

HIV Drug Resistance in KwaZulu-Natal, second line failure and third line ARVs

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Question 1: Will drug resistance jeopardize the National HIV treatment?

A) Yes

B) Maybe

C) No

D) No idea

What is the SATuRN?

a network consisting of biomedical scientists, clinicians, epidemiologists and public health experts



SATuRN managed at the UKZN and the SA-MRC

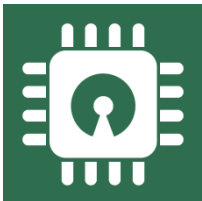
CURRENT PARTNERS includes 24 partners in southern Africa (including CAPRISA ACC)

SETUP A RESISTANCE NETWORK ONE OF THE OBJECTIVES of a previous European Commission MRC funding. Funding complemented by US CDC (2008-present).

Collaborators & implementation sites
info at www.bioafrica.net/saturn/

SATuRN Vision

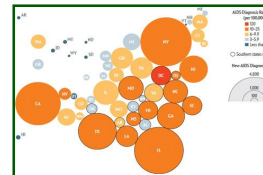
Develop advanced yet affordable HIV & TB drug resistance diagnostics, implement it at primary health care clinics in resource limited settings and create a collaborative system for surveillance, research and capacity building.



**ADVANCED
DIAGNOSTICS**



**PHC
CLINICS**



**SURVEILLANCE
& RESEARCH**

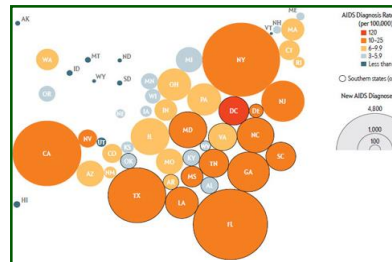


**COLLABORATION &
CAPACITY BUILDING**

HIV-1 drug resistance levels in KZN.

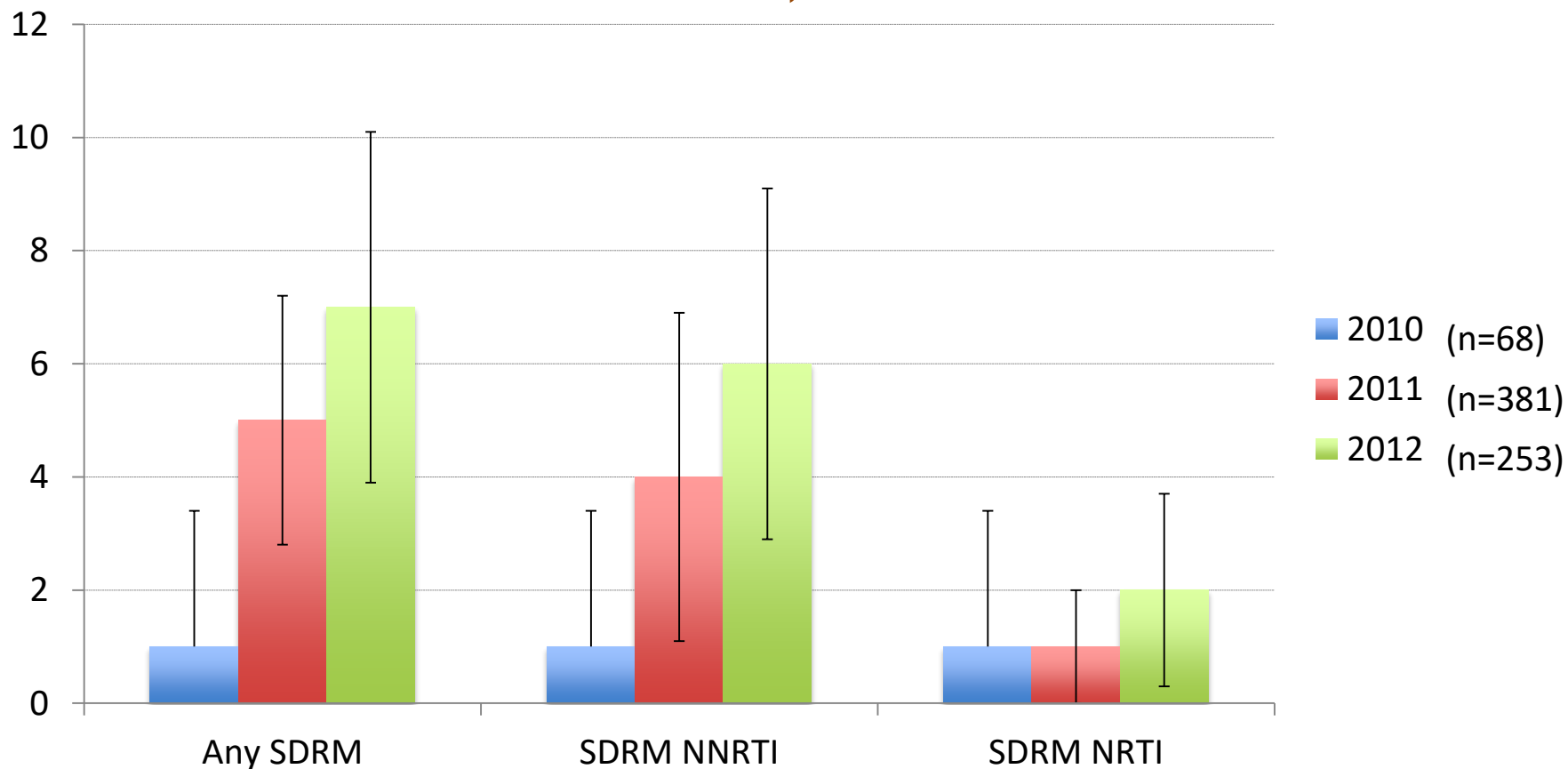
As part of CAPRISA ACC we summarize the current levels of HIV-1 drug resistance in KZN.

