First line and second line ART resistance

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25 October 2018

Current SA public sector regimens

First line	Tenofovir (TDF) Emtricitabine (FTC) Efavirenz (EFV)
Second line	Zidovudine (AZT) Lamivudine (3TC) Lopinavir/ritonavir (LPV/r)

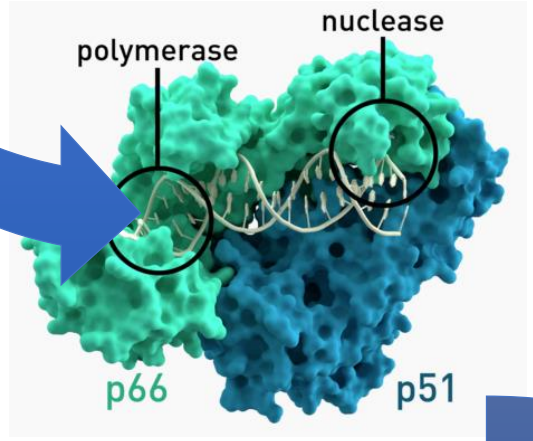
ART resistance mutations

- Most resistance mutations are base substitutions in RNA/DNA sequence of HIV resulting in amino acid substitution

- Example: M184V that causes 3TC/FTC resistance
  - At position 184 in reverse transcriptase a Methionine is substituted by a Valine

3TC

HIV Reverse Transcriptase

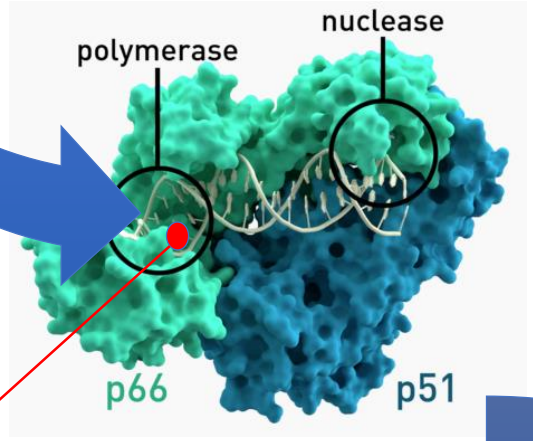


Mimics nucleoside building block in propogating viral DNA chain and thereby prevents ongoing reverse transcription by RT

