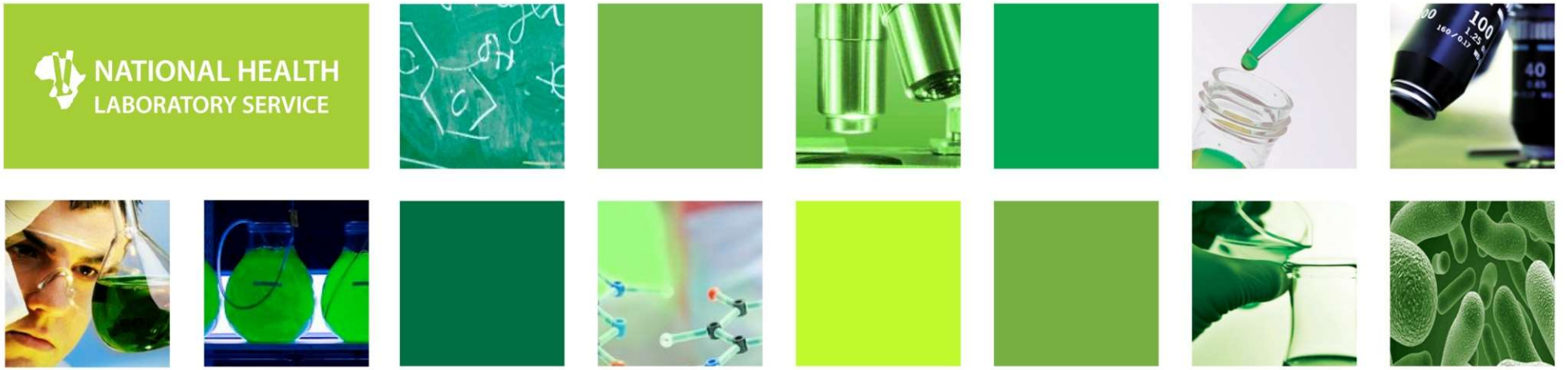

Utility of ARV exposure testing in the context of HIV Drug Resistance

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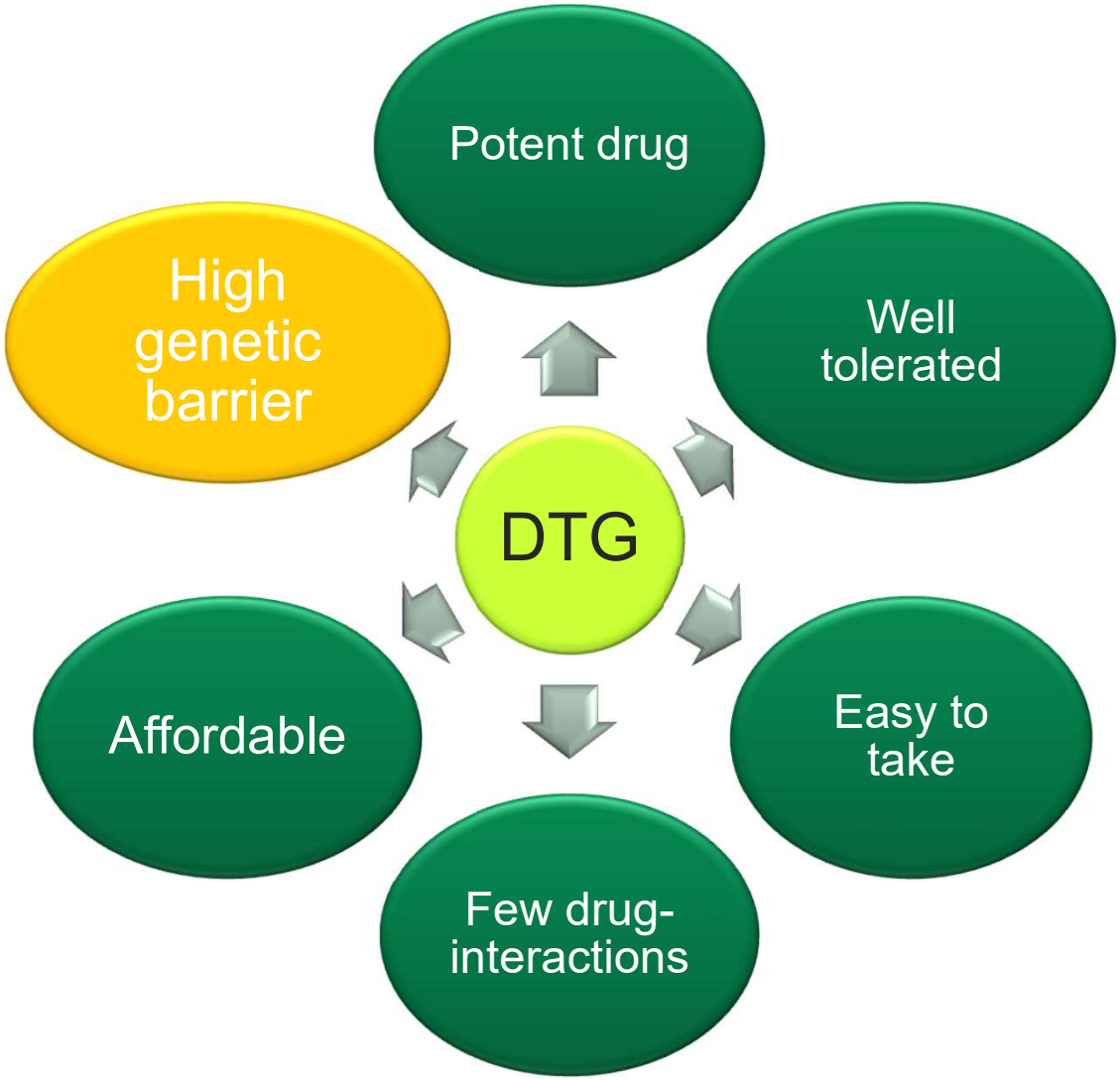
18 September 2025