The data was collated from NHLS, StanfordHIVDB CAPRISA and from published results from other cohorts in KZN (e.g. Africa Centre, Hlabisa).



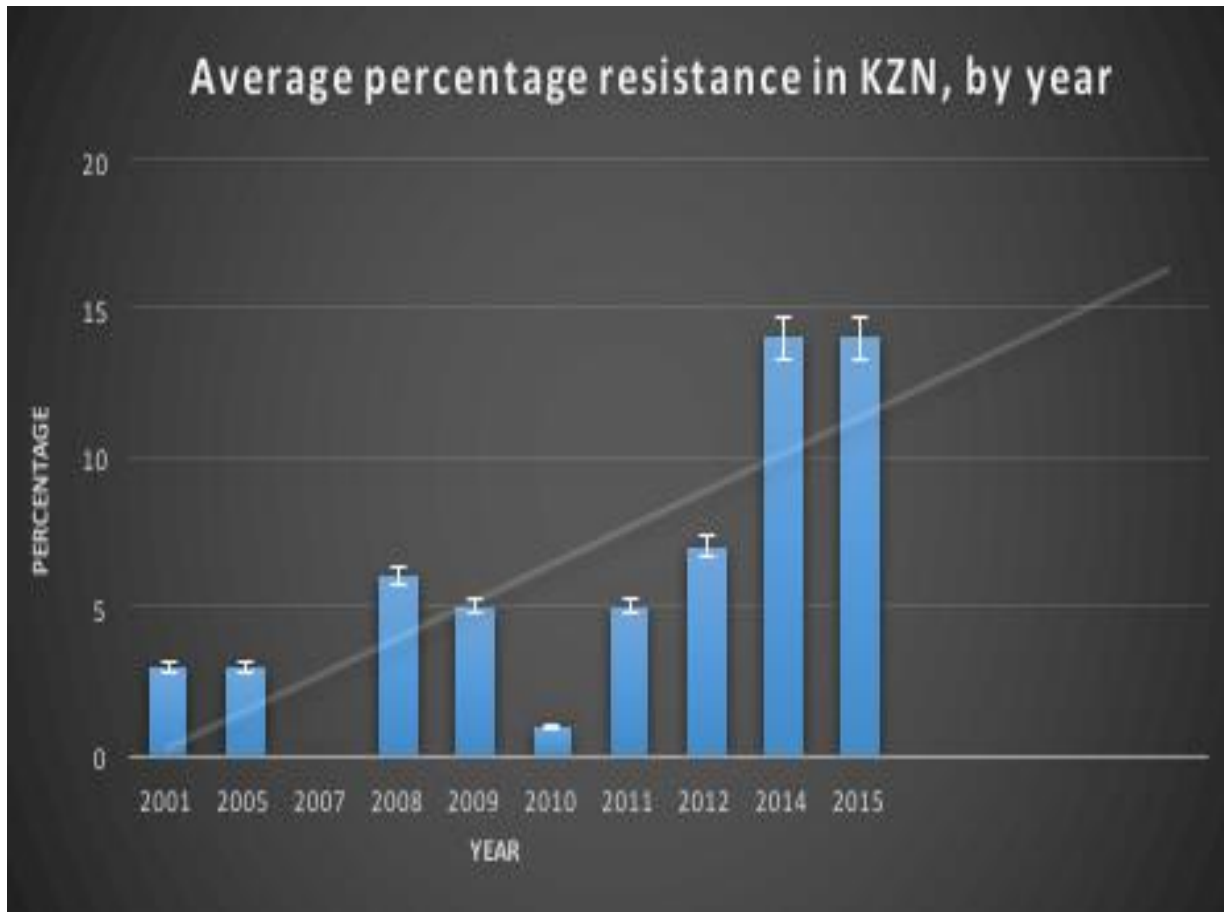
**SURVEILLANCE
& RESEARCH**

Surveillance of Drug Resistance Mutations (SDRM) increasing in treatment naïve patients (i.e. Transmitted) in KZN



Hlabisa sub-district: No TDR was detected in 2010. 2011 and 2012 TDR levels were 4.7% and 7.1% respectively. Chiqs trend test p-value= 0.0024). Majority of the mutations were NNRTI (103, 106), which provide resistance to EFV. Only 0.3% (2/701) had K65R, which is the main mutation to TDF. **Manasa ARHR 2016**

Increasing trend in prevalence of primary resistance in KwaZulu-Natal with new data (2013-2015)