HIV replication inhibited

3TC

HIV Reverse Transcriptase

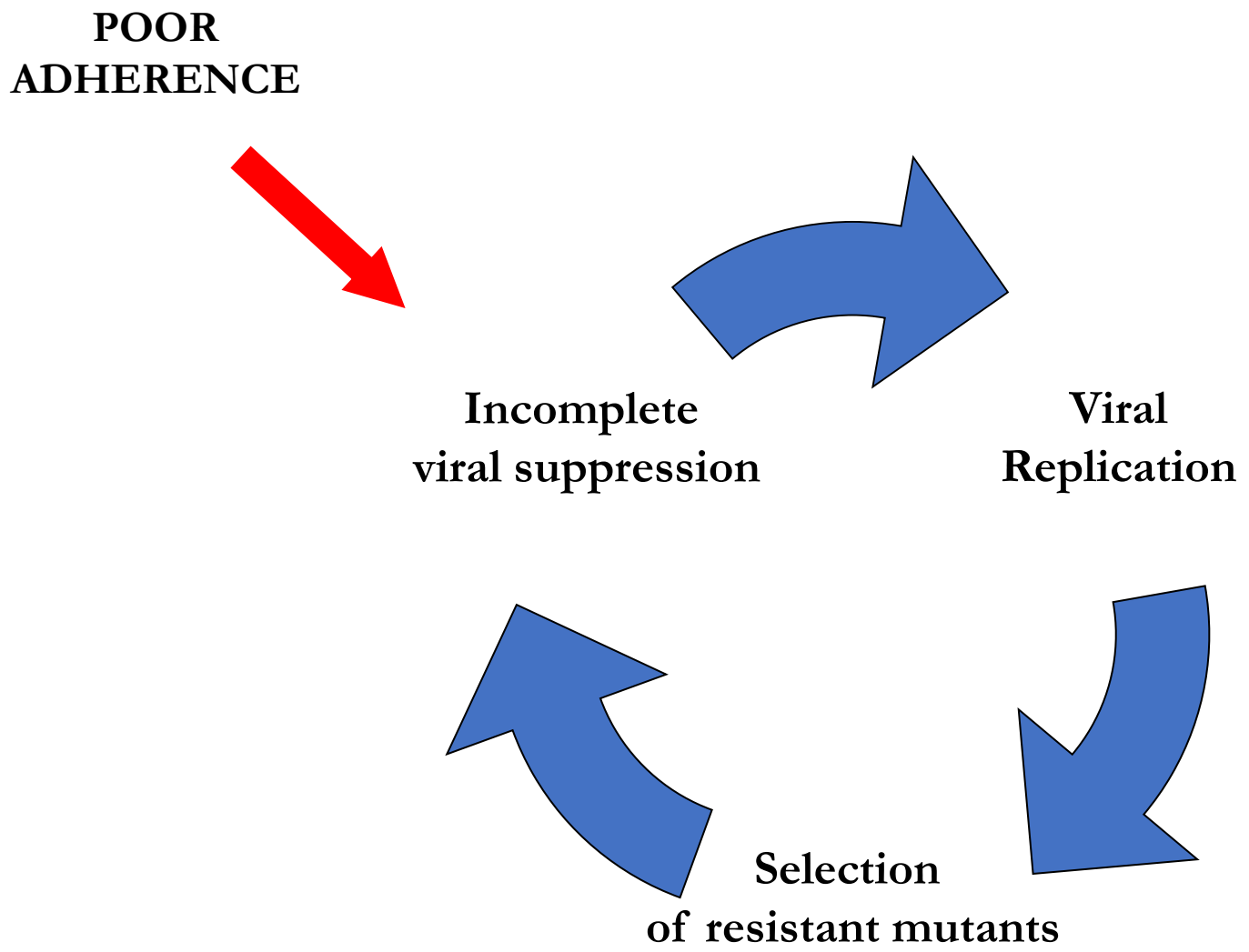


M184V

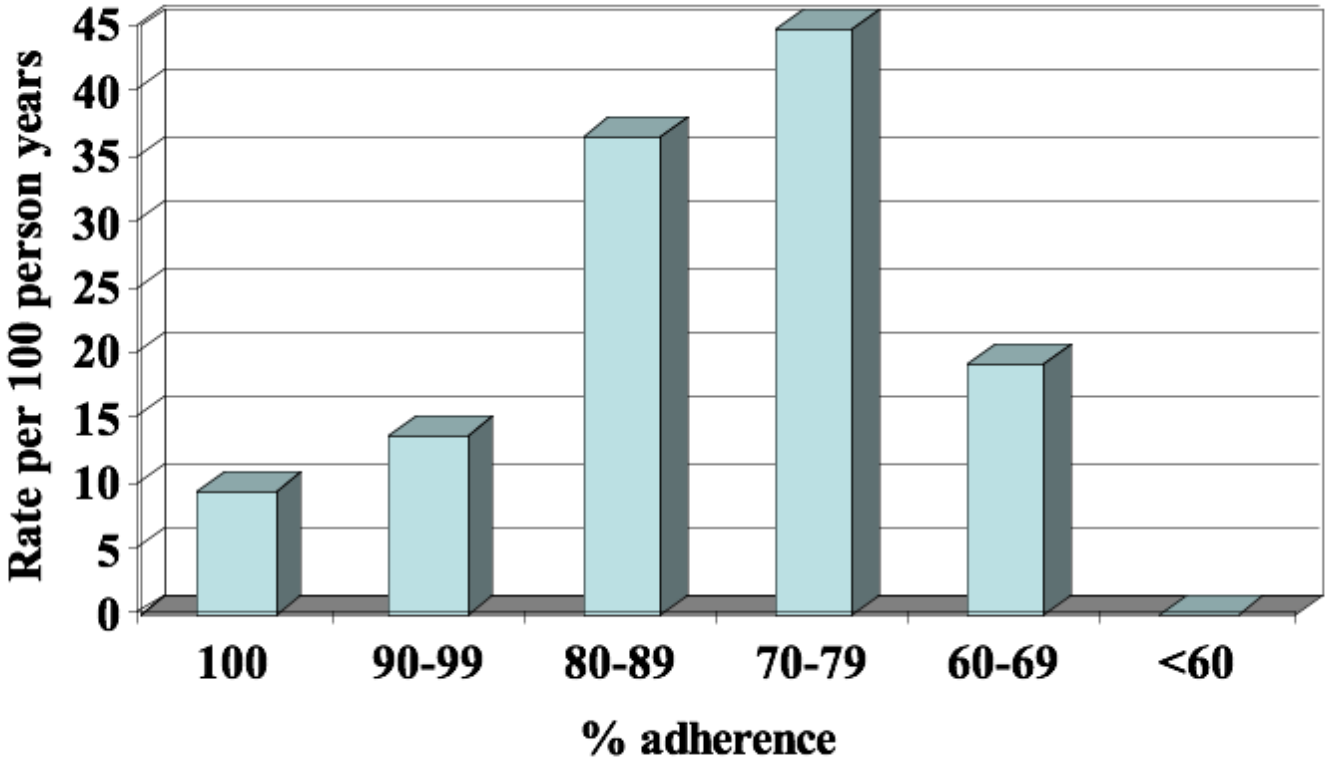
M184V resistance mutation is a methionine to valine substitution at position 184 in RT that prevents 3TC from binding to propogating viral DNA chain

X

HIV replication <u>not</u> inhibited


POOR
ADHERENCE
Incomplete
viral suppression
Viral
Replication
Selection
of resistant mutants

Relationship between resistance & adherence



Clinical Infectious Diseases 2003; 37:1112–8

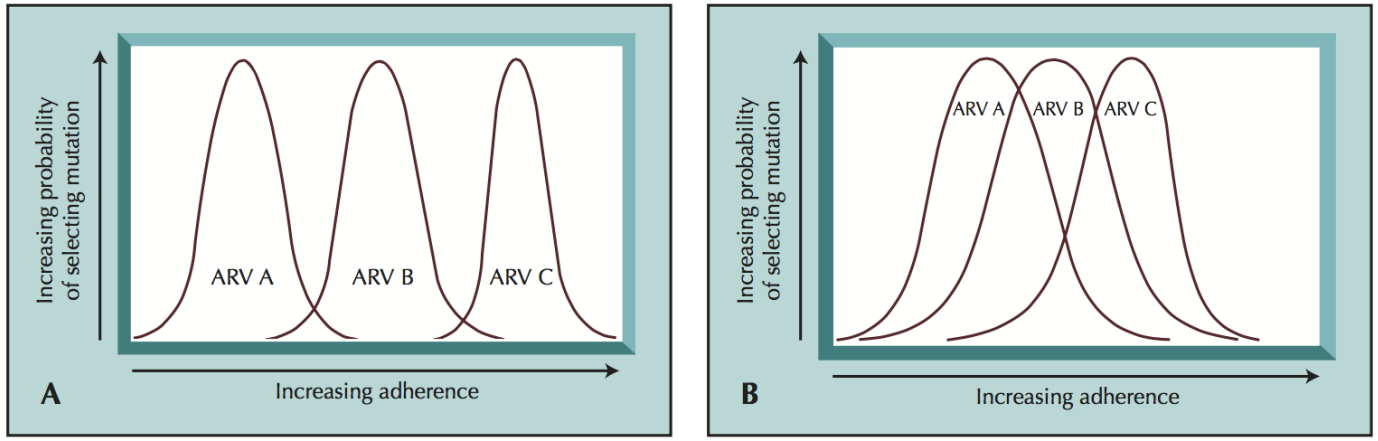


Figure 2. A, Nonoverlapping adherence-resistance windows minimize risk of resistance to each antiretroviral (ARV) medication. **B,** Overlapping adherence-resistance windows create range of adherence that select for resistance to multiple medications.

"the window of adherence that optimally selects for NNRTI resistance is likely between 2% and 60% adherence"

