State of the ART: Navigating the Future of Antiretroviral Therapy in South Africa



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Disclosures

At the time this presentation was given I had no real or perceived vested interests that related to this presentation, nor did I have any relationships with pharmaceutical companies, biomedical device manufacturers, and/or other corporations whose products or services are related to pertinent therapeutic areas. I have received funding from ViiV, Gilead, Lilly, Merck, Optinosis, Switchboard MD, and Bayer.

Outline

- Performance of ART Regimens in South Africa
- Current ART Programme Needs
- US ART Guidelines
- Suggested Changes to South Africa Guidelines



Disclaimer: Approved ART initiation and switches. Not all studies included. Excluded salvage and PrEP/PEP.

ART Programme Standings



Country	Diagnosis	ART Initiation	Suppression	Resistance
South Africa	~95%	~79%-82%	~87%-89%	~54%
Botswana	>95%	>95%	>95%	~50% – 65%
Eswatini	>95%	>95%	>95%	~50% – 60%
Lesotho	~97%	~97%	>99%	~55%
Namibia	>95%	>95%	>95%	~60%
Zambia	>95%	>95%	>95%	~50%
Zimbabwe	>95%	>95%	>95%	~55% – 70%
Regional Average*	~87%	~83%	~78%	~50% – 80%

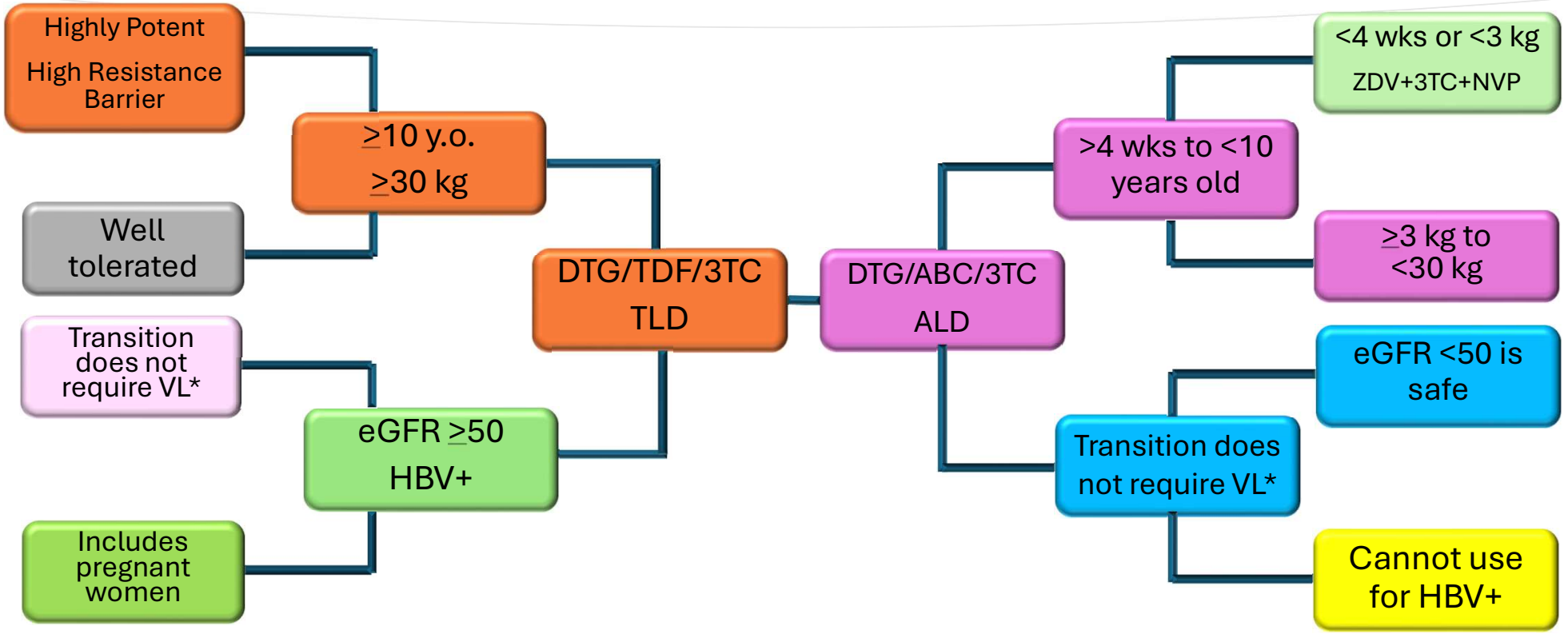
*Eastern and Southern Africa

https://www.unaids.org/sites/default/files/2025-07/2025-global-aids-update-JC3153_en.pdf
https://www.nicd.ac.za/national-hiv-drug-resistance-surveillance-among-adults-with-viral-non-suppression-in-south-africa/