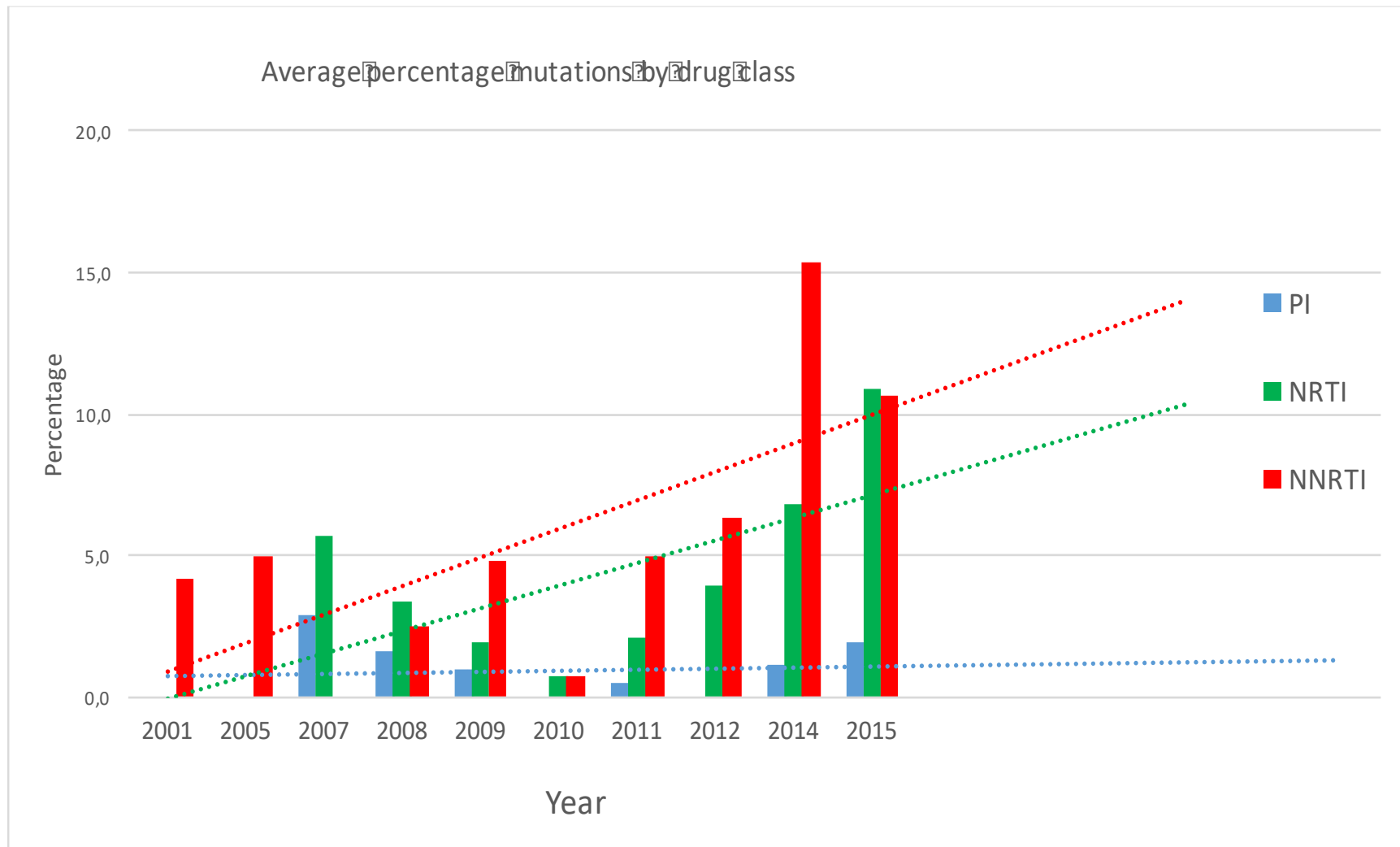


Significant threshold to change 1st line regimens or introduce resistance testing

KZN transmitted resistance: New data confirm an increase trend of transmitted drug resistance. New data include CAPRISA HIPSS (Umgungundlovu) 2014 (n=708) and 2015 (n=470). **Unpublished data.**

Increasing trend in prevalence of primary resistance in KwaZulu-Natal with new data (2013-2015).

Trend by drug class:



Question 2: Is transmission of drug resistance increasing?

A) Yes

B) No

- Concerns have been raised about potential transmission of K65R, main mutation affecting tenofovir regimens...
- Can this mutation be transmitted?