Benefits of Dolutegravir



Importance of the denominator

- 100 PWH on DTG-based ART
- 10 PWH on ART with virological failure (yellow and red)
- 3 PWH with DTG resistance (red)
- 3% PWH on ART with DTG resistance
- 30% PWH on ART and virological failure with DTG resistance

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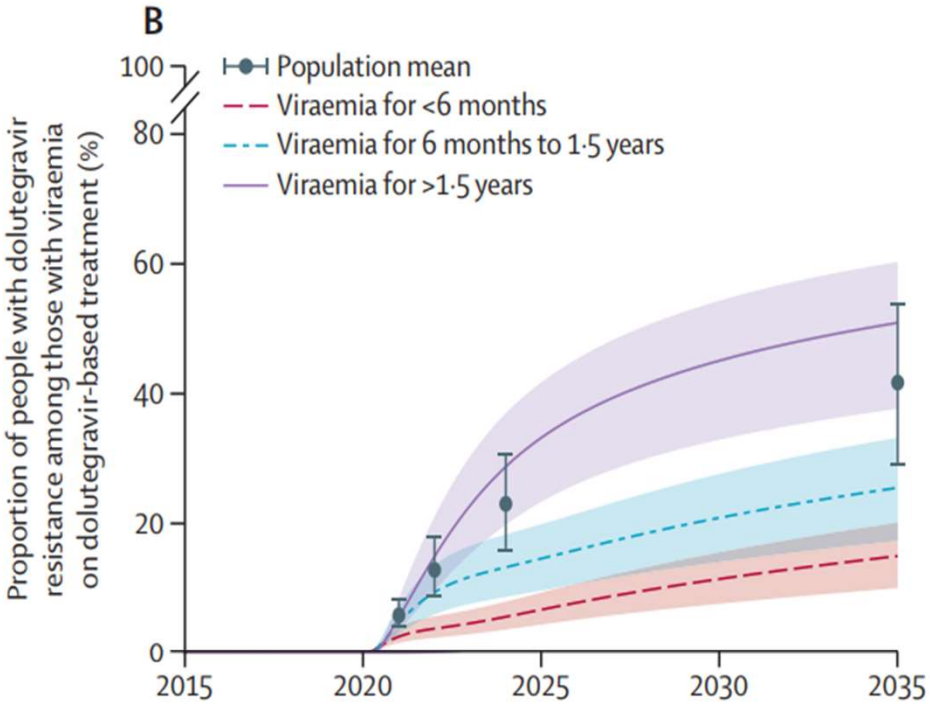
How much resistance do we expect?

- DTG resistance ≤ **0.1%** of all individuals on **1st line DTG regimen** and of those who switched with prior ART exposure, but no history of VF
- DTG resistance in **1.6%** of all individuals on **2nd of 3rd line DTG regimen**
- Not too bad… but given the magnitude of the ART programme this could still lead to a considerable amount of individuals with resistance.



- DTG resistance among those with viraemia 18.5% in 2023 (12.5-25.4%)
- Expected to increase to 41.7% (29-54%) by 2035
- Substantial differences in estimates based on duration of failure

WHO, 2024 HIV Drug resistance Report
Chu et al. Viruses 2024
Loosli et al. Lancet Global Health 2025

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Risk factors for the development of DTG resistance