Case #1

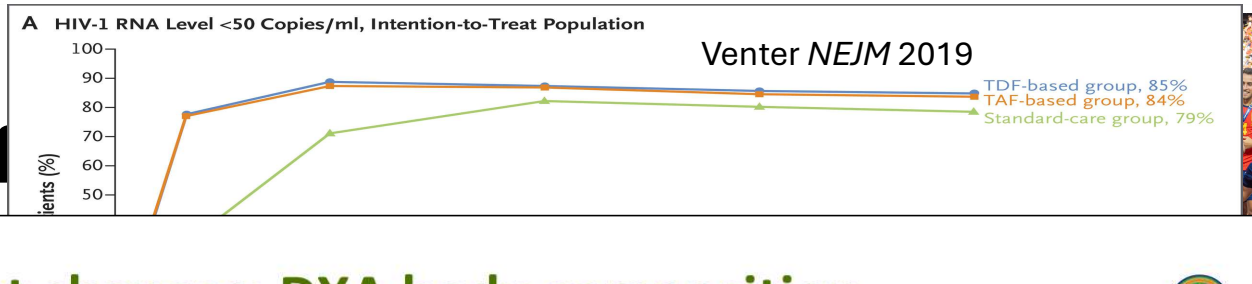
28 M from Gauteng presents to a public clinic for HIV treatment initiation with a baseline CD4 count of 312 cells/µL, eGFR 85 mL/min/1.73m^2, and Hepatitis B surface antigen (HBsAg) positive.

South Africa ART Guidelines 2023
Initiation or Never Failed (TLD1 & ALD1)



