutegravir regimen initiation categories				
Initiating	2/81 (2.5%)	Ref	Ref	Ref
Transitioning	76/771 (9.9%)	2.3 (0.67, 7.93)	1.15 (0.21, 6.14)	1.71 (0.44, 6.68)
Time on DTG, years				
< 1	15/285 (5.3%)	Ref	Ref	Ref
1-2	30/303 (9.9%)	1.28 (0.58, 2.8)	2.67 (0.96, 7.41)	1.4 (0.53, 3.68)
> 2	33/264 (12.5%)	2.24 (1.05, 4.76)	2.44 (0.92, 6.47)	2.08 (0.93, 4.66)
HIV-1 viral load of genotyped sample, copies/mL				
1,000-10,000	29/307 (9.4%)	1.38 (0.69, 2.79)	1.49 (0.6, 3.72)	1.58 (0.76, 3.32)
>10,000-100,000	36/363 (9.9%)	1.44 (0.73, 2.83)	1.77 (0.75, 4.18)	1.66 (0.79, 3.45)
>100,000	13/182 (7.1%)	Ref	Ref	Ref
Any NRTI Resistance				
No	7/618 (1.1%)	Ref	Ref	
Yes	71/234 (30.3%)	47.67 (21.06, 107.89)	31.17 (12.93, 75.14)	
Any NNRTI Resistance				
No	9/429 (2.1%)	Ref	Ref	
Yes	69/423 (16.3%)	7.23 (3.71, 14.08)	2.56 (1.12, 5.88)	
NRTI Backbone				
Abacavir	6/56 (10.7%)	0.31 (0.1, 1)	0.41 (0.1, 1.6)	0.31 (0.09, 1.03)
Tenofovir	63/759 (8.3%)	Ref	Ref	Ref
Zidovudine	9/37 (24.3%)	5.85 (2.5, 13.7)	2.39 (0.85, 6.76)	5.87 (2.45, 14.05)

da Silva CID 2026

ITREMA-2

- All 13 cases with intermediate or high-level DTG resistance had previous exposure to non-DTG treatment (and most had NNRTI DRMs)

	OR (95% CI)	p value
Age, years	0·98 (0·94–1·02)	0·34
Time on dolutegravir, months	1·00 (0·97–1·04)	0·84
Total time on ART, months	1·00 (0·99–1·01)	0·65
Sex		
Male	1 (ref)	–
Female	2·51 (0·78–8·01)	0·12
Facility		
Themba Lethu	1 (ref)	–
Ward 21	1·17 (0·32–4·30)	0·82
Virological failure category		
Two viral loads ≥1000 copies per mL	1 (ref)	–
One viral load ≥1000 copies per mL	0·36 (0·11–1·24)	0·11
Two viral loads 50–999 copies per mL	1·47 (0·33–6·53)	0·61
One viral load 50–999 copies per mL	0·60 (0·07–5·36)	0·64
Unknown	1·00 (NC)	–
Current regimen		
Tenofovir plus lamivudine plus dolutegravir	1 (ref)	–
Abacavir plus lamivudine plus dolutegravir	0·94 (0·20–4·41)	0·94
Zidovudine plus lamivudine plus dolutegravir	1·00 (NC)	–
2NRTI plus dolutegravir plus ritonavir-boosted darunavir	1·00 (NC)	–
Previous ART exposure		
Yes	1 (ref)	–
None	0·42 (0·05–3·27)	0·40
Unknown	2·21 (0·25–19·70)	0·48
Plasma dolutegravir		
Not detected	1 (ref)	–
Detected	3·18 (1·11–9·08)	0·031
Plasma dolutegravir in at least one sample		
Not detected	1 (ref)	–
Detected	10·62 (2·36–47·85)	0·0019
NRTI mutations		
Not detected	1 (ref)	–
Detected	33·45 (4·23–264·28)	0·0009
NNRTI mutations		
Not detected	1 (ref)	–
Detected	17·26 (2·20–135·66)	0·0068
M184V		
Not detected	1 (ref)	–
Detected	19·6 (4·17–92·17)	0·0002

OR=odds ratio. ART=antiretroviral therapy. ref=reference. NC=not calculated. NRTI=nucleoside reverse transcriptase inhibitor. NNRTI=non-NRTI.