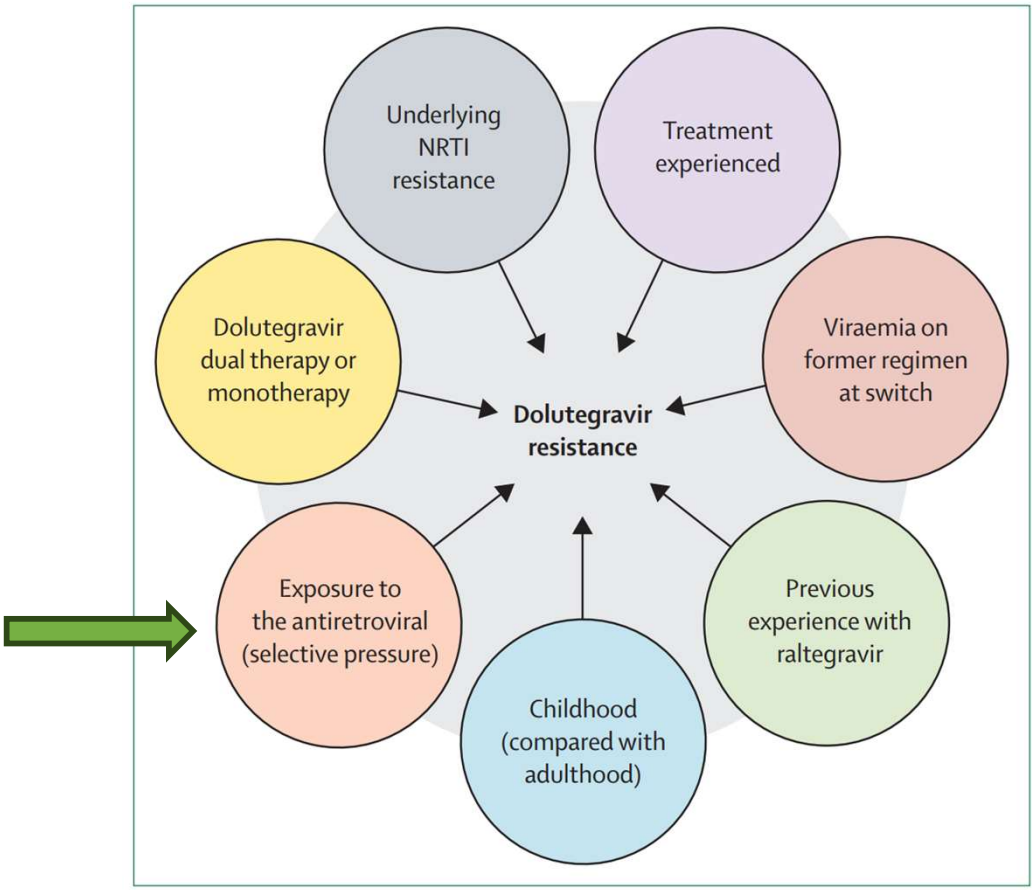
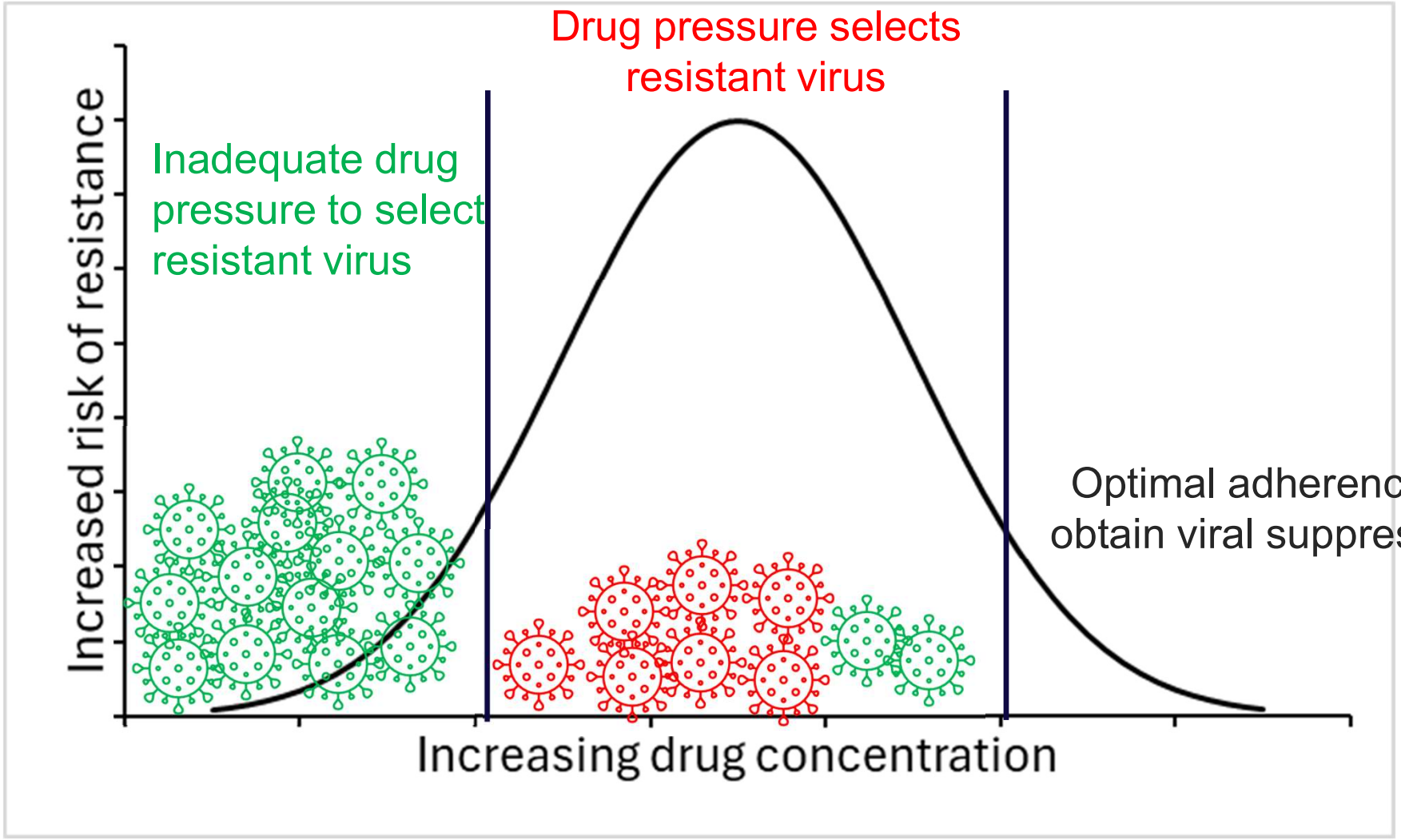


Figure: **Risk factors for the development of dolutegravir resistance on tenofovir, lamivudine, and dolutegravir**
NRTI=nucleoside or nucleotide reverse transcriptase inhibitor.

McCluskey & Gandhi, Lancet HIV 2025

Relationship between drug pressure and selection of resistance



HIV Drug Resistance Survey 2019-2023

Remnant VL samples with VL>1000 copies/mL
Proportional sampling by test volumes and virological failure
ARV drug levels as a proxy for treatment exposure

	2019	2021	2022	2023
Total number of samples tested	779	621	709	791
Any ARV detected	55.7%	52.0%	58.6%	34.1%
EFV detected	42.5%	35.8%	22.7%	11.7%
LPV/r detected	3.9%	6.9%	5.8%	4.6%
DTG detected	NA	7.2%	15.0%	18.4%
Succesful HIVDR	753	538	595	738
Any resistance	72.1%	67.6%	57.9%	53.7%
NNRTI resistance	70.5%	66.4%	56.0%	50.7%
PI resistance	2.2%	4.1%	3.1%	2.2%
INSTI resistance	NA	0.2%	1.2%	2.3%
NNRTI resistance in NNRTI+ samples	87.3%	85.2%	94.7%	84.0%
PI resistance in PI+ samples	32.3%	17.2%	31.7%	65.4%
INSTI resistance in DTG+ samples	NA	2.7%	11.1%	10.5%

Steegen et al. International Workshop on HIV drug resistance and treatment strategies, 2023