*Unless high risk

TLD1 Perf



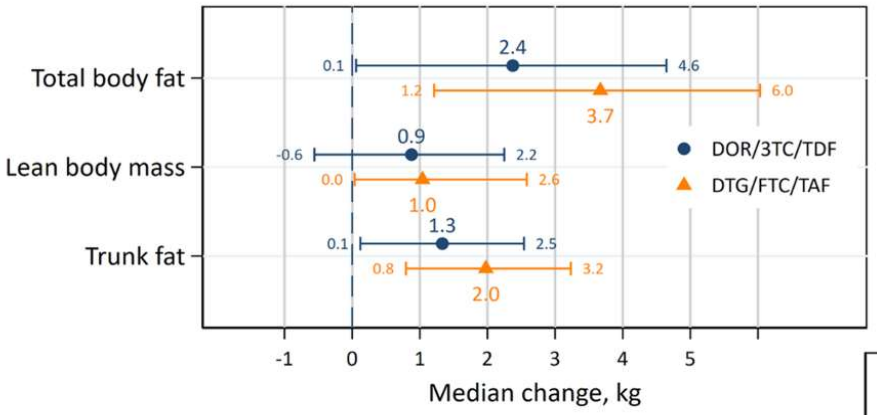
Venter *NEJM* 2019



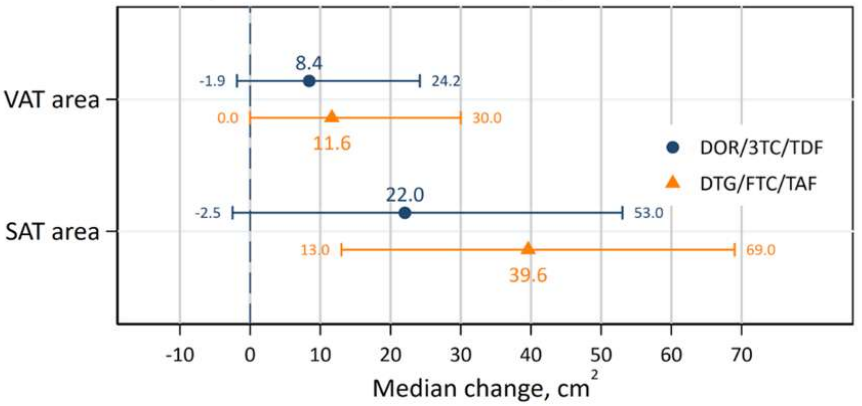
Confidential

Weight changes: DXA body composition

AIDS 2026



Values are median (IQR), error bars represent interquartile range



Woods/Venter *IAS* 2026

- Effica
- NI 48/9
- **Faster**
- Lower r
- Real W

- Safet
- Very tol
- Lower n
- **Increas**
- Increas
- Renal (8



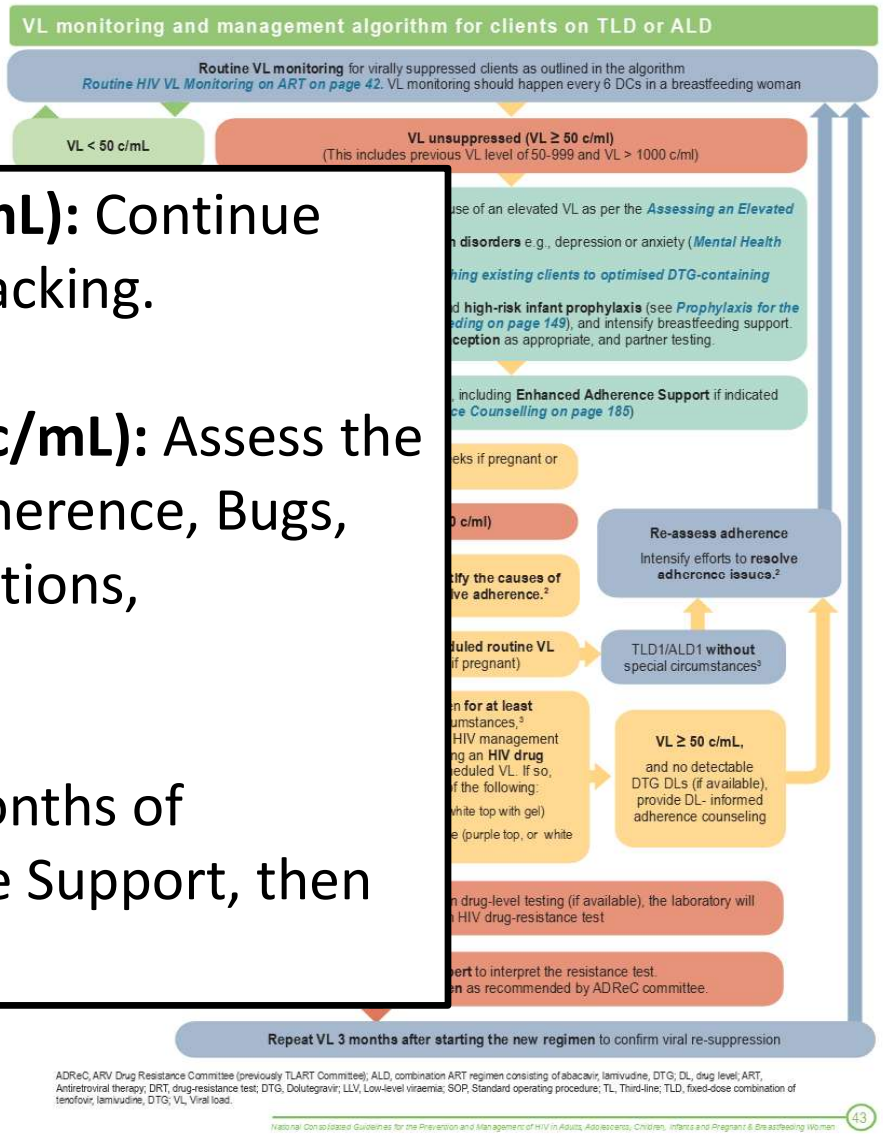
Case #2

34 F from KZN who originally initiated TLE with a baseline CD4 count of 184 cells/µL, eGFR 92 mL/min/1.73m^2, and a negative Hepatitis B surface antigen (HBsAg), now presents after 9 months with virological failure on TLD2 (viral load 8,900 copies/mL).

