Future trends of drug resistance and prospects of antiviral therapy

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- **The principles of HIV drug resistance are well established (Darwinian evolution).**

- **The mistakes and lessons learned in the developed world are being recapitulated in low and middle income countries.**

HIV drug resistance is generated by one of two major mechanisms

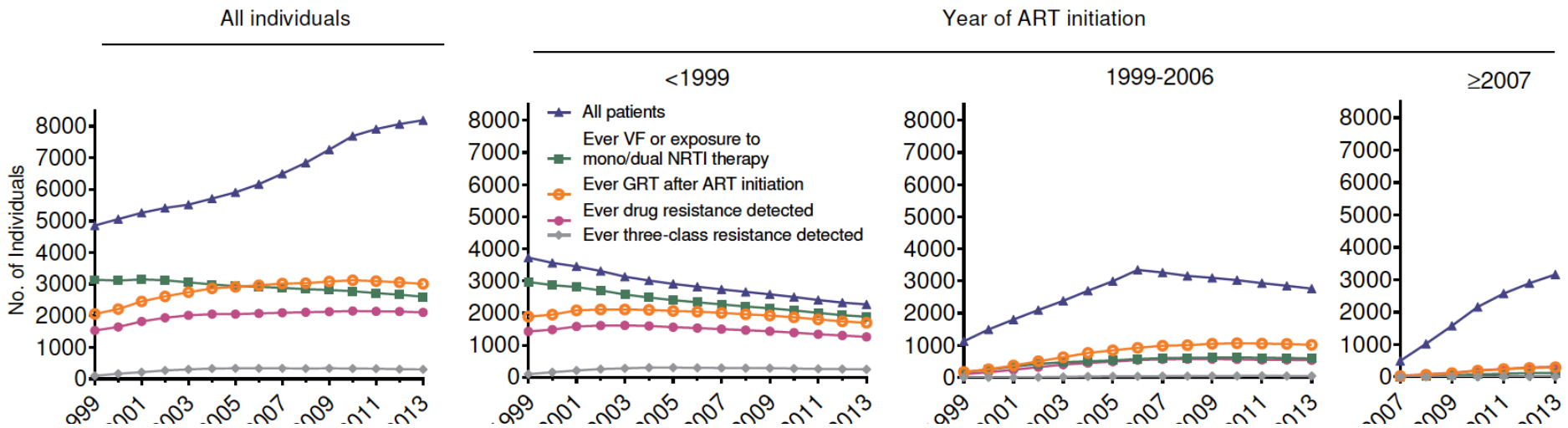
- **Acquired drug resistance following non-suppressive treatment (secondary resistance)**

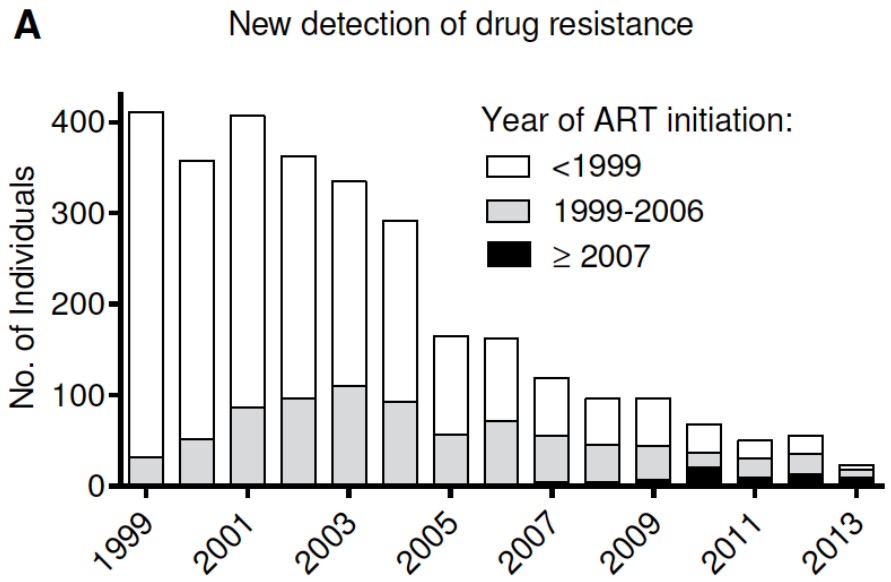
- **Transmitted drug resistance (TDR) (primary resistance)**