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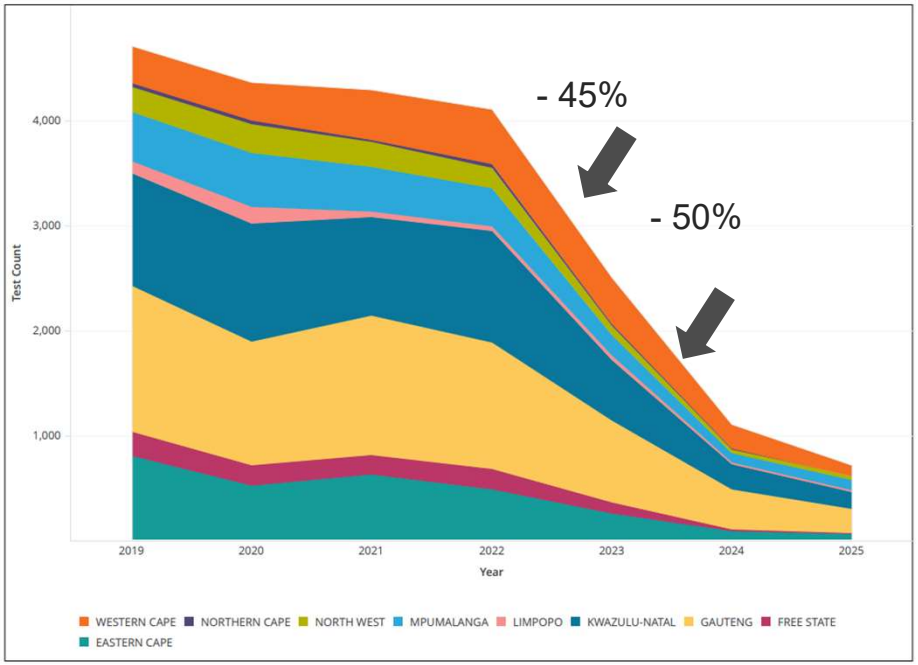
ARV drug level detection by VL category

- Remnant VL specimens from HIVDR survey (May-June 2023)
- Virological failure is often caused by non-adherence
- ARV drug level detection can be used to identify patients who do not take treatment and therefore have a very low risk for resistance.

	VL≥1000 copies/mL	**VL 50-999 copies/mL**	**VL <50 copies/mL**
	n=791	n=458	n=464
Any ARV detected	36.7%	84.7%	97.0%
DTG detected	18.4%	77.9%	88.3%
EFV detected	11.6%	12.2%	8.2%
PI detected	5.1%	5.0%	2.3%

Steegen et al unpublished data

NHLS HIVDR testing volumes 2019-2025



NHLS Corporate Data Warehouse 2025

Possible reasons for drop in testing:

- More PLH are suppressed (roll-out DTG)
- Belief that DTG resistance is very rare
- Complicated guidelines/gatekeeping before resistance testing request is approved