Suppressed (<50 c/mL): Continue routine 12-month tracking.

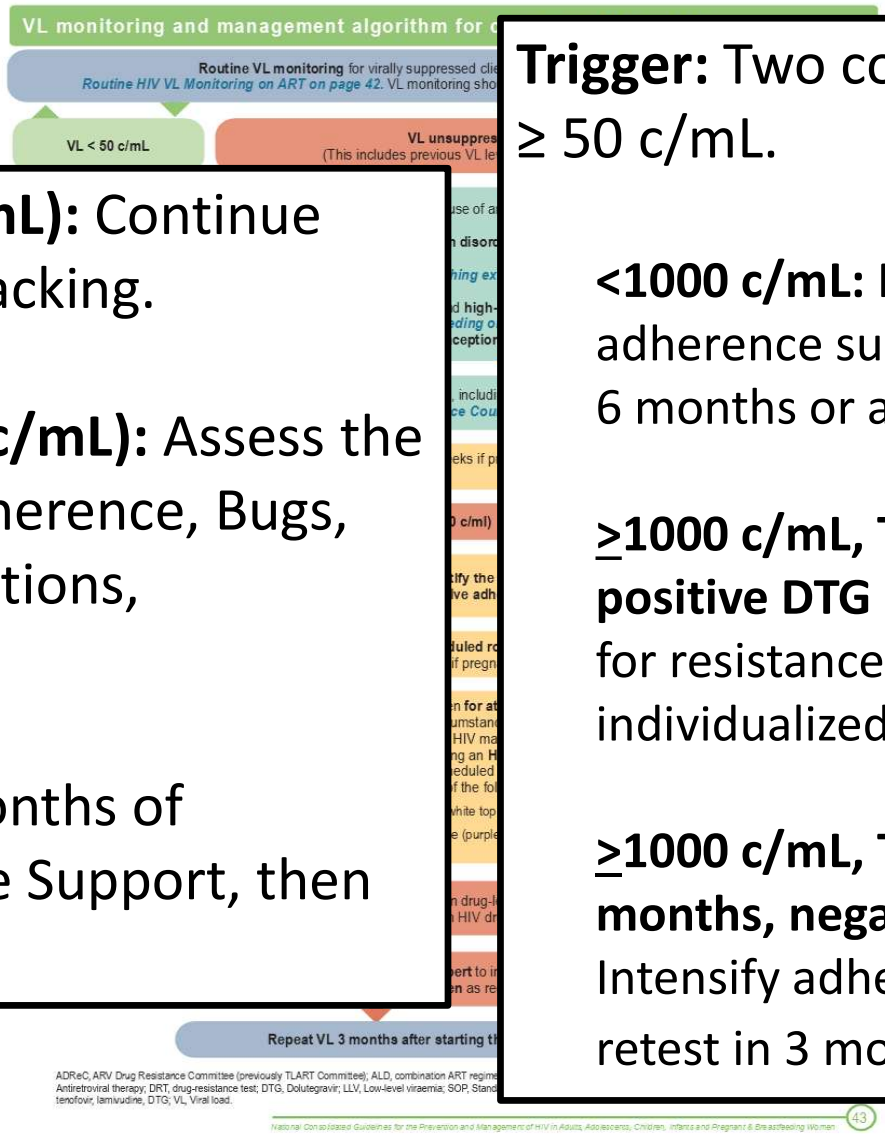
Unsuppressed (≥50 c/mL): Assess the "ABCDE" causes (Adherence, Bugs, Dosage, Drug interactions, rEsistance).

Action: Provide 3 months of Enhanced Adherence Support, then repeat the VL.



Case #2 (continued)

After 3 months of adherence support, now presents with confirmed virological failure while on TLD2 (viral load 5,200 copies/mL).



Suppressed (<50 c/mL): Continue routine 12-month tracking.

Unsuppressed (≥50 c/mL): Assess the "ABCDE" causes (Adherence, Bugs, Dosage, Drug interactions, rEsistance).

Action: Provide 3 months of Enhanced Adherence Support, then repeat the VL.

Trigger: Two consecutive VL results ≥ 50 c/mL.