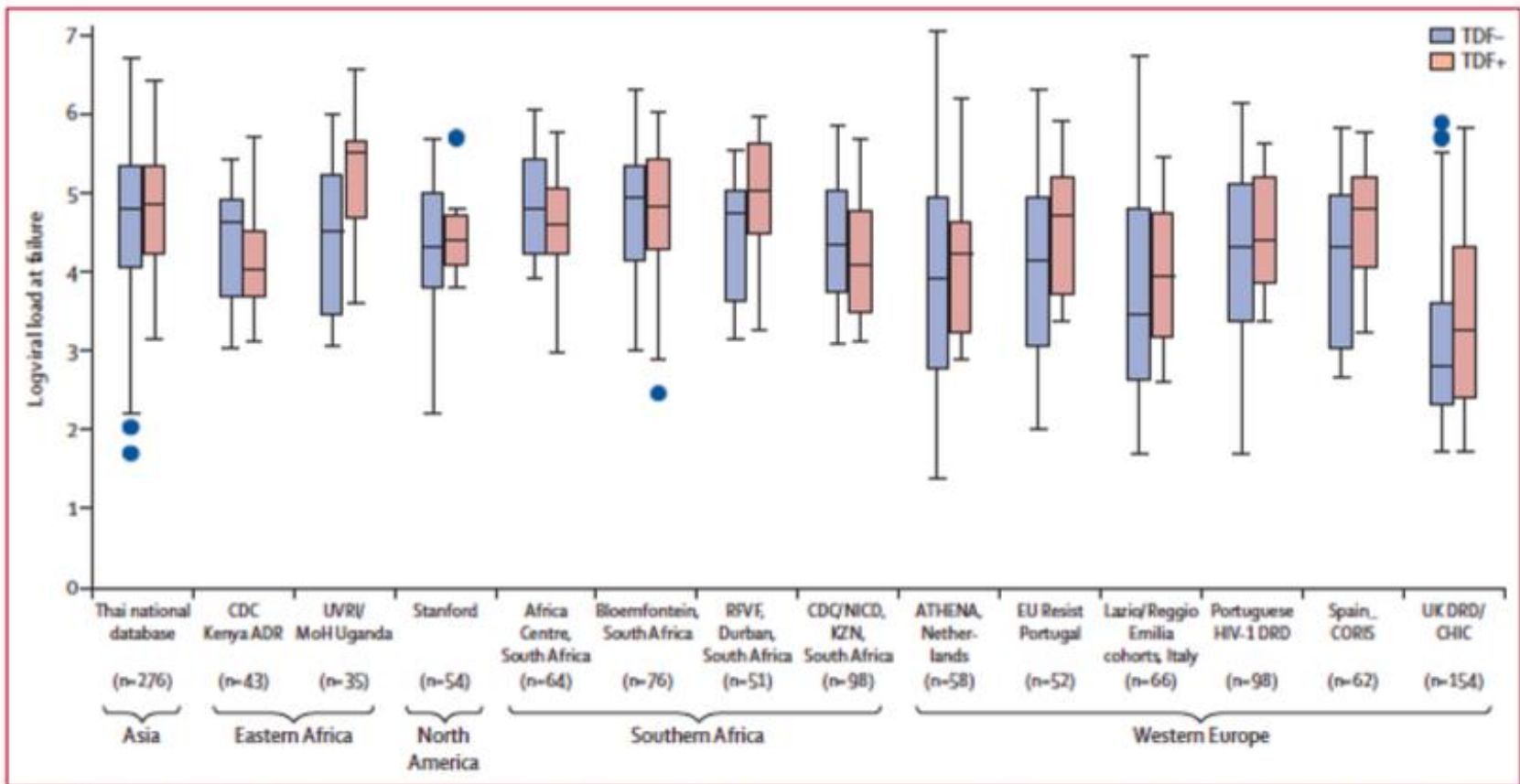


Figure 4: Boxplot of log viral load by presence (TDF-positive) or absence (TDF-negative) of tenofovir resistance at viral failure in studies with at least ten patients with TDF resistance and a viral load measurement at treatment failure

No fitness cost for K65R: Results show that K65R individuals have similar viral load as resistance naïve. There is the potential that K65R transmission of K65R can increase. Our recent data show this mutation at low frequency, but important to survey it as TDR levels are already high in KZN. *The TenoRes Study Group**. *Lancet Infectious Diseases, 2016*

Conclusion : Transmitted resistance

- Transmitted drug resistance seems to be increasing over time
- KZN has the highest level of transmitted resistance in South Africa (> 10%).
- Still low levels of TDF transmitted resistance.
- Need to continue surveillance of transmitted resistance in KZN.
- Need to closely follow viral load monitoring for patients on 1st line therapy as resistance may increase failure rates to first line therapy.

Surveillance of Drug Resistance Mutations (SDRM) in patients failing 1st line ART

Results	Adult* 2010-2013 (n=491)	Children* 2011-2012 (n=90)
Proportion with any HIVDR mutation	82%	83%
Proportion with HIVDR to ≥ 2 drugs	74%	71.8%
GSS for the standard second-line regimen was <2 , suggesting a significantly compromised standard regimen	17%	7%
Average time on therapy	47 months	39 months
Average time on failing regimen	27 months	20 months

- Approximately 15% of Adults and 25% of children have a viral load $> 1,000$ on failing regimen.

Question 4: Which of the factors are involved in the development of failure and drug resistance?

- A) Adherence
- B) Poor absorption
- C) Toxicities
- D) Social issues
- E) All of the above.