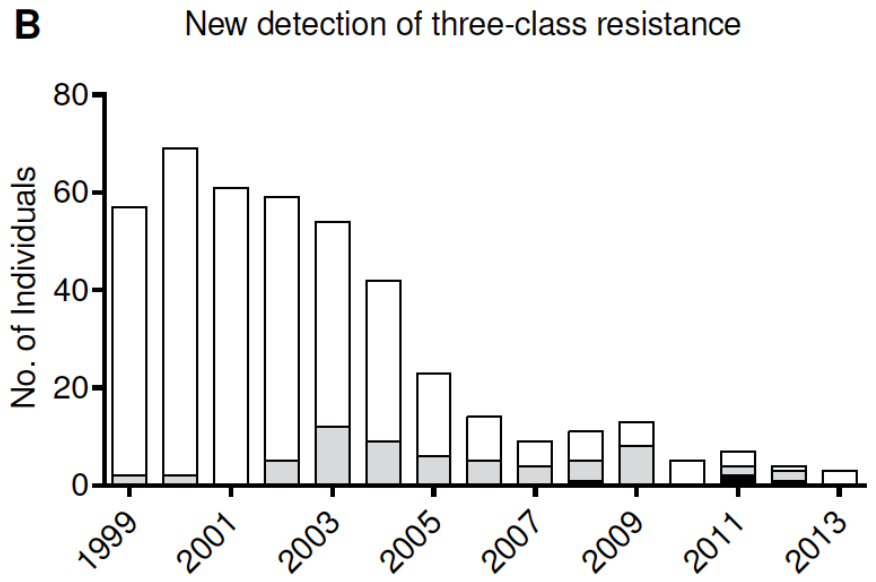
(PDR combines both TDR and resistance acquired from previous treatment, disclosed or not, after infection)

- **Both mechanisms are too prevalent.**
- **Prevention strategies for these two mechanisms are completely different.**