<1000 c/mL: Focus strictly on adherence support and repeat VL in 6 months or at delivery if pregnant.

≥1000 c/mL, TLD2/3 ≥9 months, positive DTG level: Consult an expert for resistance testing and a new individualized regimen.

≥1000 c/mL, TLD1 or TLD2/3 <9 months, negative DTG level: Intensify adherence support and retest in 3 months.

Switching after Failure (TLD2)

- TLE failure switch directly
- ATV/r or LPV/r
  - Suppressed ≤2 years switch
  - Suppressed >2 years requires VL
  - Failure requires genotype & likely DRV/r or DRV/r+DTG
- Recycling TDF and 3TC despite extensive NRTI resistance (~80% suppress w/ rare DTG resistance)

TRIAL NAME	GEOGRAPHIC LOCATIONS	KEY FINDINGS REGARDING NRTI BACKBONE	PRIMARY PUBLICATION YEAR
SECOND-LINE	37 global sites including South Africa & Nigeria	Recycled NRTI + PI provided highly durable viral suppression despite accumulated first-line NRTI mutations (vs bPI+RAL).	2013
EARNEST	Uganda, Zimbabwe, Malawi, Kenya, Zambia	Excellent suppression using standard bPI even with extensive baseline NRTI resistance mutations (vs bPI+RAL vs bPI).	2014
DAWNING	13 countries including South Africa & Kenya	DTG was superior to LPV/r; suppression was unaffected by the presence of baseline M184V/I (preserving ≥1 NRTI).	2019
NADIA	Uganda, Kenya, Zimbabwe	Recycling TDF/3TC was NI to ZDV/3TC switch; DTG maintains high suppression despite no predicted NRTIs activity (vs DRV/r).	2021 (W48) / 2022 (W96)
VISEND	Zambia	Switching to DTG with recycled TDF/3TC or TAF/FTC was superior to standard-of-care bPI + ZDV/3TC	2022 (W48) / 2024 (W144)
D2EFT	14 countries including South Africa, Zimbabwe, & Asia	DTG with recycled TDF/XTC had virological superiority vs standard-of-care DRV/r + 2 NRTIs vs DTG + DRVr.	2024 (W48) / 2025 (W96)



Gap Analysis

- Obesity and CKM crisis
- Adherence and VL Monitoring challenges
- Persistent socioeconomic and structural inequalities
- Limited access to resistance testing
- Fragmented electronic health record for migrating patients



U.S. ART Guidelines

Table 6a. Recommended Initial Regimens for Most People With HIV

Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use. Choice of ART during pregnancy should be guided by recommendations from the Perinatal Guidelines.

For people who do not have a history of using CAB-LA as PrEP, one of the following regimens is recommended[a]:

- BIC/TAF/FTC **(AI)**
- DTG plus (TAF or TDF)[b] plus (FTC or 3TC) **(AI)**
- DTG/3TC **(AI),** except for individuals—
  - With HBV coinfection.
  - With unknown HBV serostatus.
  - Without results from genotypic resistance testing for reverse transcriptase.
  - For whom rapid ART initiation is planned.

For people who have a history of CAB-LA use as PrEP, INSTI genotypic resistance testing should be performed before starting INSTI-based ART. If ART is to be started before results of genotypic testing, the following regimen is recommended:

- DRV/c[c] or DRV/r plus (TAF or TDF)[b] plus (FTC or 3TC)—pending the results of the genotype test **(AIII)**

Rating of Recommendations: *A = Strong; B = Moderate; C = Weak*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials, observational cohort studies with long-term clinical outcomes, relative bioavailability/bioequivalence studies, or regimen comparisons from randomized switch studies; III = Expert opinion*