Conclusion : 1st line resistance

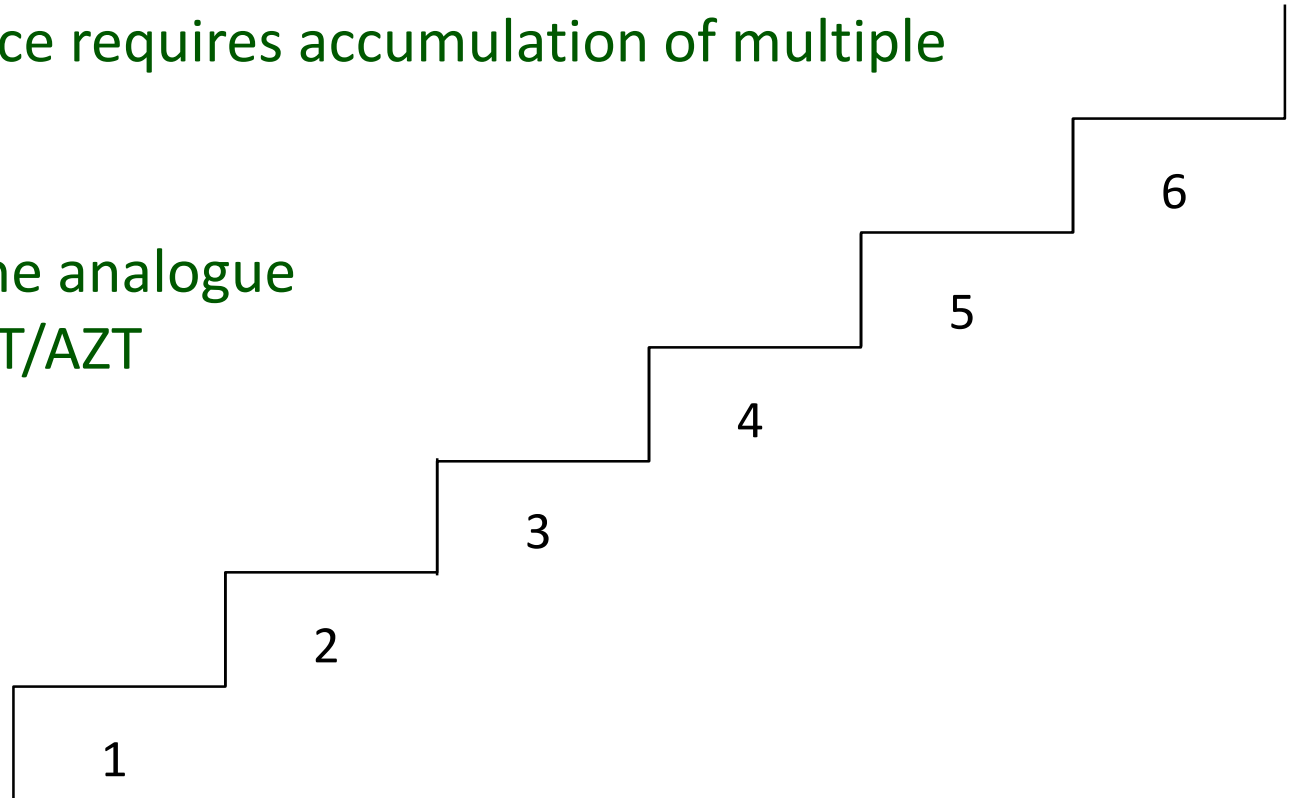
- The majority (> 80%) of patients that FAIL first line therapy have drug resistance mutations.
- Drug resistance testing for first line (or more surveys) do not seem necessary as the results are consistent.
- It is important that national guidelines are followed and patients failing 1st line are switched to 2nd line.
- **It is worrisome** that in many of the publications, patients keep failing 1st line ART for a long time (ranging from 5.7 months to 42 months). This may be one of the reasons why transmitted resistance is on the increase. Furthermore, these patients harbor high level resistance, which may jeopardize 2nd line ART.