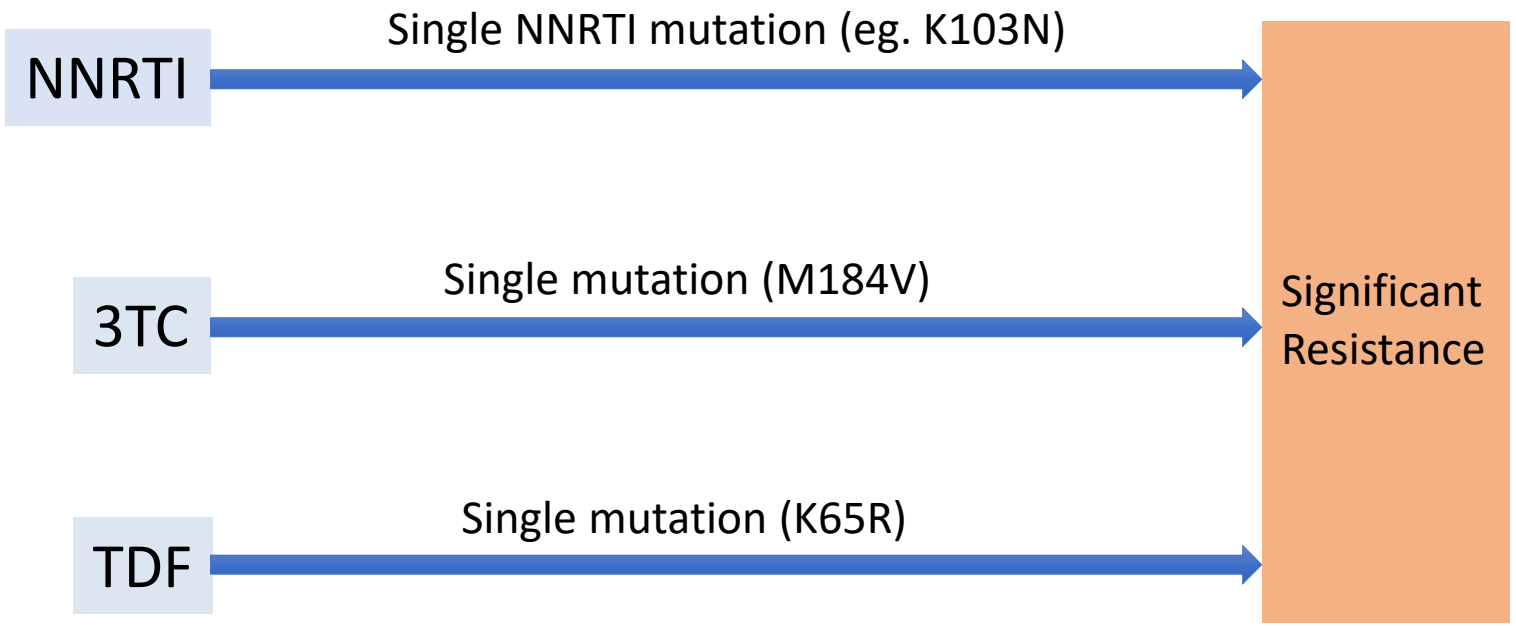
Bangsberg, Current HIV/AIDS Reports 2007

Possible resistance at 1st line failure

- Single mutations compromise each of the drugs
  - "Low genetic barrier" therefore resistance at failure common
- Tenofovir selects for **K65R**
  - Tenofovir and abacavir resistance
  - Hypersusceptibility to AZT
- FTC selects for **M184V**
  - Resistance to FTC and 3TC
- Efavirenz selects for **K103N** or other NNRTI mutations
  - Single mutation causes high-level resistance to efavirenz and nevirapine

Accumulation of Resistance

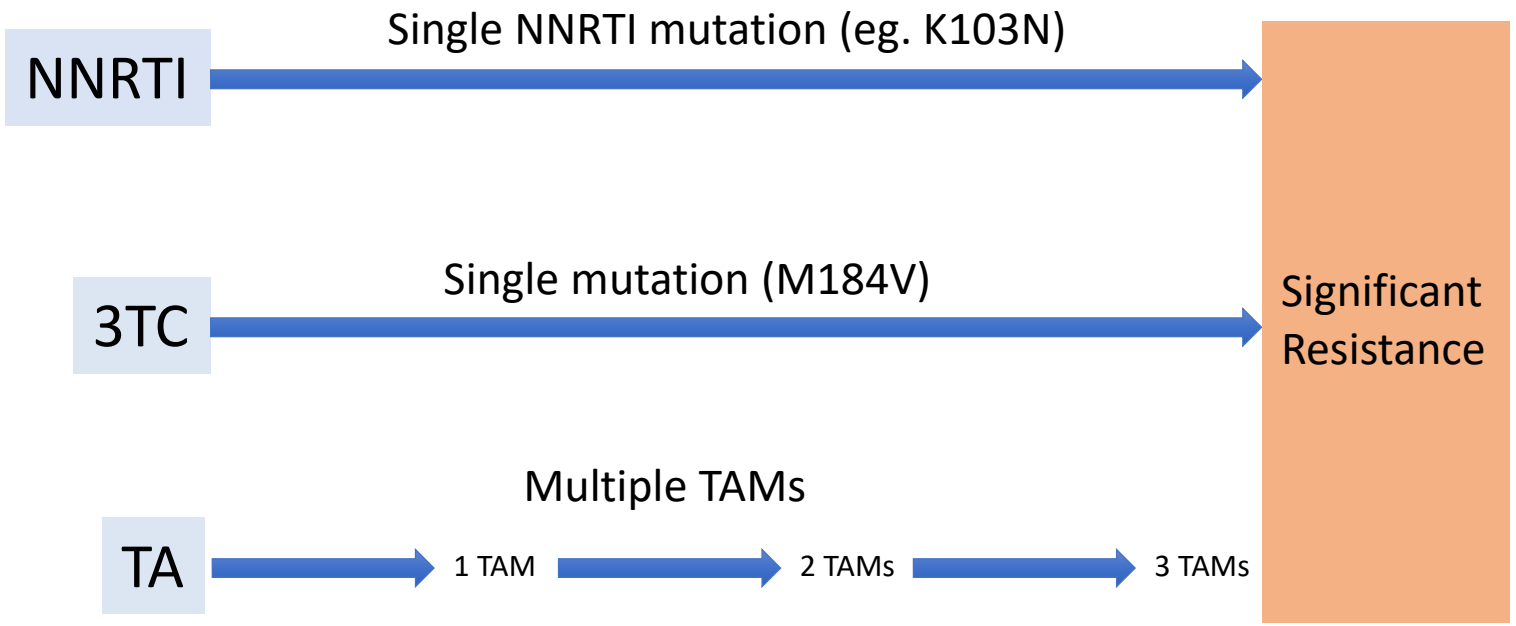
Tenofovir + 3TC + NNRTI regimen



NNRTI = Non-nucleoside reverse transcriptase inhibitor (Nevirapine or Efavirenz)

Accumulation of Resistance

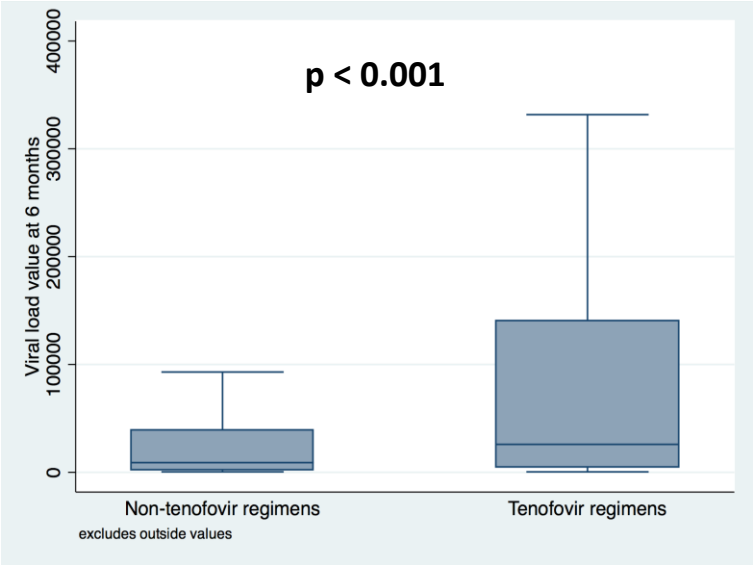
Thymidine analogue + 3TC + NNRTI regimen



TA = Thymidine analogue (D4T or AZT)
NNRTI = Non-nucleoside reverse transcriptase inhibitor (Nevirapine or Efavirenz)
TAMs = Thymidine analogue mutations. These accumulate gradually over months to years;
3 to 4 TAMs are required to confer high level resistance to D4T and AZT.