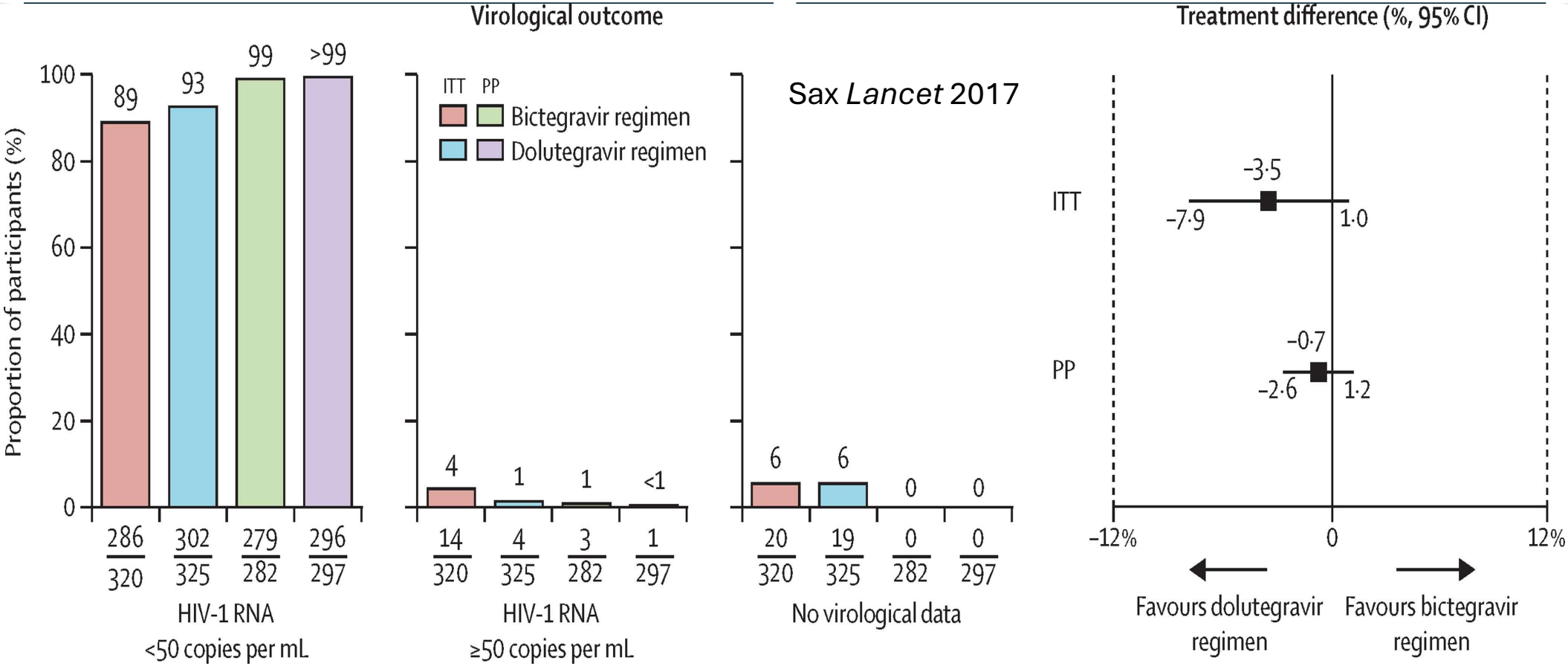
[a] Because of the current low rates of transmitted INSTI resistance in the United States, even when there is suspicion that HIV was acquired from a partner with virologic failure while on an INSTI, an INSTI-based regimen can be started pending the results of the INSTI genotype.

[b] TAF and TDF are two forms of TFV approved by the U.S. Food and Drug Administration. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.

[c] COBI should be avoided in pregnancy because lower concentrations of COBI and DRV have been reported during the second and third trimesters. For further information, refer to the Perinatal Guidelines.

Oral Daily 3 Drug Regimens





Oral Daily 2DR



STUDY NAME	POPULATION	STUDY DESIGN	MAIN EFFICACY OUTCOME	MAIN SAFETY OUTCOME	DRUG RESISTANCE	YEAR PUBLISHED
GEMINI 1/2	Naïve	Phase 3 DB, NI	DTG+3TC NI to DTG+TDF/FTC at W48/144	Lower AEs, better renal/bone markers	0 RAMs	2019
DOLCE	Naïve	Phase 4 OL	High suppression regardless of high VL (23% > 500K)	Safe, well tolerated in advanced disease	Minimal VF	2024
VOGUE	Naïve	Phase 3b OL	DTG+3TC NI to BIC/TC/TAF; Rapid Time to Supp. 4.1wks	Comparable safety	0 RAMs	2026
ASPIRE	Switch	Pilot OL	Maintained suppression, stable residual viremia, W48	Safe, well tolerated	1 VF/arm, 0 RAMs	2018
TANGO	Switch	Phase 3 OL	DTG+3TC NI to TAF regimens at W144	Favorable bone/renal biomarkers	<1% VF rate, 0 RAMs	2019
SALSA	Switch	Phase 3 OL	DTG/3TC NI to baseline ART at W48	Similar AEs, improved renal function	0 RAMs	2021
PASO DOBLE	Switch	Phase 4 OL	DTG+3TC NI to BIC/FTC/TAF at W48/96	Significantly lower weight gain	0 failures w/ RAMs	2024