Resistance to protease inhibitors

Classically occurs in an ordered stepwise process

High-level resistance requires accumulation of multiple mutations

Similar to thymidine analogue mutations with d4T/AZT



Resistance to lopinavir/ritonavir

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					T			F		
R									L					T		
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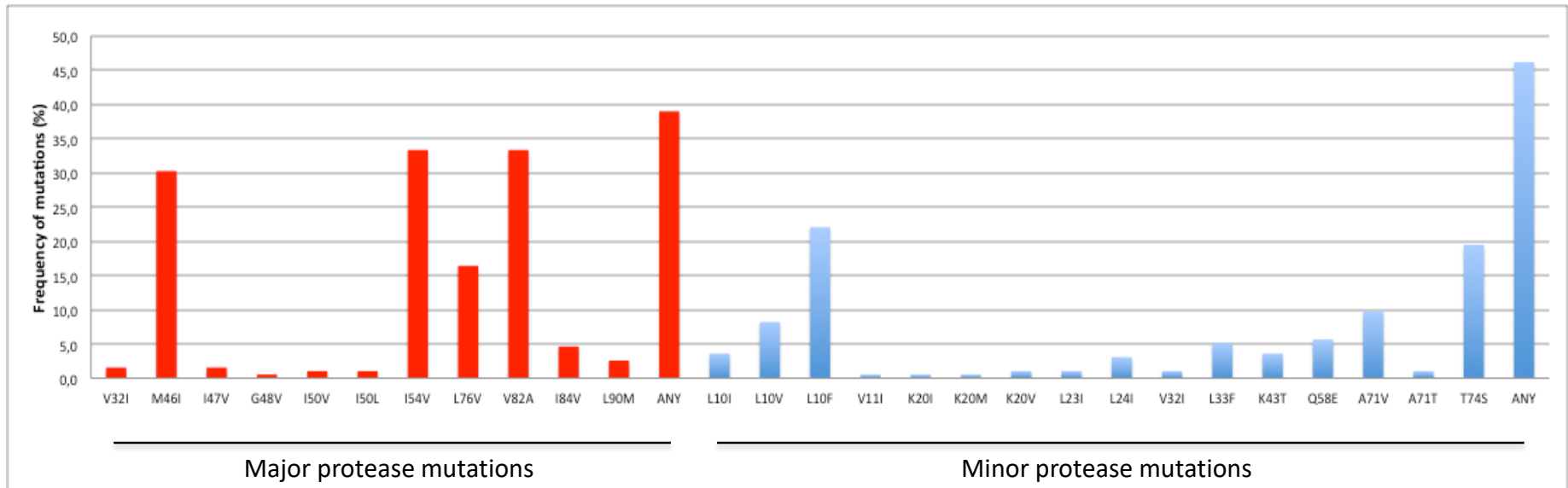
- The accumulation of six or more mutations is associated with reduced virological response to LPVr
- Emerging evidence that specific mutations (I47A, V32I) are associated with high-level resistance

Resistance at second-line ART failure in South Africa

Study author	N	Criteria for genotype	Duration on second-line ART (median)	Drug resistance
Wallis	75	2 x VL >5000	16 months	39% no major DRAM 7% major PI mutations
El-Khatib	35	1 x VL >400	-	6% major PI mutations
van Zyl	33	1 x VL >5000	-	85% no major DRAM 6% major PI mutations
Levison	33	2 x VL >1000	10 months	67% no major DRAM No major PI mutations
Sigaloff	15	1 x VL >1000	>12 months	40% no major DRAM 7% major PI mutations
Berhanu	65	1 x VL >400 then 1 x VL >1000	-	18% no major DRAM 26% PI mutations

Sources: *AIDS Res Treat* 2011; 769627. *AIDS* 2010; 24: 1679. *JAIDS* 2011; 56: 333. *PLoS ONE* 2012; 3: e32144. *JID* 2012; 205: 1739-44; *CROI* 2016 [abstract 1049]

Surveillance of Drug Resistance Mutations (SDRM) in patients failing 2nd line ART KwaZulu-Natal