Viral load value if viraemic

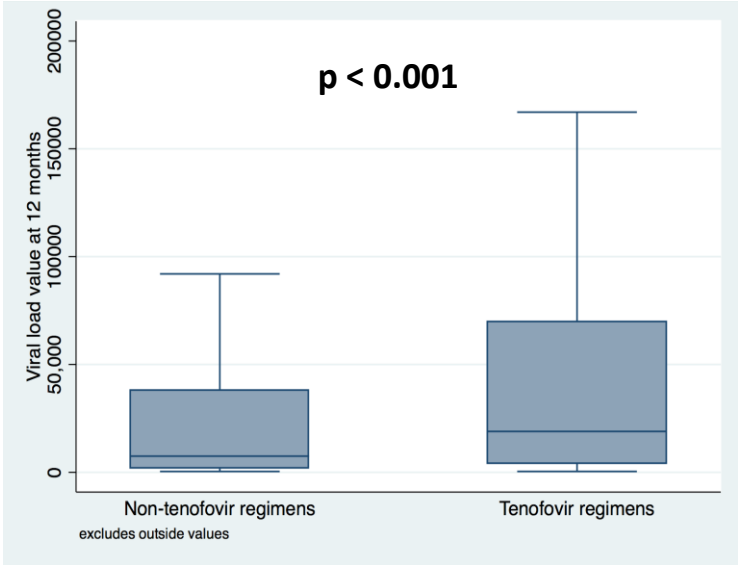
6 months



Median 9,000
(IQR 1,900 – 39,000)

Median 25,909
(IQR 4,512 – 140,392)

12 months



Median 7,500
(IQR 1,900 - 38,000)

Median 18,963
(IQR 4,044 -69,575)

No difference in viral load at 24 months:
Median 7,880 (TDF) vs 9,521 (non-TDF) (p=0.98)

Meintjes, unpublished

J Antimicrob Chemother 2017; **72**: 210–219
doi:10.1093/jac/dkw358 Advance Access publication 22 September 2016

Journal of Antimicrobial Chemotherapy

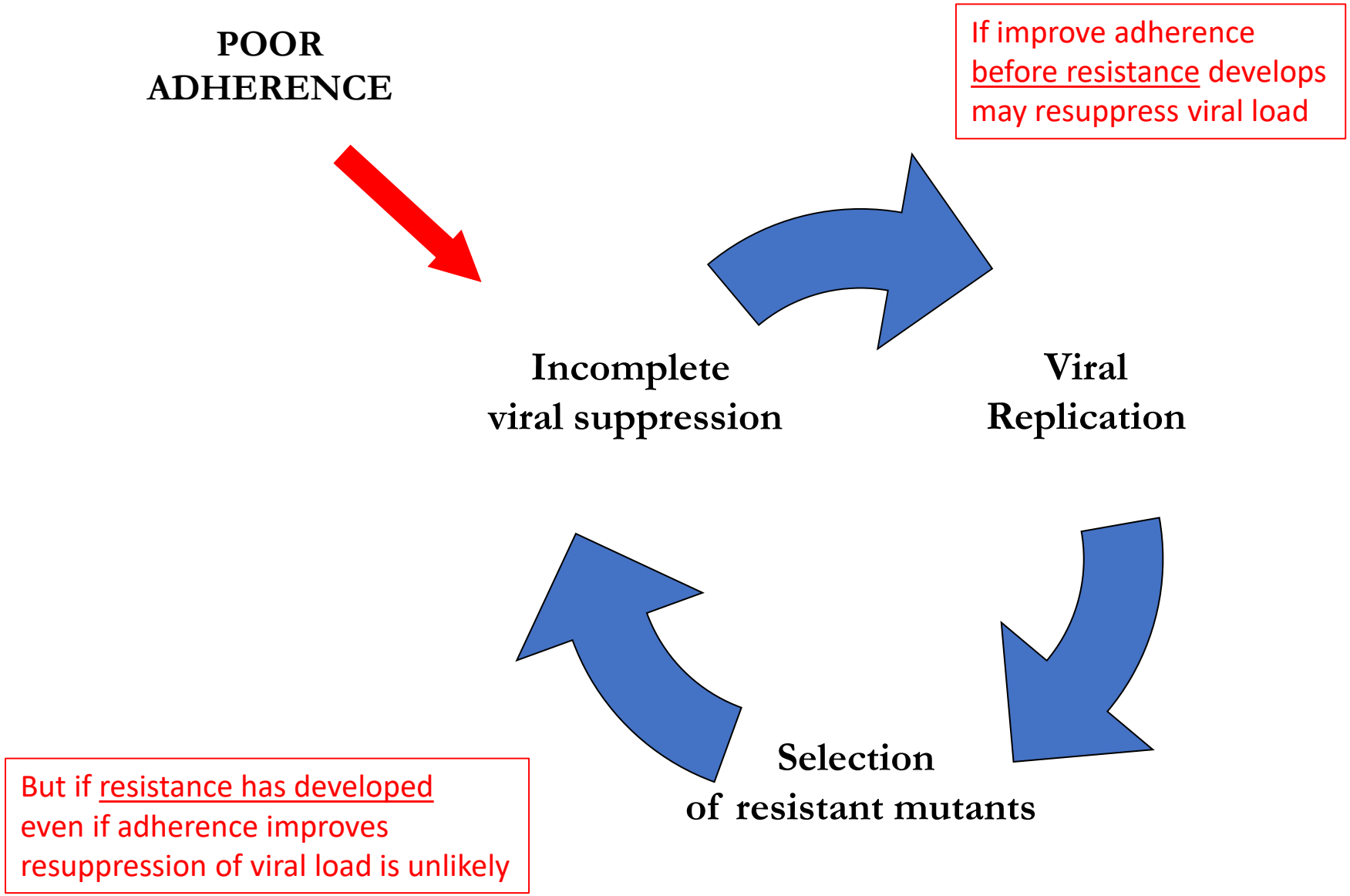
HIV-1 antiretroviral drug resistance patterns in patients failing NNRTI-based treatment: results from a national survey in South Africa

K. Steegen[1]*, M. Bronze[2], M. A. Papathanasopoulos[1], G. van Zyl[2,3], D. Goedhals[2,4], E. Variava[5–7], W. MacLeod[8,9], I. Sanne[10], W. S. Stevens[1,2] and S. Carmona[1,2]