Table 3: ORs for dolutegravir resistance from univariable regression models

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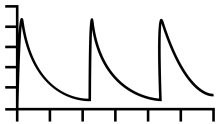
Why do we not see drug resistance with TLD1?



3 drugs



Fixed-dose combination



Drugs with similar half-lives



Low likelihood of pre-treatment drug resistance

Given all the different adherence patterns occurring in the real world, this suggests that adherence on its own is not a driver of emergent DTG resistance

Why is the risk higher with TLD2?



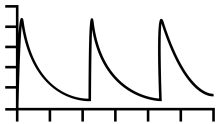
3 drugs

✓



Fixed-dose combination

✓



Drugs with similar half-lives

✓



Low likelihood of pre-treatment drug resistance

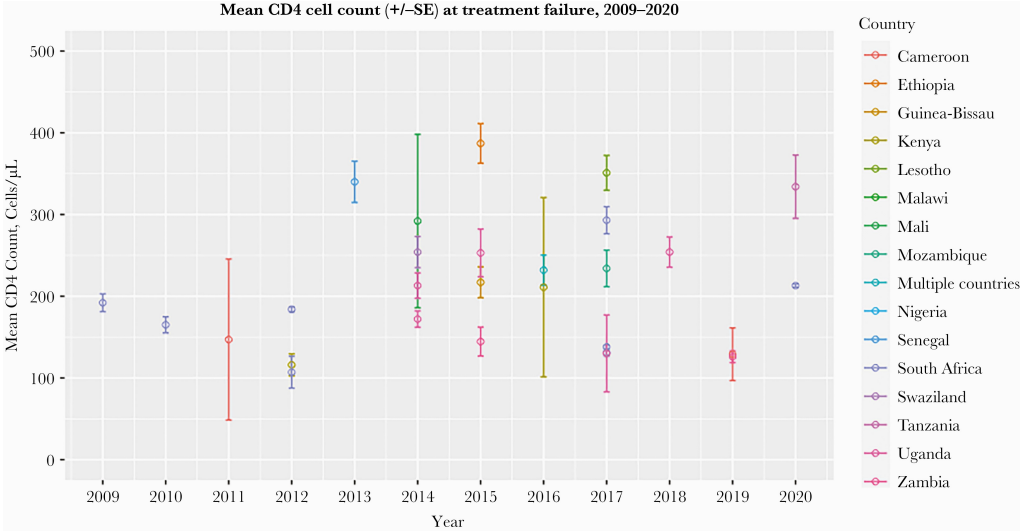
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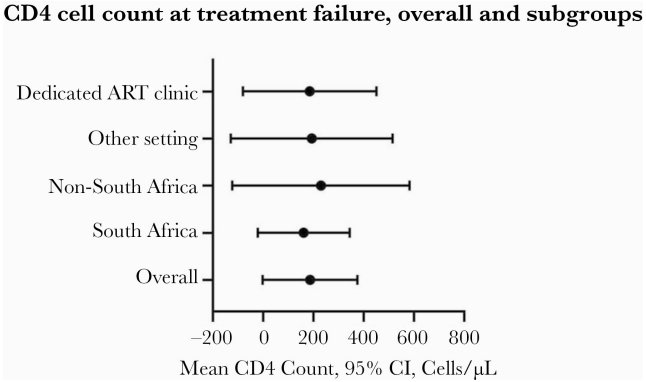
Higher likelihood of TDF/3TC resistance

TLD1 with special circumstances

- Patients with advanced HIV disease (AHD)
- Current or previous drug interactions (rifampicin, carbamazepine, phenytoin, phenobarbital, or polyvalent cations)
- Incorrect classification as TLD1 (prior ART exposure)
- Perinatally infected adolescents (perinatally infected adolescents should be classified as TLD2)