Diminishing drug resistance with superior regimens

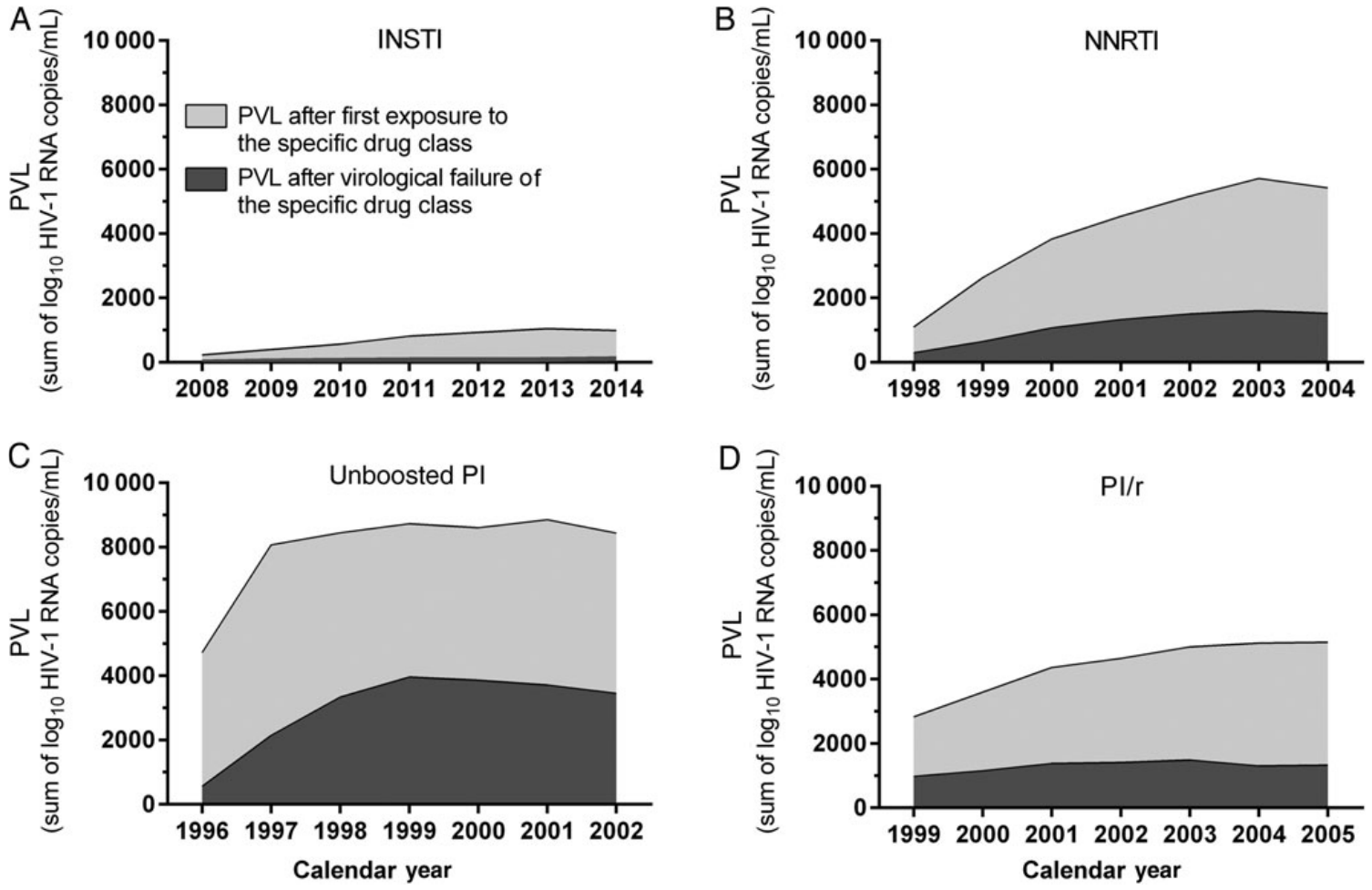






Scherrer et al, CID, 2016

If resistance appears, it is often less fit resulting in lower viral loads



Scherrer A, et al. J Infect Dis 2017

How did this reduction in resistance with more expanded treatment happen?

- **Better drugs**
  - More potent and better half-lives (TDF/FTC, better PIs, integrase inhibitors)
  - More tolerable and less toxic
  - Introduction of several new compounds at the same time
  - Multiple fixed dose combinations

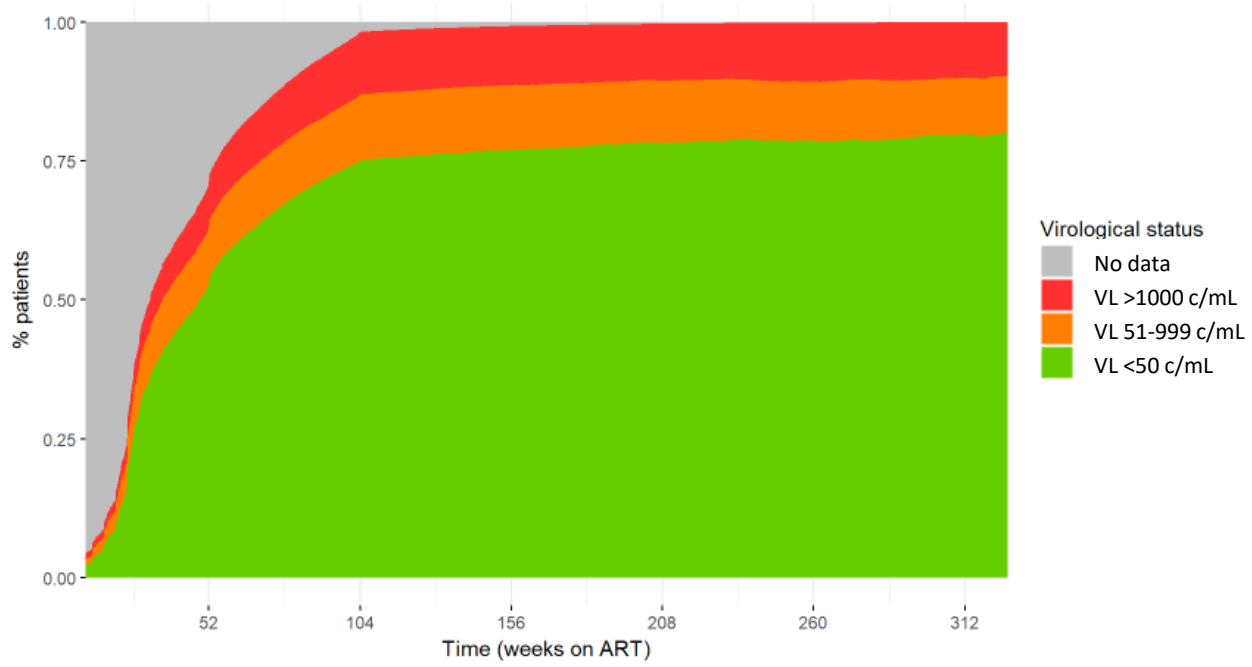
- **Better monitoring of failure and then use of drug resistance testing and better drugs for treatment failure**