- Adult surveillance resistance testing from all provinces (n=788)
- Patients failing 1st line (median 36 months on ART)
- M184V/I in 83%
- K65R in 58% failing TDF without prior D4T
- NNRTI mutations > 90%

DOH: Indication for switching to 2nd line

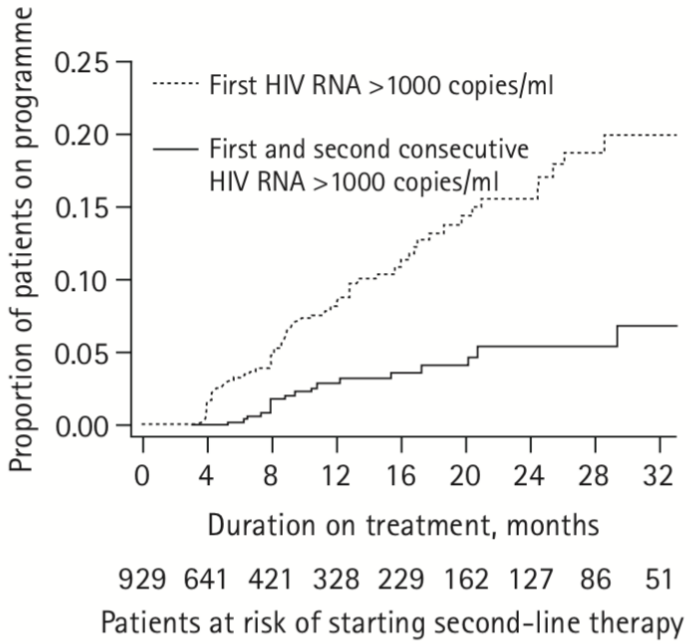
- Two viral loads > 1000 copies/ml
- Taken 2 months apart
- With an adherence intervention in between


POOR
ADHERENCE
If improve adherence
before resistance develops
may resuppress viral load
Incomplete
viral suppression
Viral
Replication
Selection
of resistant mutants
But if resistance has developed
even if adherence improves
resuppression of viral load is unlikely

Early adherence intervention for viraemia

- Targeted intervention if VL >1000:
  - Pill box and dosing diary
  - Increased frequency of home visits
  - Re-attended the 3 education sessions
  - Only once the patient's VL had fallen below 50 was the alert status removed and routine visits recommenced
- By 32 months: 20% had a VL >1000
- Virological failure subsequently confirmed in only 29% of these patients

Figure 3. Kaplan–Meier failure estimate for time to first, then second consecutive HIV RNA level >1,000 copies/ml



Orrell, Antiviral Therapy 2007;12:83

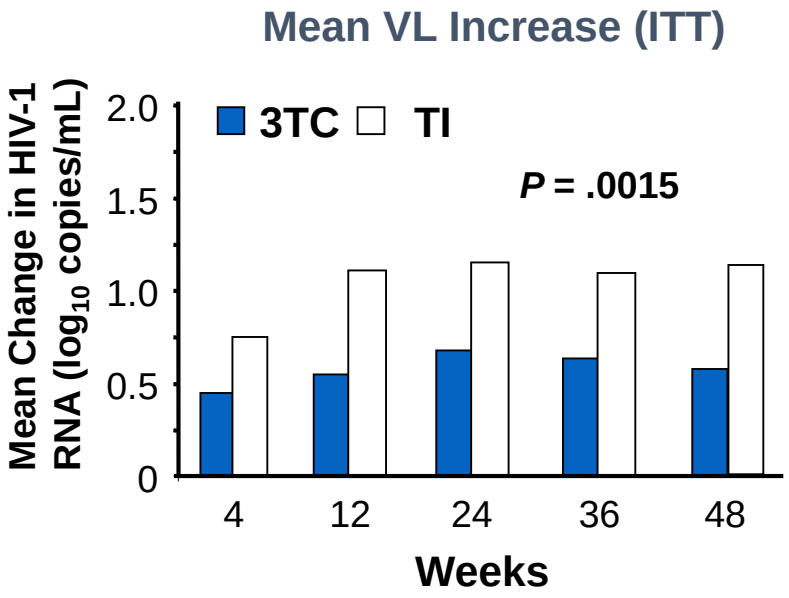
Switching from 1st to 2nd line

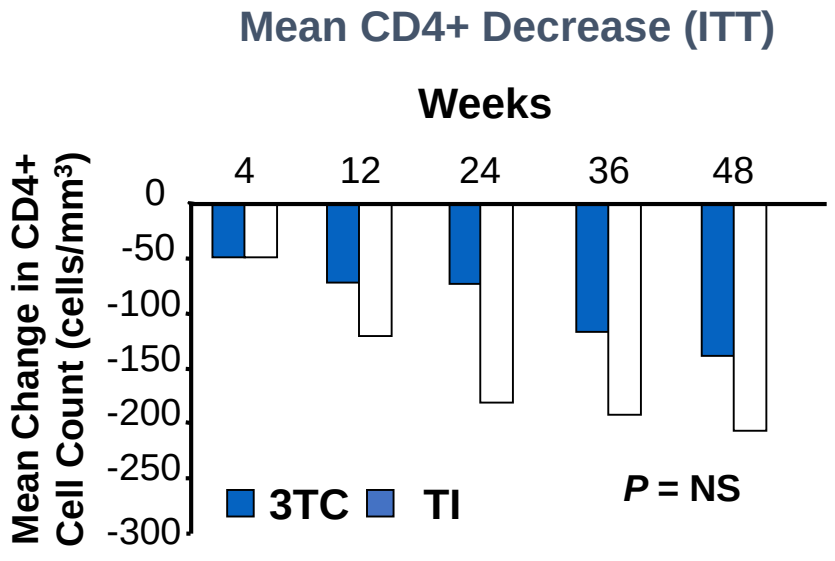
1st line	2nd line	Comment
TDF	AZT	No cross resistance K65R sensitizes virus to AZT
FTC	3TC	M184V results in complete cross-resistance
EFV	LPV/r	Class switch

M184V selected by 3TC or FTC

- Single mutation required for high level resistance to 3TC & FTC
- Reduces viral fitness by 1/3
- Slows selection of TAMs
- When it occurs with TAMs, increases susceptibility to AZT
- Also resensitizes to TDF in presence of K65R

3TC Alone vs Treatment Interruption in Patients Failing 3TC-Based ART





Castagna A, et al. IAS 2005. Abstract WeFo0204.

How does our 2nd line perform in the presence of NRTI resistance?