Virological failure and AHD





AHD is common in people with virological failure - identification of those with AHD, or those at high risk of progression to AHD is critical

Bernabé Open Forum Infect Dis 2022

Virological failure and AHD

Additional considerations if VL > 1000 c/mL

- Monitor CD4 count every 6 months see *Monitoring on ART on page 41*
- If CD4 < 200 cells/mm^3, discuss with an HIV expert
- Consider eligibility for cotrimoxazole prophylaxis see *Indications for Starting and Stopping Cotrimoxazole Preventive Therapy on page 30*

- Significant gaps in implementation – resumption of CD4 monitoring in people with viraemia/virological failure
- Delayed identification of AHD and delayed action (CPT, CrAg screening, TB evaluation, etc.)
- Contributes to ongoing morbidity and mortality

Incorrect classification

- Several studies have documented undisclosed current/prior ART use in people presenting as ART naïve
- Studies have also shown cases with DTG resistance can be retrospectively reclassified from TLD1 to TLD2 with more extensive evaluation

At certain times, the distinction between a TLD1 and TLD2 classification may not be clear. This is especially true for clients re-engaging in care after a treatment interuption. Many clients initiating ART as TLD1 may well be TLD2, but are not disclosing their earlier ART exposure. If in doubt, discuss with an expert, or err on the side of caution and classify as TLD2, as misclassification may affect their eligibility for resistance testing.

Sithole AIDS Behav 2021
Sithole J Int AIDS Soc 2025
Naidoo 26th AIDS [WEPEB136]

Importance of NRTI backbone

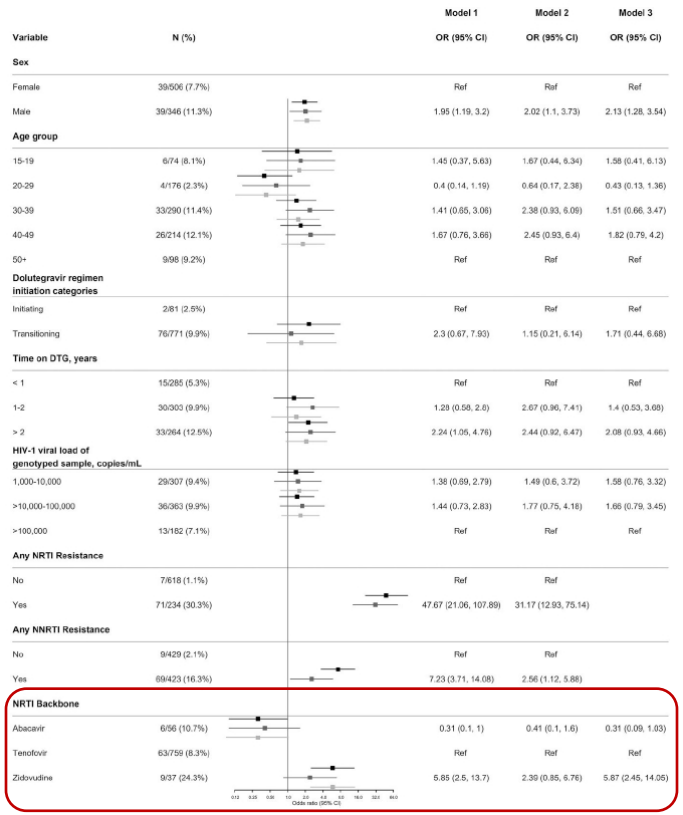
- Data from four cohort studies (adults and children)
- 21/183 (11%) intermediate or high-level DTG resistance
- DTG resistance strongly associated with ZDV or ABC-containing regimen