All this happened before the availability of second generation integrase inhibitors.

Now, how do we approach the availability of TlD or TFD

Virological suppression of individuals on ART in South Africa

- Data from 69,454 patients on 1st line ART
- 57 rural and urban clinics
- Monitoring according to SA guidelines

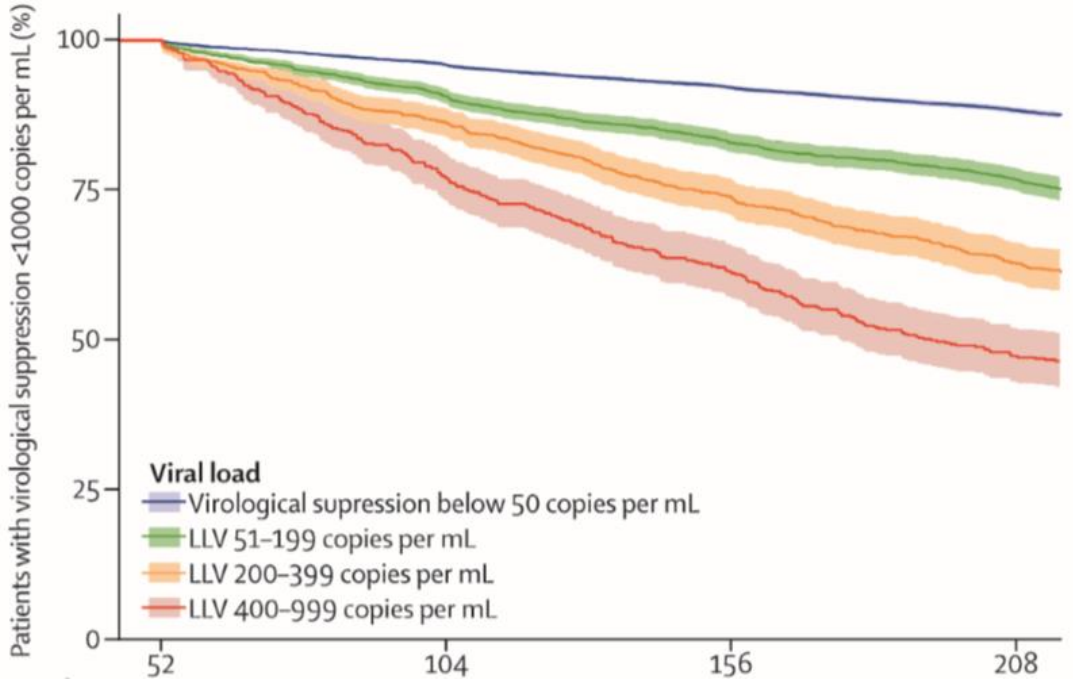


time	26.0	52.0	78.0	104.0	130.0	156.0	182.0	208.0	234.0	260.0	286.0	312.0
n_at_risk	17340.0	28360.0	30713.0	30190.0	25852.0	21966.0	17875.0	14256.0	11097.0	8975.0	6881.0	5502.0
VL_below_50_OT	70.0	74.2	75.8	76.4	77.1	77.5	78.1	78.5	79.1	78.7	79.0	79.9
VL_51_999_OT	18.9	14.5	12.6	12.2	11.9	11.8	11.3	11.3	10.9	10.6	10.5	10.2
VL_above_1000_OT	11.2	11.3	11.6	11.5	11.0	10.7	10.5	10.3	10.1	10.7	10.5	10.0