Curtesy of Dr Wessels

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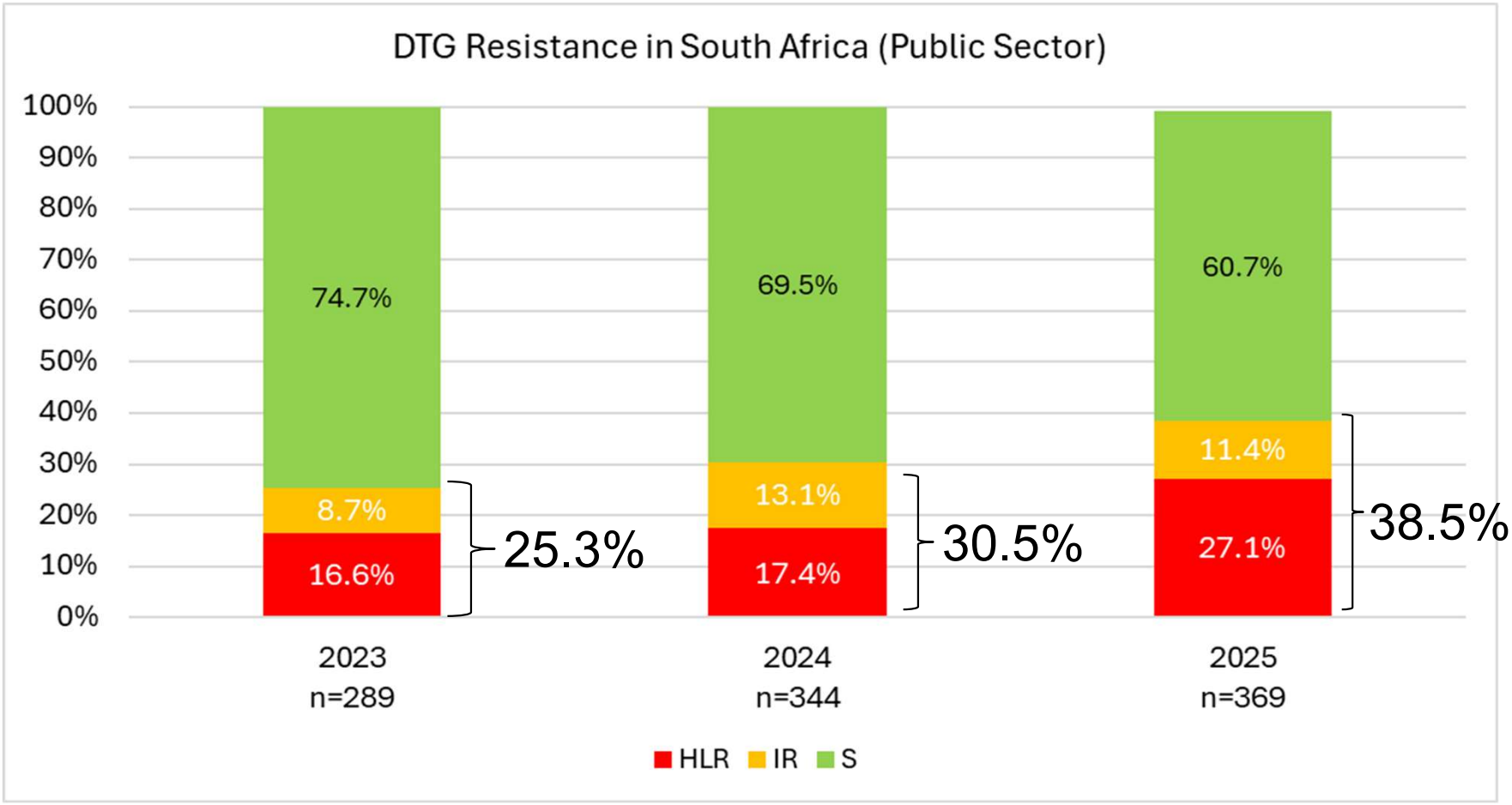
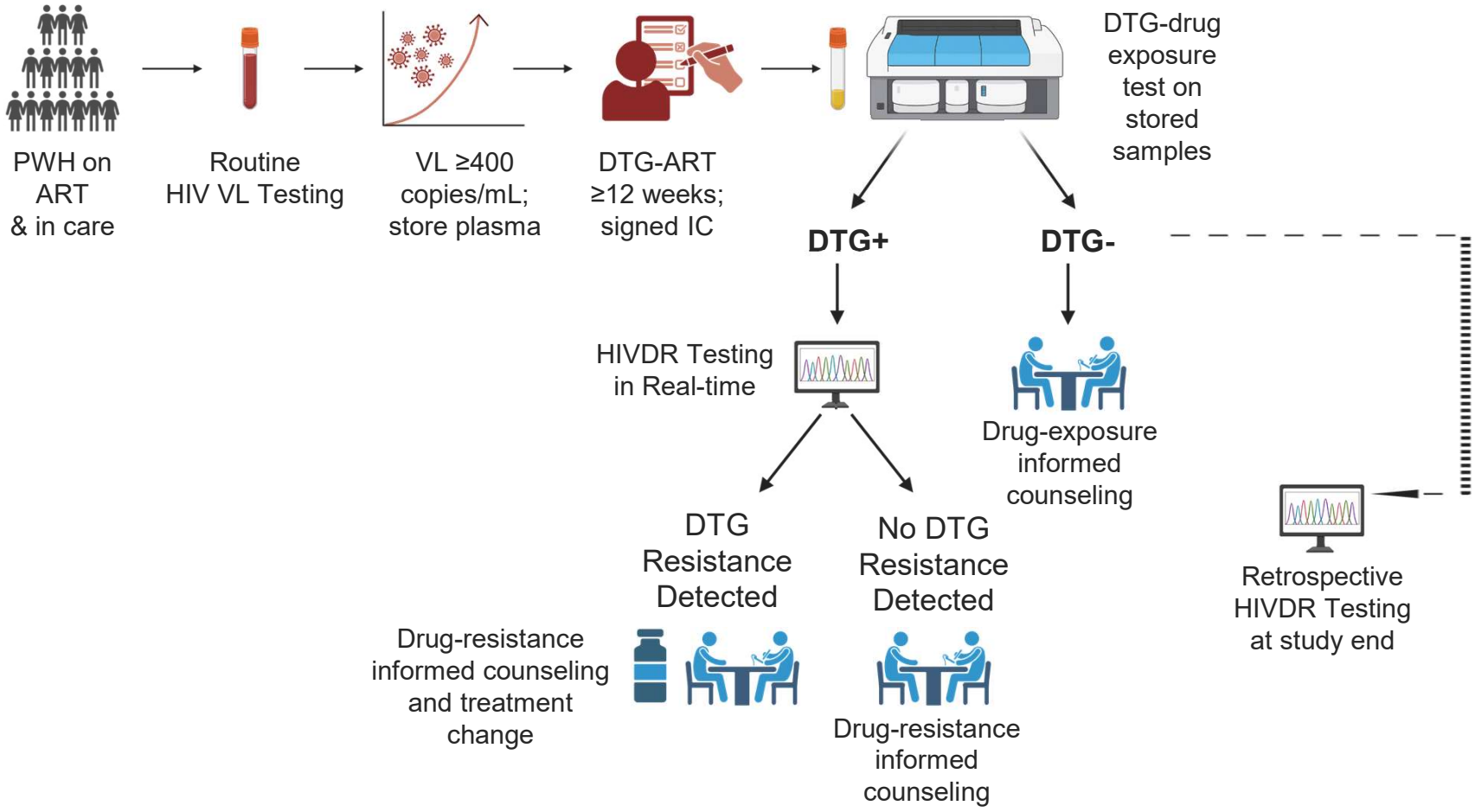
DTG resistance in South Africa: NHLS data



ITREMA-2 Implementation Trial: Interim data

Plasma dolutegravir exposure testing to identify patients at highest risk for integrase resistance