Factor	Stanford Resistance Score <30 for Dolutegravir (n = 162)	Stanford Resistance Score ≥30 for Dolutegravir (n = 21)	Chi-square *P*-value	Univariate Odds Ratio (95% CI)	Multivariate Odds Ratio (95% CI)
Gender			.6		
Female	68	10 (12.8%)		1.3 (0.5–3.1)	
Male	94	11 (10.5%)		Ref.	
Age (y) at enrollment			**.006**		
<10	34	11 (24.4%)		**5.1 (1.7–14.8)**	
11–20	34	4 (10.5%)		1.8 (0.5–6.9)	
21+	94	6 (6.0%)		Ref.	
HIV subtype[a]					
A (any)	104	5 (4.6%)	**<.001**	Ref.	Ref.
B	5	5 (50.0%)	**<.001**	**22.5 (4.7–108.1)**	**15.7 (2.5–98.3)**
C	36	8 (18.2%)	.15	**4.7 (1.4–16.0)**	2.2 (0.6–7.9)
D	19	1 (5.0%)	.3	0.8 (0.1–9.1)	Ref.
Other	7	3 (30.0%)	.06	**9.6 (1.8–50.7)**	Ref.
ART prior to DTG-ART			.5		
No	4	1 (20.0%)		Ref.	
Yes	158	20 (11.2%)		0.5 (0.1–4.8)	
PDR to NRTI[b]			.16		
No	11	5 (31.3%)		3.1 (0.6. 14.7)	
Yes	5	7 (58.3%)			
Cohort			**<.001**		
Kenya DREAM	92	1 (1.1%)		Ref.	
OPT4Kids	37	2 (5.1%)		4.9 (0.4–56.5)	
P1093	17	12 (41.4%)		**64.9 (7.9–533)**	
Pretoria DREAM	16	6 (27.3%)		**34.5 (3.9–306)**	
NRTI coadministered[c]			**<.001**		
ABC	27	4 (12.9%)		3.7 (0.9–25.8)	**5.4 (1.1–25.8)**
ZDV[d]	11	12 (52.2%)		**27.1 (8.1–90.9)**	**19.4 (5.1–74.3)**
TDF	124	5 (3.9%)		Ref.	Ref.
Plasma HIV RNA at viremic episode (copies/mL)			**.01**		
<1000	52	3 (5.6%)		Ref.	Ref.
1000–10 000	36	11 (23.4%)		**5.1 (1.4–20.0)**	2.1 (0.6–7.0)
10 000+	74	7 (8.6%)		1.6 (0.4–6.5)	Ref.
Duration (wk) of DTG-based ART (mean, std)[e]	139.3 (63.7)	118.7 (82.4)	.18	0.89 (0.74–1.06)	
Sequencing method applied to viremic specimen			.2		
PacBio	138	20 (12.7%)		Ref.	
Sanger	24	1 (4.0%)		0.3 (0.04–2.2)	0.2 (0.02–2.2)

Beck CID 2026

Importance of NRTI backbone

- Multicountry study
- 965 sequences from adults and adolescents with at least one VL ≥1000 copies/mL on DTG-containing ART
- DTG resistance strongly associated with ZDV (not ABC-containing regimen)