Hermans et al, CROI, 2018

Low-level viremia increases risk of viral rebound

- Data from same dataset
- Association corrected for demographics, baseline CD4
- Risk also increased for confirmed failure and switch

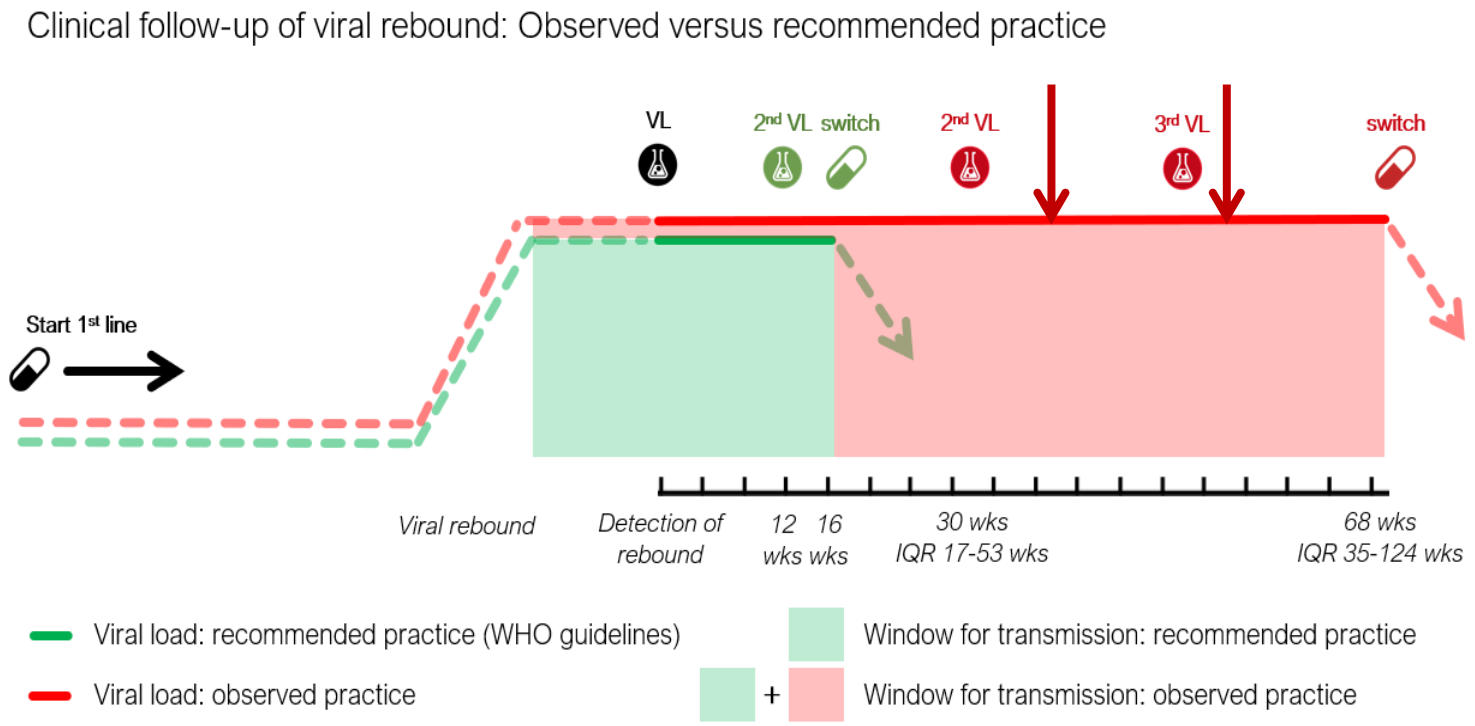


	Adjusted HR (95% CI)	p value
Virological suppression <50 copies per mL	1 (ref)	..
LLV 51–999 copies per mL	2·6 (2·5–2·8)	<0·0001
LLV 51–199 copies per mL	1·9 (1·8–2·1)	<0·0001
LLV 200–399 copies per mL	3·2 (2·9–3·5)	<0·0001
LLV 400–999 copies per mL	4·7 (4·2–5·2)	<0·0001