EARNEST trial

HIV+ adults/adolescents
More than 12 months NNRTI first line
No previous PI
WHO clinical, immunological, virological failure
VL > 400 copies/ml

n=1277 randomised 1:1:1

2 or 3 NRTIs + Lopinavir/r

Lopinavir/r + Raltegravir

Lopinavir/r + Raltegravir for 12 weeks

Lopinavir/r monotherapy

NRTIs selected based on clinical algorithm

Paton
NEJM 2014

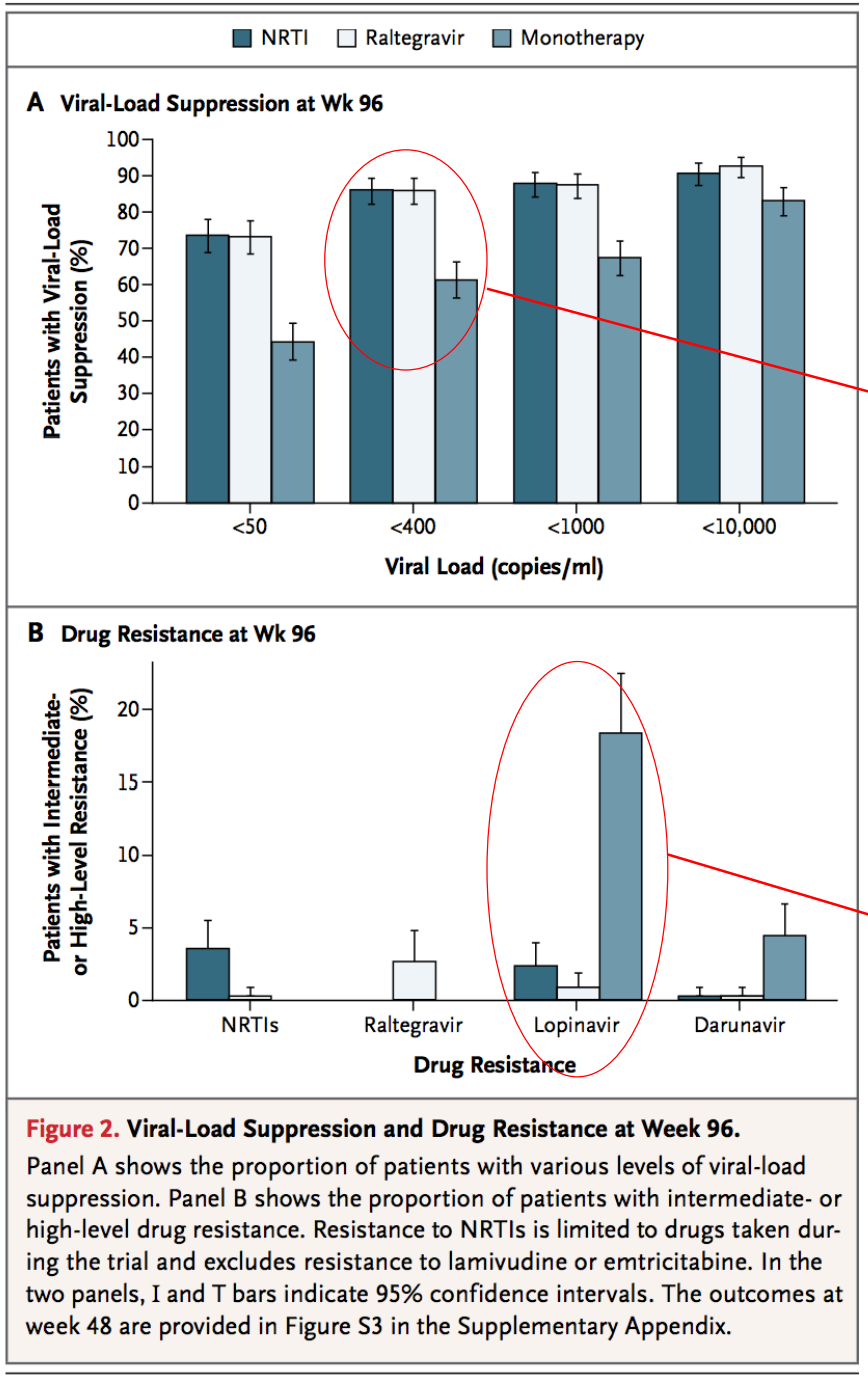


Figure 2. Viral-Load Suppression and Drug Resistance at Week 96.
Panel A shows the proportion of patients with various levels of viral-load suppression. Panel B shows the proportion of patients with intermediate- or high-level drug resistance. Resistance to NRTIs is limited to drugs taken during the trial and excludes resistance to lamivudine or emtricitabine. In the two panels, I and T bars indicate 95% confidence intervals. The outcomes at week 48 are provided in Figure S3 in the Supplementary Appendix.

VL < 400 at 96 weeks

NRTI arm = 86% (was 86% at wk 144)

Monotherapy = 61%

Raltegravir arm = 86% (was 81% at wk 144)