Variable	N (%)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Sex				
Female	39/506 (7.7%)	Ref	Ref	Ref
Male	39/346 (11.3%)	1.95 (1.19, 3.2)	2.02 (1.1, 3.73)	2.13 (1.28, 3.54)
Age group				
15-19	6/74 (8.1%)	1.45 (0.37, 5.63)	1.67 (0.44, 6.34)	1.58 (0.41, 6.13)
20-29	4/176 (2.3%)	0.4 (0.14, 1.19)	0.64 (0.17, 2.38)	0.43 (0.13, 1.36)
30-39	33/290 (11.4%)	1.41 (0.85, 3.06)	2.38 (0.93, 6.09)	1.51 (0.66, 3.47)
40-49	26/214 (12.1%)	1.67 (0.76, 3.66)	2.45 (0.93, 6.4)	1.82 (0.79, 4.2)
50+	9/98 (9.2%)	Ref	Ref	Ref
Dolutegravir regimen initiation categories				
Initiating	2/81 (2.5%)	Ref	Ref	Ref
Transitioning	76/771 (9.9%)	2.3 (0.67, 7.93)	1.15 (0.21, 6.14)	1.71 (0.44, 6.68)
Time on DTG, years				
< 1	15/285 (5.3%)	Ref	Ref	Ref
1-2	30/303 (9.9%)	1.28 (0.58, 2.8)	2.67 (0.96, 7.41)	1.4 (0.53, 3.68)
> 2	33/264 (12.5%)	2.24 (1.05, 4.76)	2.44 (0.92, 6.47)	2.08 (0.93, 4.66)
HIV-1 viral load of genotyped sample, copies/mL				