Hermans et al, Lancet ID, 2018

In case of failure: Switch of ART is seriously delayed

- Observed clinical practice is delayed in comparison to guideline-recommended practice
- VL is measured repeatedly after rebound
- Switch is <u>often postponed or not performed at all</u>



Hermans et al, CROI, 2018

Table 22: Estimates of HIV drug resistance among people failing ART, by study/cohort and region in the acquired HIV drug resistance literature review in adults

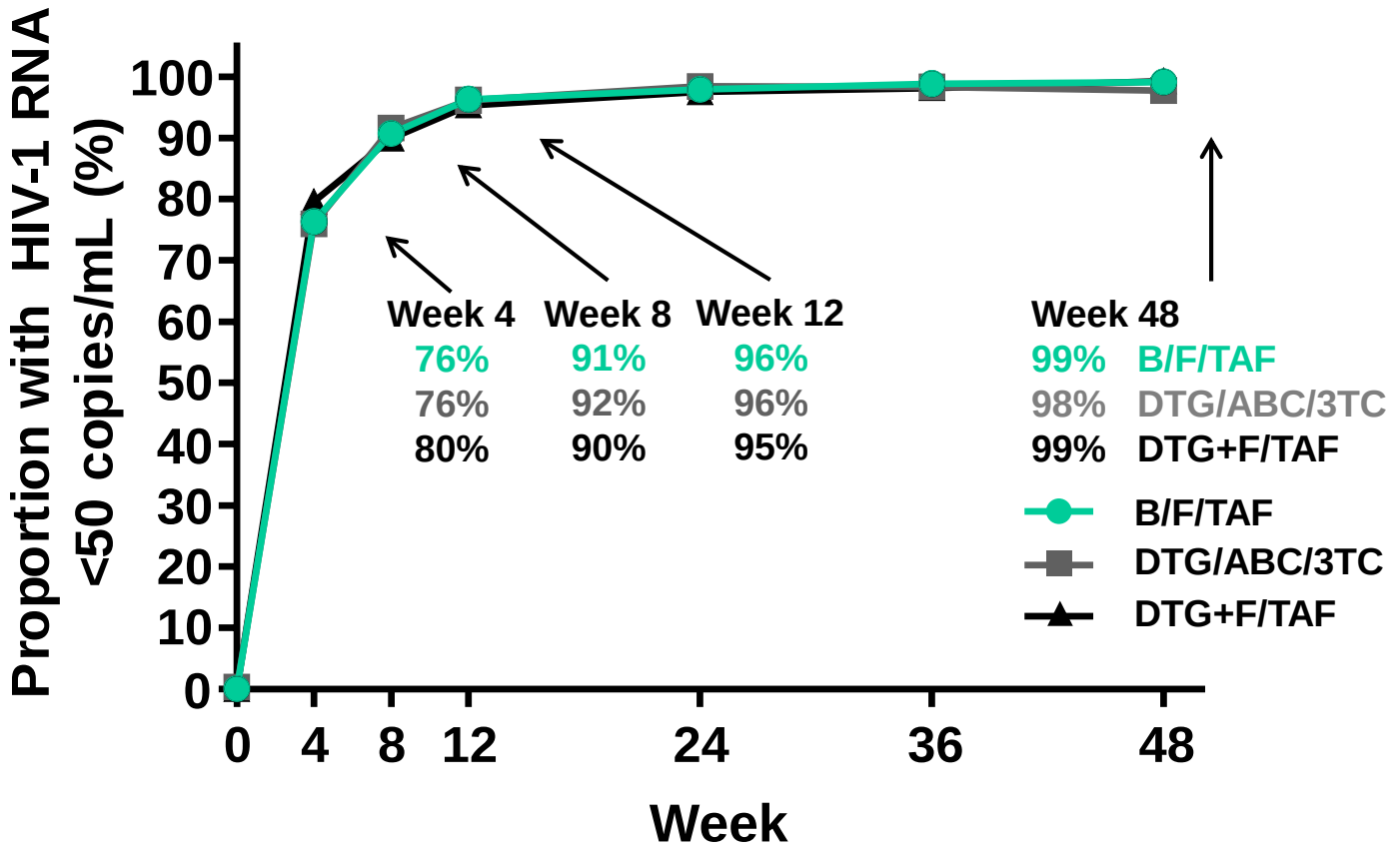
Country	Study author	% with resistance	CI (%)
Africa			
Cameroon	Zoufaly et al.	71%	54.1–84.6
Guinea	Diouara et al.	68%	47.6–84.1
Kenya	Hassan et al.	53%	38.8–66.3
Kenya	Kantor et al.	91%	78.7–97.5
Kenya	Koigi et al.	41%	26.3–56.7
Liberia	Loubet et al.	71%	55.9–83
Mali	Diouara et al.	93%	68–99.8
Mali	Fofana et al.	92%	83.5–96.5
Mauritania	Fall-Malick et al.	73%	59.7–83.6
Mozambique	Bila et al.	47%	30.4–64.5
Mozambique	Ruperez et al.	89%	77.7–95.2
Senegal	Diouara et al.	70%	49.8–86.2
Senegal	Diouara1 et al.	79%	65.3–88.9
Togo	Konou et al.	99%	96.6–99.9