Intermediate/high level resistance to lopinavir

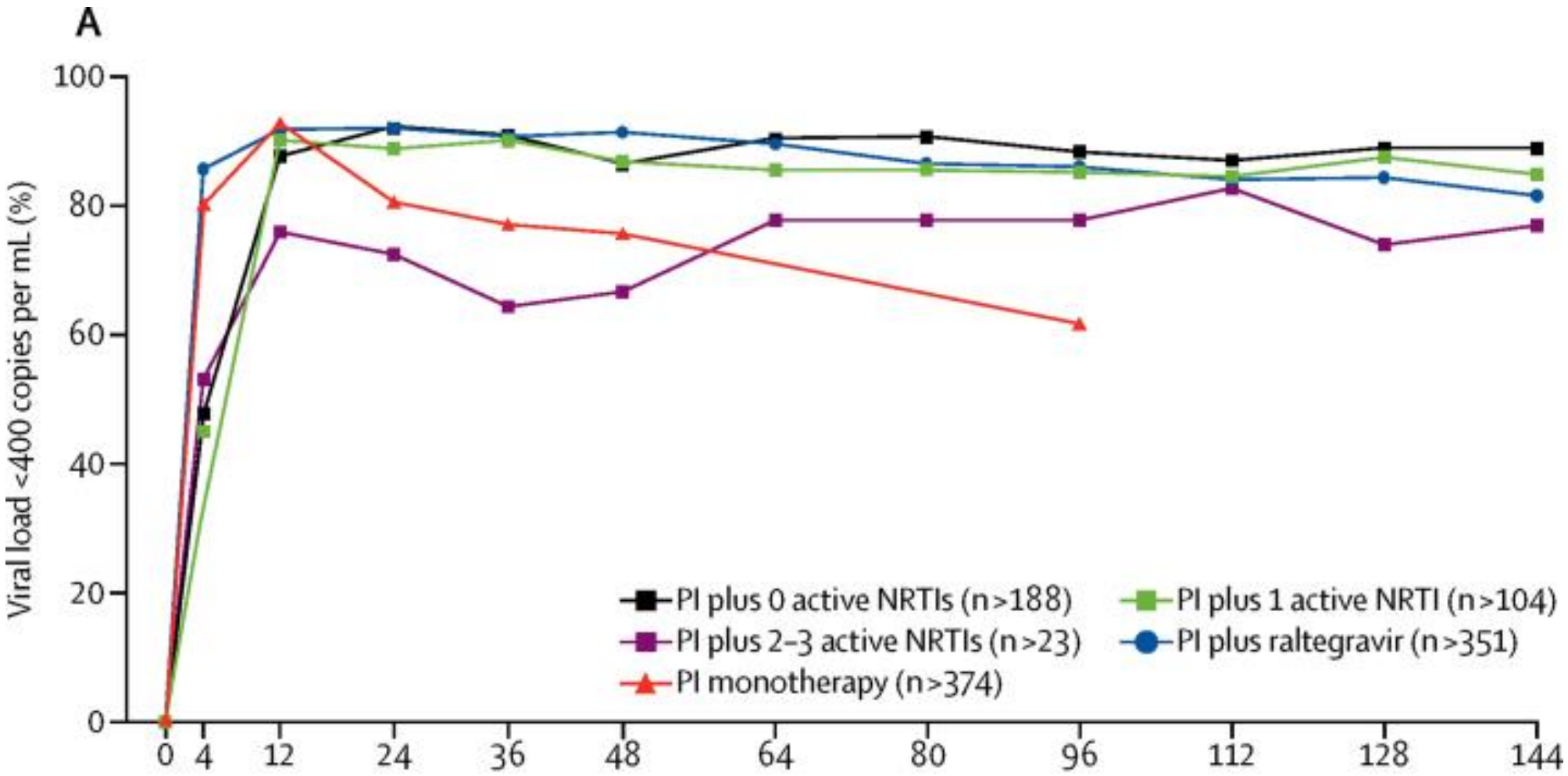
2% NRTI arm

1% Raltegravir am

18% monotherapy

Table S2: NRTI susceptibility at randomization in the PI/NRTI arm

	PI/NRTI participants N (%)
Total with baseline genotypes available	391 (100%)
Intermediate-high level resistance to	
- Tenofovir	223 (57%)
- Zidovudine	290 (74%)
- Lamivudine	371 (95%)
- Emcitrabine	71 (95%)
- Abacavir	318 (81%)
- Didanosine	301 (77%)
- Stavudine	309 (79%)
Number of NRTIs in initial second-line regimen with no more than low-level resistance	
- 0	230 (59%)
- 1	128 (33%)
- 2	33 (8%)



Weeks

Paton
Lancet HIV 2017

	Treatment	Active NRTIs	HIV RNA suppression
EARNEST (HIV RNA <400 copies per mL; week 144)	Two NRTIs plus ritonavir-boosted lopinavir	0	176/198 (89%)
		1	95/112 (85%)
		2	20/26 (77%)
SECOND-LINE (HIV RNA <500 copies per mL; week 96)	Two NRTIs plus ritonavir-boosted lopinavir	0–0·75	61/66 (92%)
		1	69/80 (86%)
		1·25–3	56/69 (81%)
ODIN (HIV RNA <50 copies per mL; week 48)	Two NRTIs plus ritonavir-boosted darunavir	0	31/34 (91%)
		1	101/128 (79%)
		2 or more	276/412 (67%)
DAWNING (HIV RNA <50 copies per mL; week 24)	Two NRTIs plus dolutegravir	<2	212/251 (84%)
		2	45/61 (74%)
DAWNING (HIV RNA <50 copies per mL; week 24)	Two NRTIs plus ritonavir-boosted lopinavir	<2	180/248 (73%)
		2	35/64 (55%)

NRTIs=nucleoside reverse-transcriptase inhibitors.

***Table:* HIV RNA suppression rates by number of active NRTIs, in four randomised trials**

Hill and Venter
Lancet Infect Dis 2017

No activity from NRTI defined by intermediate or high level resistance (Stanford score 30 or more)

Baseline HIV-1 resistance, virological outcomes, and emergent resistance in the SECOND-LINE trial: an exploratory analysis

Mark A Boyd, Cecilia L Moore, Jean-Michel Molina, Robin Wood, Juan S Madero, Marcelo Wolff, Kiat Ruxrungtham, Marcelo Losso, Boris Renjifo, Hedy Teppler, Anthony D Kelleher, Janaki Amin, Sean Emery, David A Cooper, for the SECOND-LINE study group

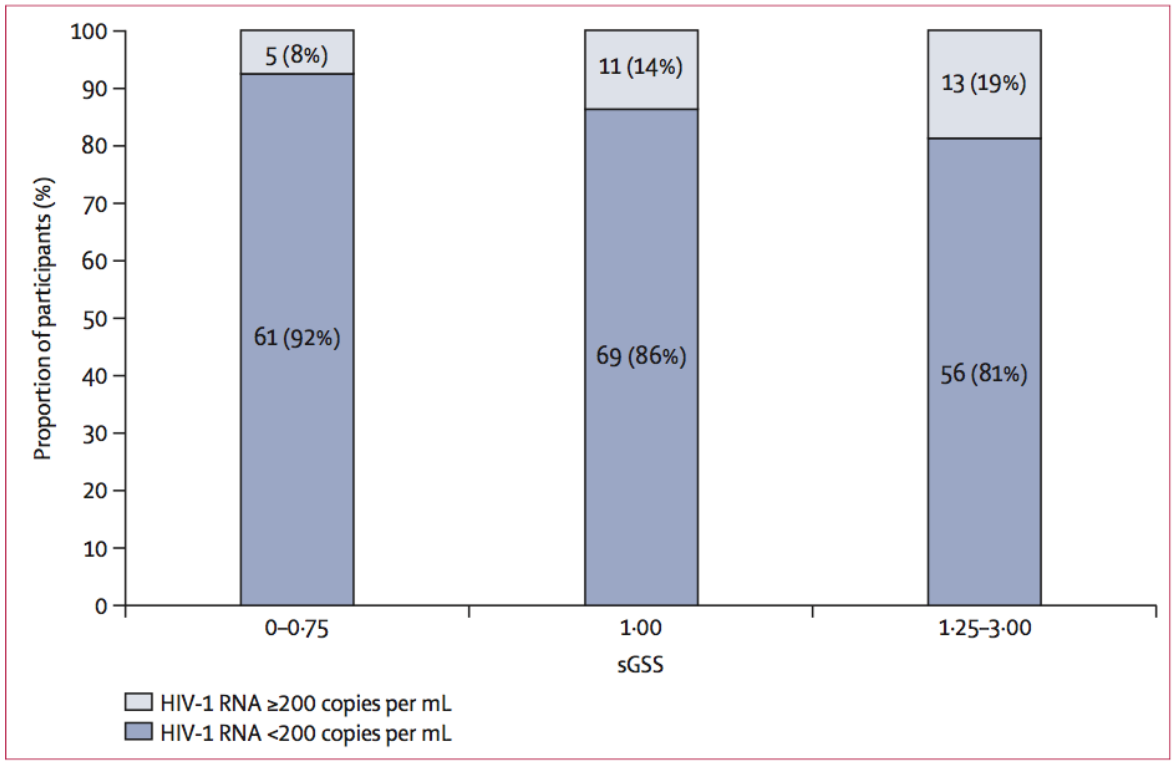


Figure 3: **Frequency of virological failure at 96 weeks by sGSS at baseline in the NtRTI group**
sGSS is the number of active NtRTIs in the regimen. sGSS=specific genotype sensitivity score. NtRTI=nucleoside or nucleotide reverse transcriptase inhibitor.