1,000-10,000	29/307 (9.4%)	1.38 (0.89, 2.79)	1.49 (0.6, 3.72)	1.58 (0.76, 3.32)
>10,000-100,000	36/363 (9.9%)	1.44 (0.73, 2.83)	1.77 (0.75, 4.18)	1.66 (0.79, 3.45)
>100,000	13/182 (7.1%)	Ref	Ref	Ref
Any NRTI Resistance				
No	7/618 (1.1%)	Ref	Ref	
Yes	71/234 (30.3%)	47.67 (21.06, 107.89)	31.17 (12.93, 75.14)	
Any NNRTI Resistance				
No	9/429 (2.1%)	Ref	Ref	
Yes	69/423 (16.3%)	7.23 (3.71, 14.08)	2.56 (1.12, 5.88)	
NRTI Backbone				
Abacavir	6/56 (10.7%)	0.31 (0.1, 1)	0.41 (0.1, 1.6)	0.31 (0.09, 1.03)
Tenofovir	63/759 (8.3%)	Ref	Ref	Ref
Zidovudine	9/37 (24.3%)	5.85 (2.5, 13.7)	2.39 (0.85, 6.76)	5.87 (2.45, 14.05)

da Silva CID 2026

Why might the risk of resistance be different with ZDV or ABC-based regimens?



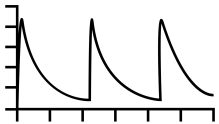
3 drugs

✓



Fixed-dose combination

✗



Drugs with similar half-lives

✗



Low likelihood of pre-treatment drug resistance

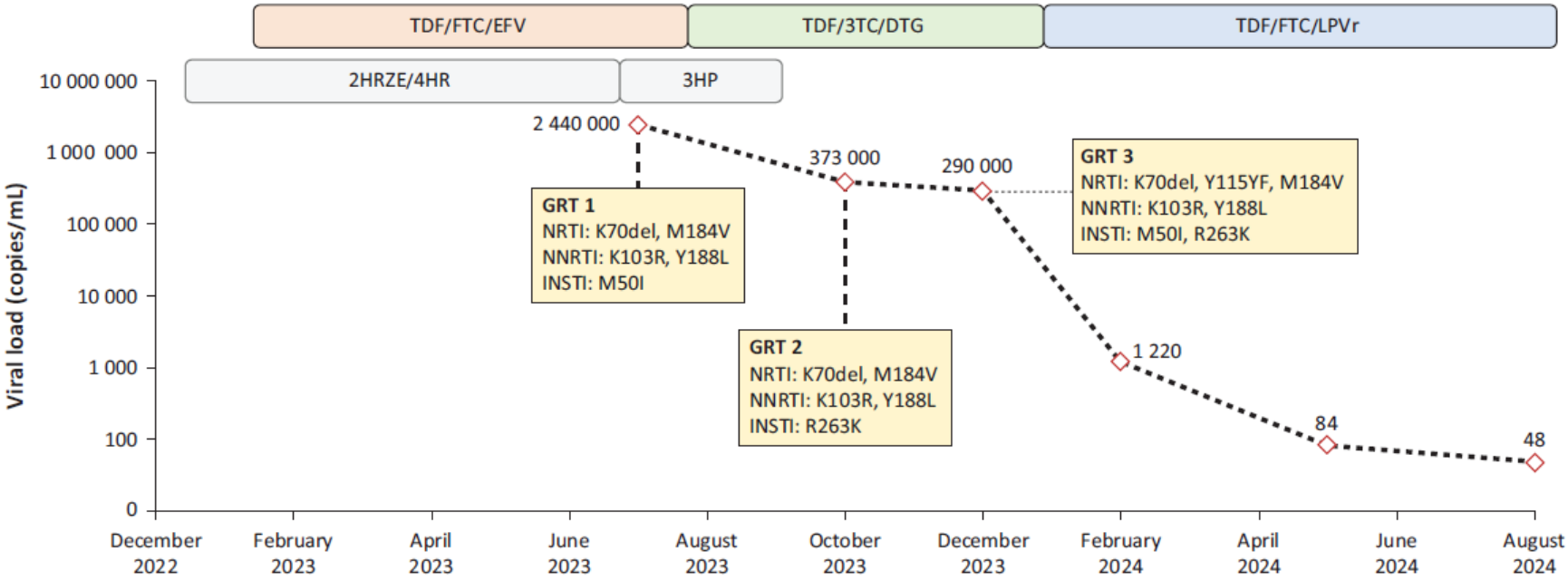
?