Created in bioRENDER

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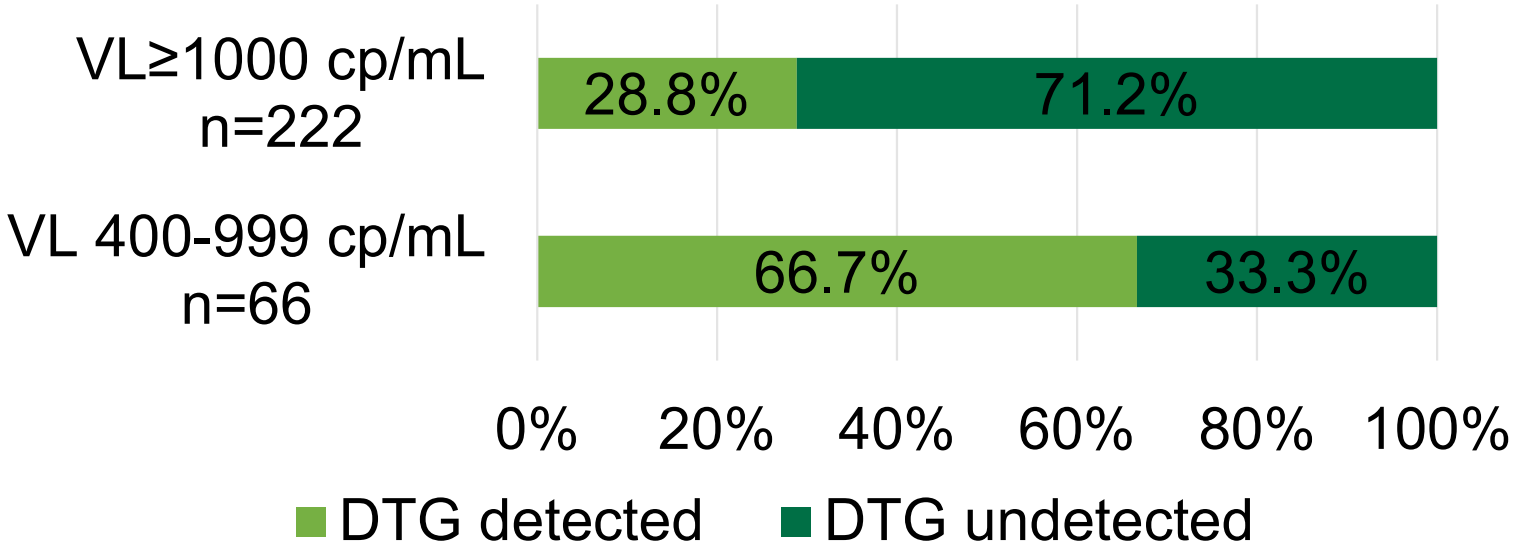
Baseline Characteristics

- 288 individuals enrolled, 400 samples
- Median age: 43 years, 56% Female
- 82% on TLD, 13% on ALD, 5% on other regimens
- Median time on ART 89 months, on DTG 13 months
- 82% had previous ART exposure

DTG Exposure Testing

- Enzyme immune assay (ARK Diagnostics), reported as detected/not detected

- Undetectable plasma DTG levels → no drug intake ~ 7 days



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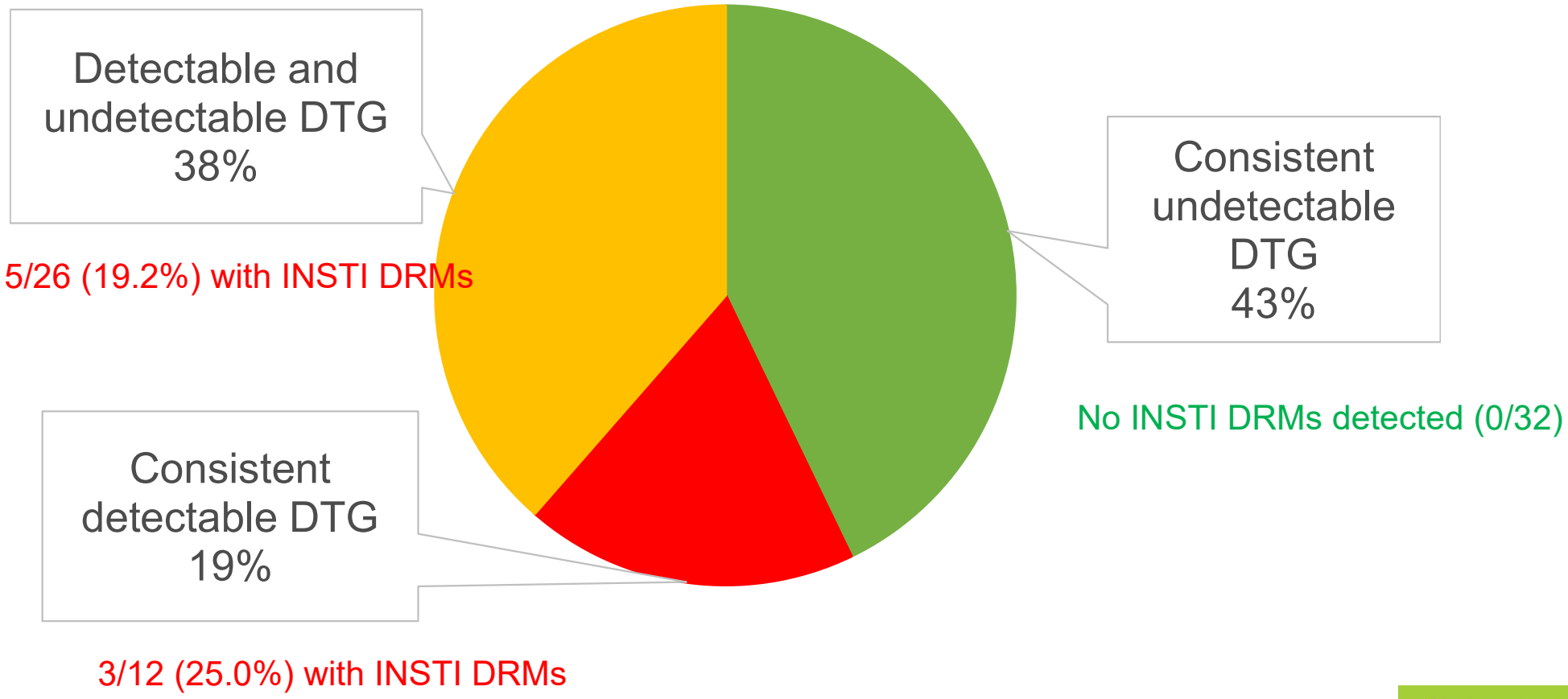
DTG exposure over time