<u>sGSS = specific genotypic sensitivity score of NRTIs patient on summed</u>:

0 = High-level resistance
0.25 = Intermediate resistance
0.5 = Low-level resistance
0.75 = Potential low-level resistance
1 = Susceptible

Lancet HIV 2015

Potential explanations for residual NRTI effect

- Fitness cost associated with NRTI mutations
- Residual antiviral effect of NRTIs despite mutations and *in vitro* phenotypic resistance
- Increased susceptibility to PI/r due to less fit virus?

Important caveat: NRTIs were switched in all these studies
TDF/FTC to AZT/3TC and visa versa

Possible resistance at 2nd line failure

- This regimen has “high genetic barrier” to resistance because of the boosted PI

- AZT selects for **thymidine analogue mutations (TAMs)**
  - M41L, D67N, K70R, L210W, T215Y/F and K219Q/E
  - Need 2-3 out of 6 TAMs to cause significant AZT resistance
  - Thus gradual accumulation of resistance

- For 3TC, the **M184V** is typically present when start this regimen

- Lopinavir selects for **PI mutations (major and minor)**
  - Need multiple mutations for significant resistance
  - Unusual for resistance in the first 2 years of taking the drug
  - Most patients failing 2nd line early on do not have PI resistance

OPEN ACCESS Freely available online

PLoS one

Virologic Failure of Protease Inhibitor-Based Second-Line Antiretroviral Therapy without Resistance in a Large HIV Treatment Program in South Africa

Julie H. Levison[1,2,4*], Catherine Orrell[3☯], Sébastien Gallien[4,6☯], Daniel R. Kuritzkes[4,6], Naishin Fu[1], Elena Losina[1,5,6], Kenneth A. Freedberg[1,2,5,6], Robin Wood[3]

43/322 (13%) adults/adolescents patients with virologic failure on 2nd line

33 resistance test (mean time from start 2nd line to resistance test =17 months)

- **22 patients (67%) had wild-type virus**
- **No major resistance to PIs found**
- **Most mutations were NNRTI mutations (residual fromn 1st line)**

PLoS One 2012

Predicting PI resistance on 2nd line

- SA private sector
- PI resistance in 146/339 (43%) failing second line

- Significantly associated with:
  - Age (aOR for 10 year increase = 1.9)
  - PI duration (aOR per year = 1.1)
  - Adherence (aOR per 10% increase = 1.2)

Table 4. Clinical prediction rule for major PI resistance mutations

Risk factor	Points assigned
Age (years)	
18-29	0
30-39	2
40-49	4
50-59	6
60-65	8
Duration on PI (years)	
<2 years	0
2-4 years	1
5-11 years	3
Adherence last 4 months	
0-39%	0
40-59%	2
60-79%	3
80-100%	4

Score	Predicted probability	Sensitivity	Specificity
0-2	≤8.6%	100%	≤2%
3	11.8%	99%	8%
4	15.8%	99%	12%
5	20.9%	98%	19%
6	27.2%	94%	31%
7	34.5%	82%	48%
8	42.6%	75%	67%
9	51.1%	60%	75%
10	59.6%	38%	85%
11	67.5%	32%	90%
12	74.6%	5%	98%
13	80.5%	5%	98%
14-15	≥85.4%	≤1%	100%

Cohen, Abstract 604, CROI 2015

MUTATIONS IN THE PROTEASE GENE ASSOCIATED WITH RESISTANCE TO PROTEASE INHIBITORS[p,q,r]

	L	G	K	L	V	L	E	M	M	G	I	F	I	D	I	I	A	G	V	I	I	N	L	I
Atazanavir +/- ritonavir[s]	10	16	20	24	32	33	34	36	46	48	**50**	53	54	60	62	64	71	73	82	**84**	85	**88**	90	93
	I	E	R	I	I	I	Q	I	I	V	L	L	L	E	V	L	V	C	A	V	V	V	S	M	L
	F		M			F		L	L			Y	V			M	I	S	T						M
	V		I			V		V					M			V	T	T	F						
	C		T										T				L	A	I						
			V										A												
Darunavir/ ritonavir[t]		V			V	L			I		I		I					T		I		L		
		11			32	33			**47**		**50**		**54**					74	**76**	**84**		89		
		I			I	F			V		V		M					P	V	V		V		
													L											
Fosamprenavir/ ritonavir	L				V				M	I	I		I				G		L	V		I		L
	10				32				46	47	**50**		54				73		76	82		**84**		90
	F				I				I	V	V		L				S		V	A		V		M
	I								L				V							F				
	R												M							S				
	V																			T				
Indinavir/ ritonavir[u]	L		K	L	V			M	M		I						A	G	L	V	V	I		L
	10		20	24	32			36	**46**		54						71	73	76	77	**82**	**84**		90
	I		M	I	I			I	I		V						V	S	V	I	A	V		M
	R		R						L								T	A			F			
	V																				T			
Lopinavir/ ritonavir[v]	L		K	L	V	L			M	I	I	F	I		L		A	G	L		V	I		L
	10		20	24	**32**	33			46	**47**	50	53	54		63		71	73	**76**		**82**	84		90
	F		M	I	I	F			I	V	V	L	V		P		V	S	V		A	V		M
	I		R						L	A			L				T				F			
	R												A								T			
	V												M								S			
													T											
													S											

PROTEASE INHIBITOR MUTATIONS

2017 IAS-USA Resistance Mutations Update

Darunavir cross-resistance

- 2+ these mutations at baseline associated with a decreased virologic response to DRV/r (some have greater effect):
  - V11I
  - V32I
  - L33F
  - I47V
  - I50V
  - I54L or M
  - T74P
  - L76V
  - I84V
  - L89V
- V82A has positive impact on virologic response

2017 IAS-USA Resistance Mutations Update

Key messages

- 1st line has low genetic barrier to resistance, but if intervene early when not suppressed (with adherence intervention) many will re-suppress

- 2nd line has high genetic barrier to resistance and most patients failing do not yet have resistance, but require improved adherence. This changes after several years on ART.