Duration of DTG-containing ART

- 2026 guidelines on GRT testing shifted from requiring at least 24 months of DTG-containing ART to 9 months
- Accumulating evidence that duration of DTG-containing ART is not strongly associated with DTG resistance
- Multiple reports of emergent DTG resistance within 12-24 months

Case report – early emergent DTG resistance

Adult, TLD2



Naidoo SA J HIV Med 2025

ITREMA-2

Patient ID	VL (copies/mL)	Plasma DTG level	ART at time of testing	Time on DTG	Total time on ART	INSTI DRM	PI DRM	NRTI DRM	NNRTI DRM
P017	52 500	Not detected	AZT-3TC-DTG	31m	42m	E138K, S147G, N155H, *S230R*	None	M184V	K103N, E138K
	45 900	Detected		36m	47m	E138K, S147G, **Q148QR**, N155H, *S230R*	None	M184V	K103N, E138K
P067	1 470	Not detected	TDF-3TC-DTG	**14m**	165m	G140A, Q148R, *L74M*	None	A62V, K65R, M184V	K101E, V106M, G190A
	5 550	Detected		17m	168m	**E138K,** G140A, Q148R, *L74M*	None	A62V, K65R, M184V	K101E, V106M, G190A
	4 210	Detected		19m	170m	E138K, G140A, Q148R, *L74M*	None	A62V, K65R, M184V	K101E, V106M, G190A
P071	6 850	Detected	TDF-3TC-DTG	36m	50m	E138A, G140A, Q148R	None	M184V	K103N, P225H
	3 800	Detected		37m	51m	E138A, G140A, Q148R	N/A	N/A	N/A
	10 700	Detected		38m	52m	E138A, G140A, Q148R	None	M184V	K103N
	10 500	Not detected		47m	61m	E138A, G140A, Q148R	N/A	N/A	N/A
	6 541	Detected		50m	64m	E138A, G140A, Q148R	None	M184V	K103KN, P225PH
P091	278 000	Not detected	TDF-3TC-DTG	**8m**	30m	Q146QR	None	M184V	K103N, P225H
	7 990	Detected		11m	33m	N155H, *H51HY*	None	M184V	K103N, P225H
	46 600	Not detected		18m	40m	*H51HY*	None	M184V	K103N, P225H
	1 216	Not detected		22m	44m	*H51HY*	None	M184V	K103N, P225H
P105	875	Detected	TDF-3TC-DTG	**10m**	57m	G118R	N/A	N/A	N/A
	703	Detected		13m	60m	**T66A,** G118R, **E138K**	N/A	N/A	N/A
P121	8 220	Detected	TDF-3TC-DTG	**4m**	54m	G118R	M46I, I50L, V82A, *L33F, Q58E, T74P*	D67N, K70R, M184V, L210W, T215F, K219E	K103N, P225H
	21 200	Detected		5m	56m	G118R	M46MI, I50IL, V82A, *L33LF, Q58QE, T74TP*	D67N, K70R, M184V, L210W, T215F, K219E	K103N, P225H
	109 000	Not detected		8m	59m	**T66I,** G118R, **E138EAKT**	M46I, I50L, V82A, *L33F, Q58E, T74P*	D67N, K70R, M184V, L210W, T215F, K219E	K103N, P225H
	254 000	Detected		10m	61m	T66TI, G118R, E138K	M46I, I50L, V82A, *L33F, Q58E, T74P*	D67N, K70R, M184V, L210W, T215F, K219E	K103N, P225H
P152	15 100	Detected	TDF-3TC-DTG	38m	202m	E138K, G140A, S147SG, Q148K	None	D67N, K70R, M184V, K219Q	K103KN, P225H
	9 500	Not detected		46m	210m	E138K, G140A, S147G, Q148K	None	D67N. K70R, M184V, K219Q	K103N, P225H
P157	129 000	Detected	AZT-3TC-DTG	**9m**	101m	E138EK, S147G, N155H, *H51HY, T79TA*	None	D67DN, K70KR, M184V	K103N, V108I
	55 700	Detected		12m	104m	E138K, **G140A,** S147G, **Q148R,** N155H	None	D67N, K70R, M184V	K103N, V108I
	27 700	Detected		15m	107m	E138K, G140A, S147G, Q148R, N155H	None	D67N, K70R, M184V	A98G, K103N
P258	780	Detected	TDF-3TC-DTG	**4m**	176m	R263K	None	D68G, M184V	None
P413	328 000	Detected	TDF-3TC-DTG	**13m**	Unknown	R263K	None	K65R, S68G	A98G, E138A, G190E
P486	1 486	Detected	TDF-3TC-DTG	**15m**	102m	R263K	None	None	E138EG, G190A
P2-045	869	Detected	TDF-3TC-DTG	**5m**	104m	T66I, G118R, E138A	N/A	N/A	N/A
P2-302	34 497	Detected	TDF-3TC-DTG	**18m**	47m	T66I, G118R, E138K, *E157Q*	None	D67E, S68R, T69G, K70R, M184V, T215I, K219KE	K103N, Y188L
P026	1 100	Not Detected	TDF-3TC-DTG	**23m**	111m	R263KR	None	M184V	K101PS, K103N
P104	706	Not Detected	ABC-3TC-DTG	43m	48m	R263K	N/A	N/A	N/A
P2-019	123 000	Not Detected	ABC-3TC-DTG	**15m**	211m	R263K	None	M184V	E138A

For the 13 cases with DTG resistance, median time on DTG was 13 months (range 4–38)

Steegen Lancet HIV 2026

Should GRT be expanded to people with VL below 1000 copies/mL?