- 70 individuals with ≥ 1 sample



DTG Resistance

- 13 individuals with DTG resistance
  13/288 (4.5%) enrolled individuals with VL>400 copies/mL
- All individuals with resistance had prior ART exposure
- 10/13 individuals with resistance were exposed to DTG <24 months
  3 individuals presented with resistance after <6 months DTG ART
- 10/13 presented with high-level DTG resistance (≥ 3 mutations)
- 3/13 individuals with resistance has VL 400-999 copies

Predictors of DTG Resistance

- DTG resistance was **not associated** with sex, age, regimen type, facility, duration of DTG treatment, total ART duration, prior ART exposure, VL category, virological failure category

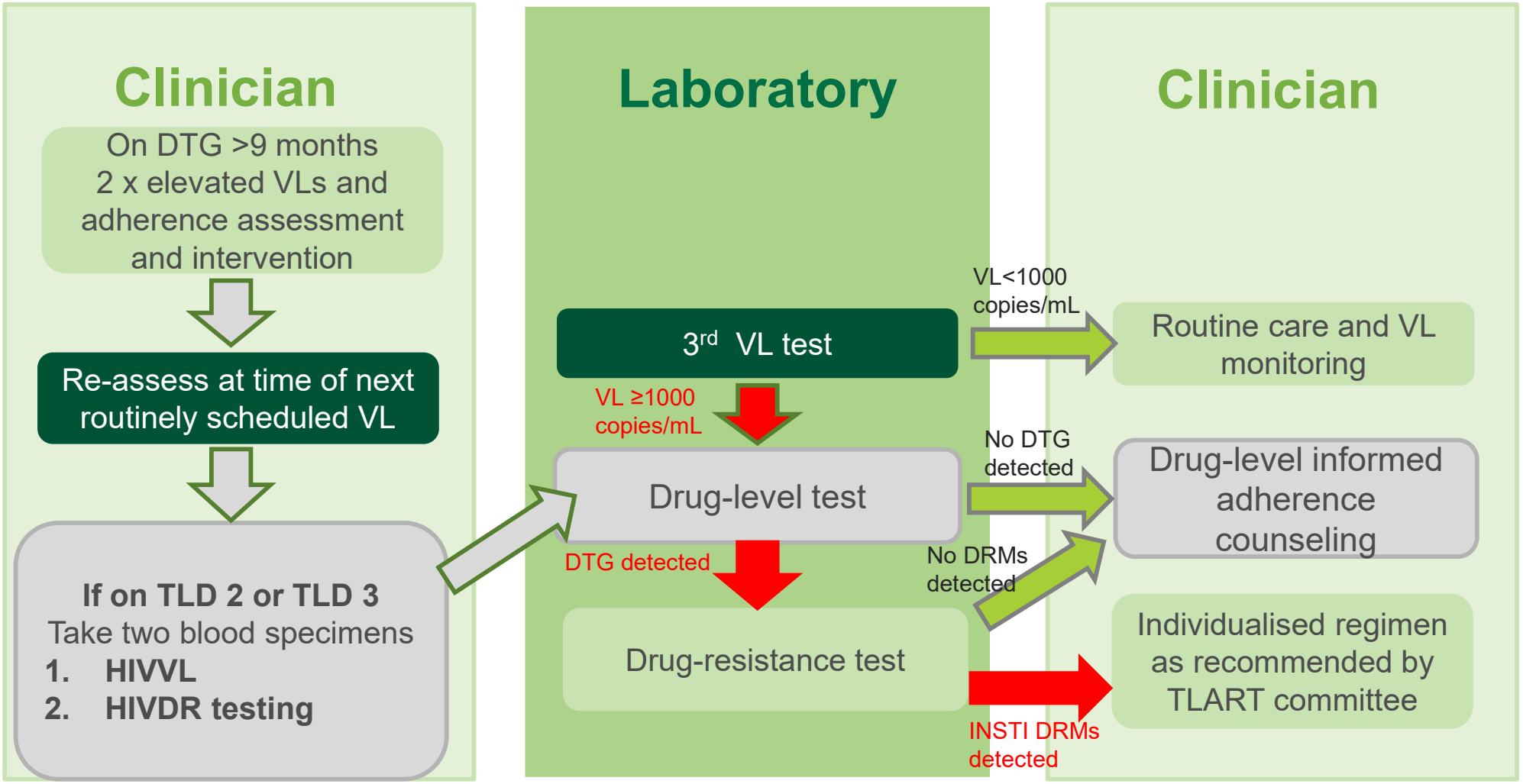
- Only detectable plasma DTG was predictive of DTG resistance
  - OR 3.85, 95% CI: 1.27-11.65, p=0.017

- In patients with follow-up samples, detectable DTG in at least one of the samples was predictive of DTG resistance
  - OR 9.79, 95% CI: 2.16-44.39, p=0.003

Negative Predictive Value

- DTG resistance was only found in 7/209 **samples** (3.3%) with undetectable plasma DTG
- DTG resistance was only found in 2/144 **patients** (2.4%) with undetectable plasma DTG
    - 2 patients had single R263K mutation and no follow-up samples