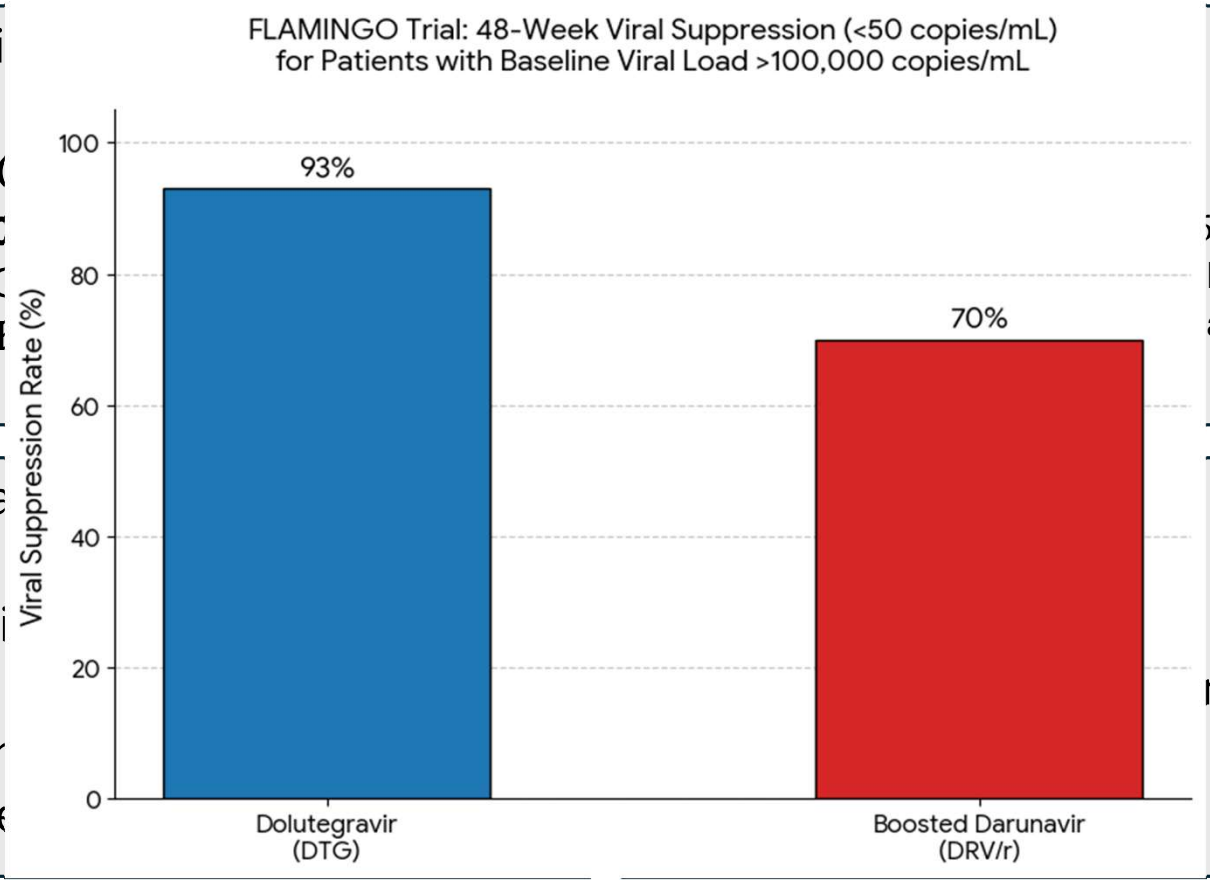
Oral Daily 4DR



Efficacy/Resi

- DRV/b+TXF+XT
  - **FLAMINGO – 90**
  - Real World (ARC
  - Prior CAB LA Pr

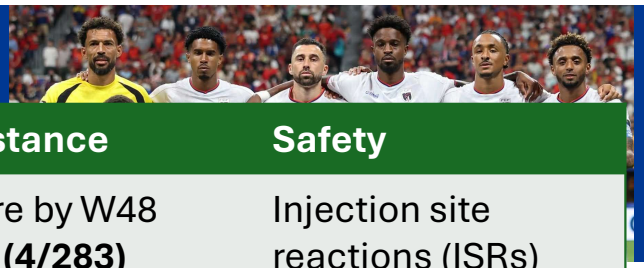
inhibitor levels
H corticosteroids
agulation meds



Safety/Tolera

- More GI tolerabi
- Higher d/c than
- Less weight gai
- Avoid cobi in pr

ne salvage
(private)



Trial / Setting	Design	Efficacy	Resistance	Safety
FLAIR (Naive First-Line)	Phase 3, OL 20-wk oral induction then randomized 1:1 to monthly CAB/RPV vs. oral pills	NI suppression (<50 c/mL) at W48: **93.6%** (Injectable) **93.3%** (Oral)	Failure by W48 **1.4% (4/283)** Emergent INSTI + NNRTI mutations (L74I, E138A/K, G140R)	Injection site reactions (ISRs) common (**86%**), mild-to-moderate, declined over time D/C <1%
ATLAS (Maintenance Switch)	Phase 3, OL Suppressed adults on oral ART randomized 1:1 to monthly CAB/RPV vs. oral ART	NI suppression (<50 c/mL) at W48: **92.5%** (Injectable) **95.5%** (Oral)	Failure by W48 **<1% (3/308)** Emergent mutations primarily E138K and N155H.	ISRs in **83%** but transient; Matched Systemic safety profiles