Literature review from WHO resistance report 2017

The levels of acquired drug resistance requires addressing the causes

- **The patient**
  - adherence
- **The prescribing care provider**
  - selecting an optimal regimen
  - counseling the patient
- **The drugs**
  - Potency
  - tolerability
  - Pharmacokinetics
- **The heathcare delivery system**
  - Provide viral load monitoring with prompt turnaround and threshold <100 copies/mL
  - Provide assays for drug resistance (or drug levels).
  - Avoid stockouts

Rapid Suppression of HIV-1 RNA to < 50 copies/mL through Week 48 (Missing = Excluded Approach)



B/F/TAF vs. DTG/ABC/3TC or vs. DTG + F/TAF: displayed rapid viral suppression and non-inferior efficacy at Week 48

AE=adverse event; DC=discontinuation; Other reasons= lost to follow-up, withdrew consent, investigator discretion, noncompliance, etc.)

White K, CROI, 2018, #532

Molepolole District

- 709 Chart reviews completed 78.9% (560) with viral load results at 12 months – All Cohorts:

4	(<1%)	VL >400 copies/mL
6	(1%)	LTFU
3	(<1%)	Deaths *(2 TB related, I unknown)*
2	(<1%)	Toxicity Grade 3

97.6% *(548/560)*

Viral Load <400 copies/mL at 12 months

Courtesy of Ava Avelos

Switches to DTG Outcomes

Reason for Switch	#	% VL <400 6 months	%VL 400 12 months
Guidelines Simplification	33	10/11 (90.9%)	20/22 (90.9%)
Toxicities	173	85/87 (97.7%)	85/86 (98.8%)
Tx Failure	135	27/37 (72.9%)	94/98 (95.9%)
Totals	341	122/135 (90.3%)	199/206 (96.6%)

Courtesy of Ava Avelos

Measures are still needed to preserve the integrase class over time - 1

- **Low level viremia ≠ treatment success**
  - High threshold may be even more dangerous with DTG, since viruses resistant to DTG are often not very fit and viral load may remain low
- **Delayed response to viral rebound puts individuals and society at risk**
- **Use tools** (like viral load monitoring and objective adherence assessment) **to generate insight in virological failure**

Measures are still needed to preserve the integrase class over time - 2

- Avoid adding 1 new drug to a failing regimen
  - What is the risk of a switch from a failing regimen with TLE to TLD?
  - Surveillance in those who start DTG with unsuppressed viral load should be promptly initiated if resistance testing is not applied at switch

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