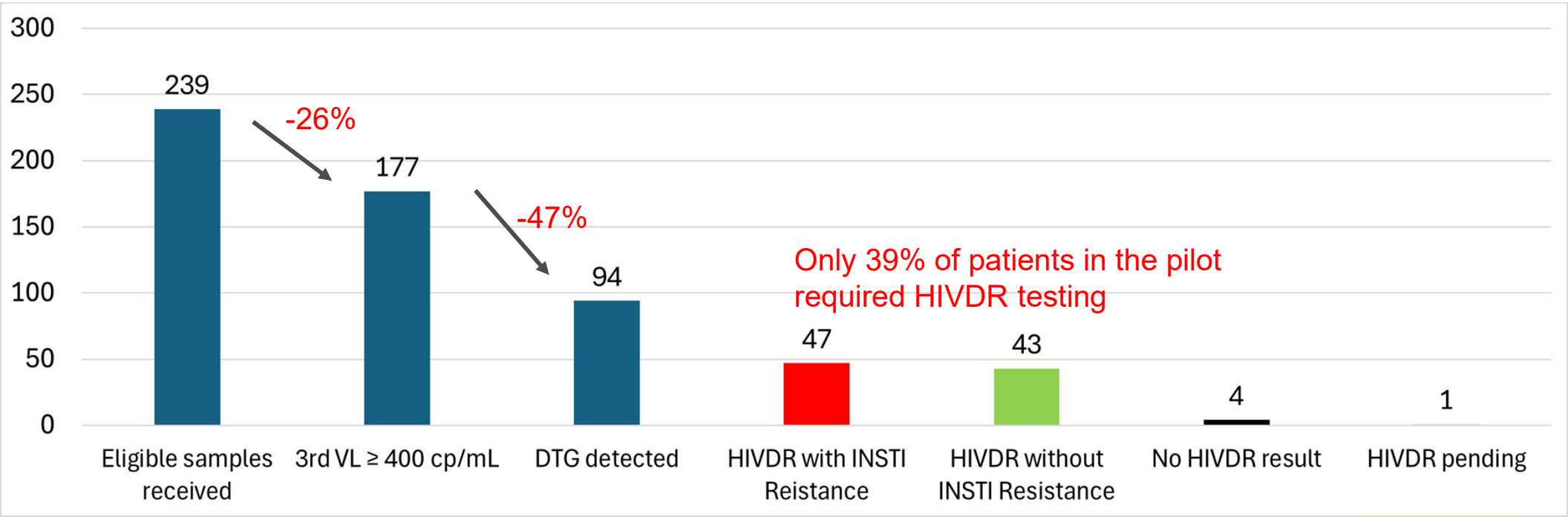
Process of “Reflex Testing”



Curtesy of Dr Wessels

DTG-Reflex Pilot (NDoH)

- Apr-Sep 2025
- 12 facilities in Gauteng
- 11 facilities in Mpumalanga



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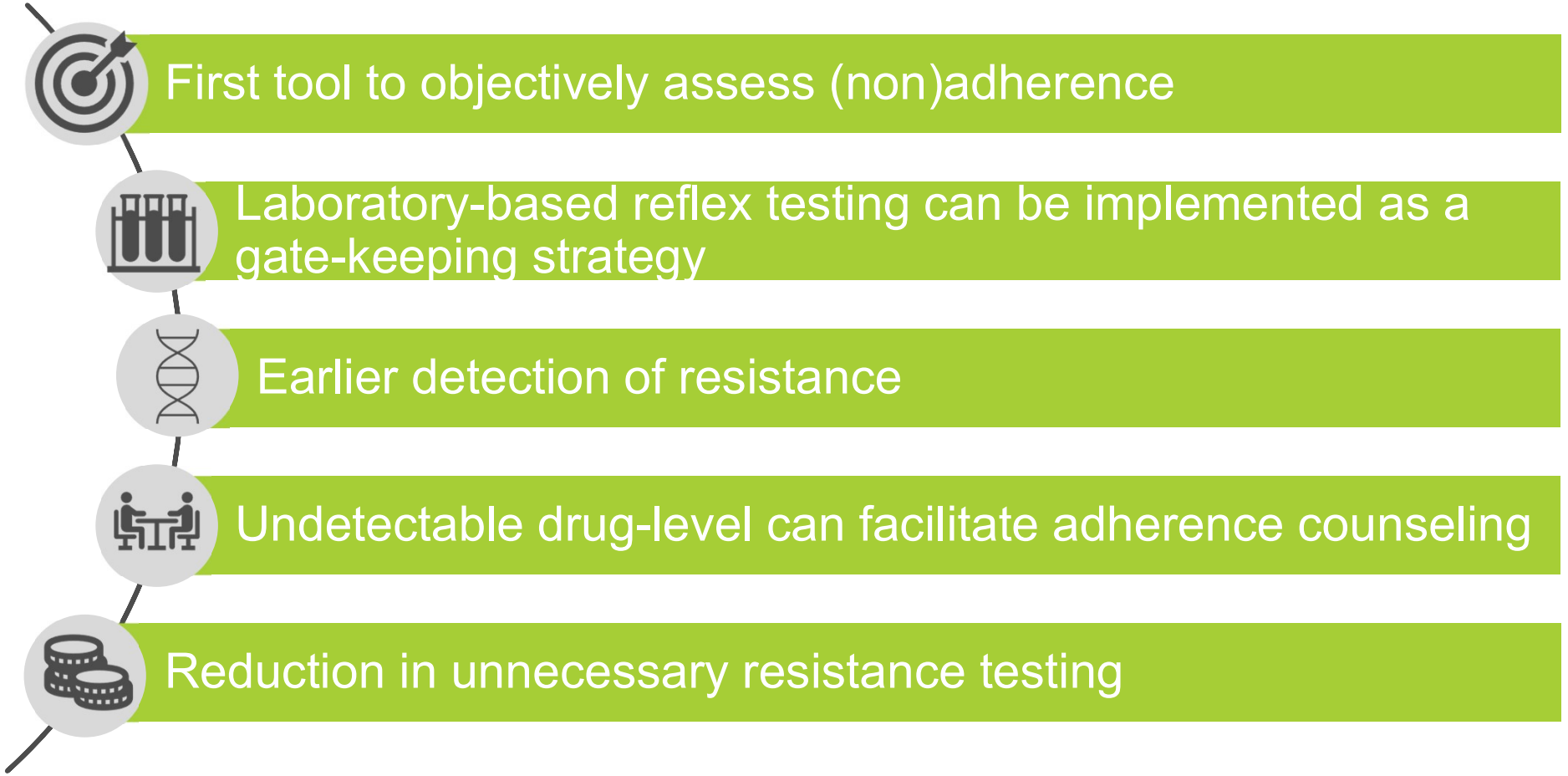
Conclusion



Undetectable plasma DTG accurately predicts the absence of DTG resistance

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