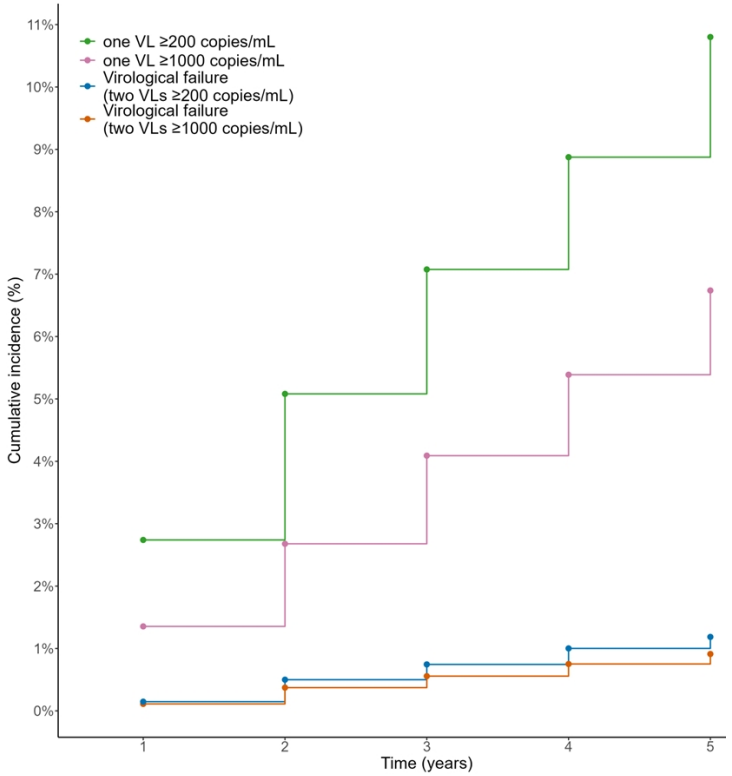
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P071	6 850	Detected	TDF-3TC-DTG	36m	50m	E138A, G140A, Q148R	None	M184V	K103N, P225H
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	21 200	Detected		5m	56m	G118R	M46MI, I50IL, V82A, *L33LF, Q58QE, T74TP*	D67N, K70R, M184V, L210W, T215F, K219E	K103N, P225H
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	27 700	Detected		15m	107m	E138K, G140A, S147G, Q148R, N155H	None	D67N, K70R, M184V	A98G, K103N
P258	780	Detected	TDF-3TC-DTG	**4m**	176m	R263K	None	D68G, M184V	None
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P486	1 486	Detected	TDF-3TC-DTG	**15m**	102m	R263K	None	None	E138EG, G190A
P2-045	869	Detected	TDF-3TC-DTG	**5m**	104m	T66I, G118R, E138A	N/A	N/A	N/A
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P026	1 100	Not Detected	TDF-3TC-DTG	**23m**	111m	R263KR	None	M184V	K101PS, K103N
P104	706	Not Detected	ABC-3TC-DTG	43m	48m	R263K	N/A	N/A	N/A
P2-019	123 000	Not Detected	ABC-3TC-DTG	**15m**	211m	R263K	None	M184V	E138A

4/16 (25%) cases with DTG resistance had VL between 400-999 copies/mL

One case had persistent LLV, with accumulation of major INSTI DRMs

Steegen Lancet HIV 2026

Should GRT be expanded to people with VL below 1000 copies/mL?



Cohort study with biobanked samples

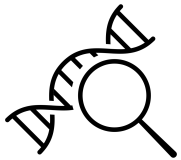
Among those with available resistance data, DTG resistance was detected in 8/67 (11.9%) with 2 x VL ≥1000 copies/mL and in 11/89 (12.8%) with 2 x VL ≥200 copies/mL

Klicpera 26th AIDS 2026 [THPEC150]

Should GRT be expanded to people with persistent viraemia below 1000 copies/mL?

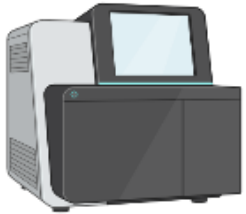
- Further evidence needed of impact and cost-effectiveness of expanding reflex GRT algorithm to people with persistent LLV
- In the meantime, if you have cases with persistent low-level viraemia who meet other criteria (i.e. TLD2) and who have had thorough adherence assessment and intervention – please discuss with virology and/or ID

Ongoing areas of uncertainty



Other DTG resistance mechanisms

Continuing reports of mutations in genetic regions outside integrase (e.g. 3`PPT, nucleocapsid, *env*) but clinical significance remains uncertain



Next-generation sequencing vs. Sanger sequencing

Low-frequency DRMs (minority variants) detectable by NGS but clinical significance uncertain – might be more important if expand GRT to low-level viraemia

Key takeaways

- Viral load monitoring and targeted genotypic resistance testing is designed to optimize individual and population health outcomes
- Identification of DTG resistance and timely switch to DRV/r-based therapy is important
- The GRT reflex testing strategy in the 2026 guidelines is evidence based, pragmatic and cost efficient
- We should all follow the guidelines – but remember to also use clinical judgement and don't be afraid to consult virology/ID

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