ATLAS-2M (Maintenance Switch)	Phase 3b, OL Suppressed adults randomized 1:1 to CAB/RPV every 4 weeks vs. every 8 weeks	Every-2-month NI to monthly Suppression at W48: **94.3%** vs. **93.5%**	Failure by W152: **2.7%** (2-month arm) **1.0%** (monthly arm); linked to high BMI, RPV RAMs	Similar ISR frequency; 2-month schedule yielded **higher patient preference** due to fewer clinic visits



Proposed Changes to SA Guidelines

- Include DTG/3TC
  - Naive if VL<500K, HBV negative, and without M184V
  - Switch if long-term suppressed, HBV negative, and without M184V*
  - Reduce renal/bone toxicity, some wt?
- Approve CAB/RPV for switch after 6 months suppression, HBV negative and no known INSTI/NNRTI resistance or PrEP history
  - Reduce renal/bone toxicity, some wt?
  - Improve adherence
  - Continued transportation challeges

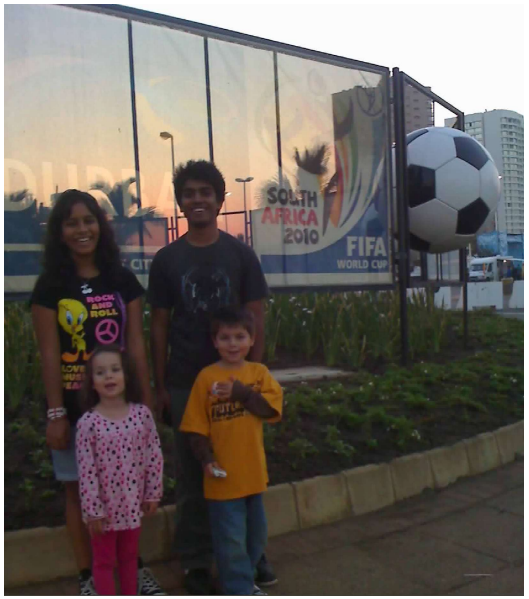
*Also DOR/ISL or BIC/LEN

Summary

- South Africa remains just <90% viral suppression
- TLD is outperforming NNRTI regimens across most metrics (efficacy, resistance, tolerability) except for metabolic/renal side effects
- Additional regimens (2DR oral and LAI) could provide beneficial options for patients with HIV in SA









Questions