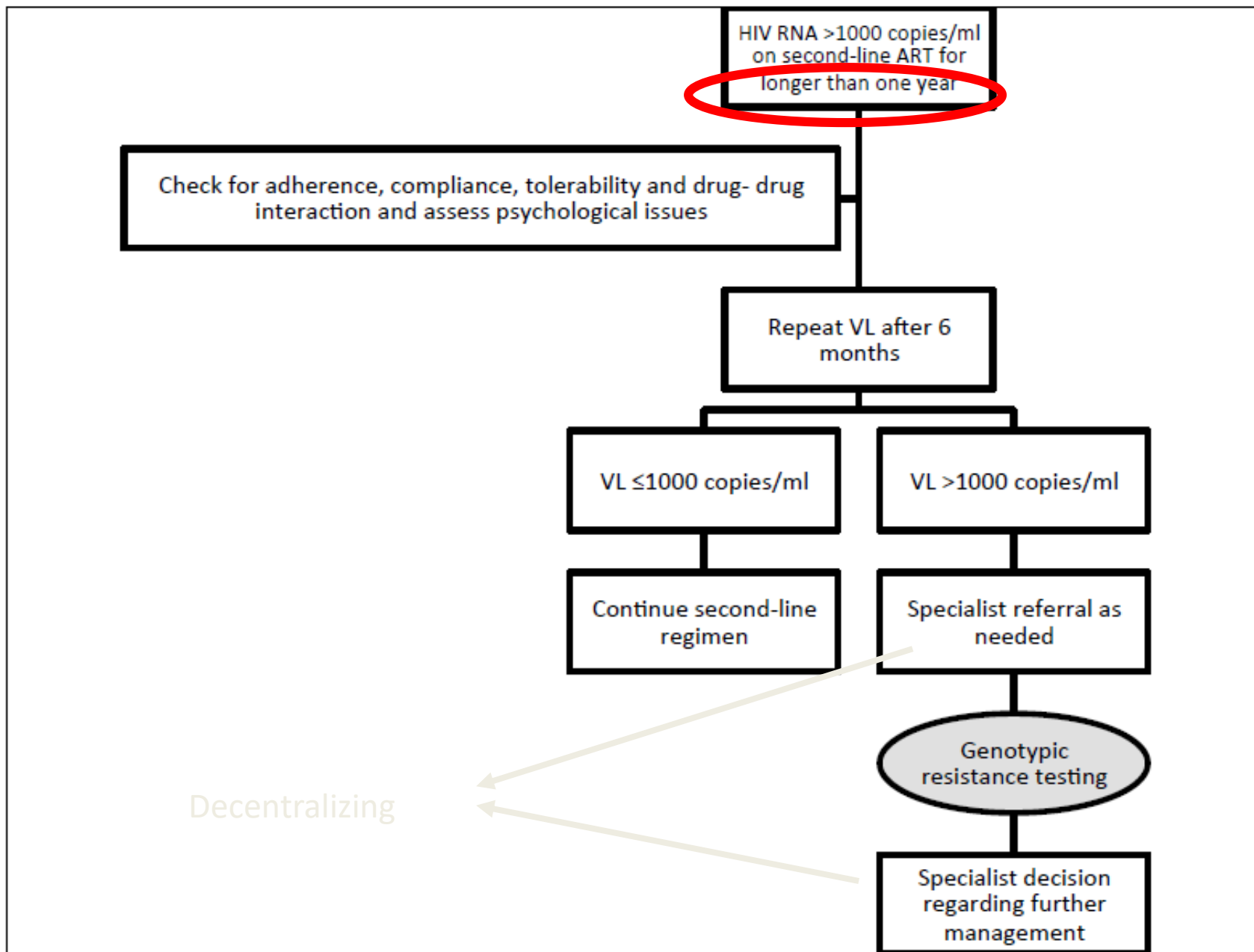


NHLS 2nd line: As part of CAPRISA ACC, we have analyzed the genotypes 195 produced in 2014 and 2015 by the NHLS in KZN. Drug resistance levels were 39% for major protease mutations (which patients need third line). These increase to 46% in minor mutations. **Unpublished**

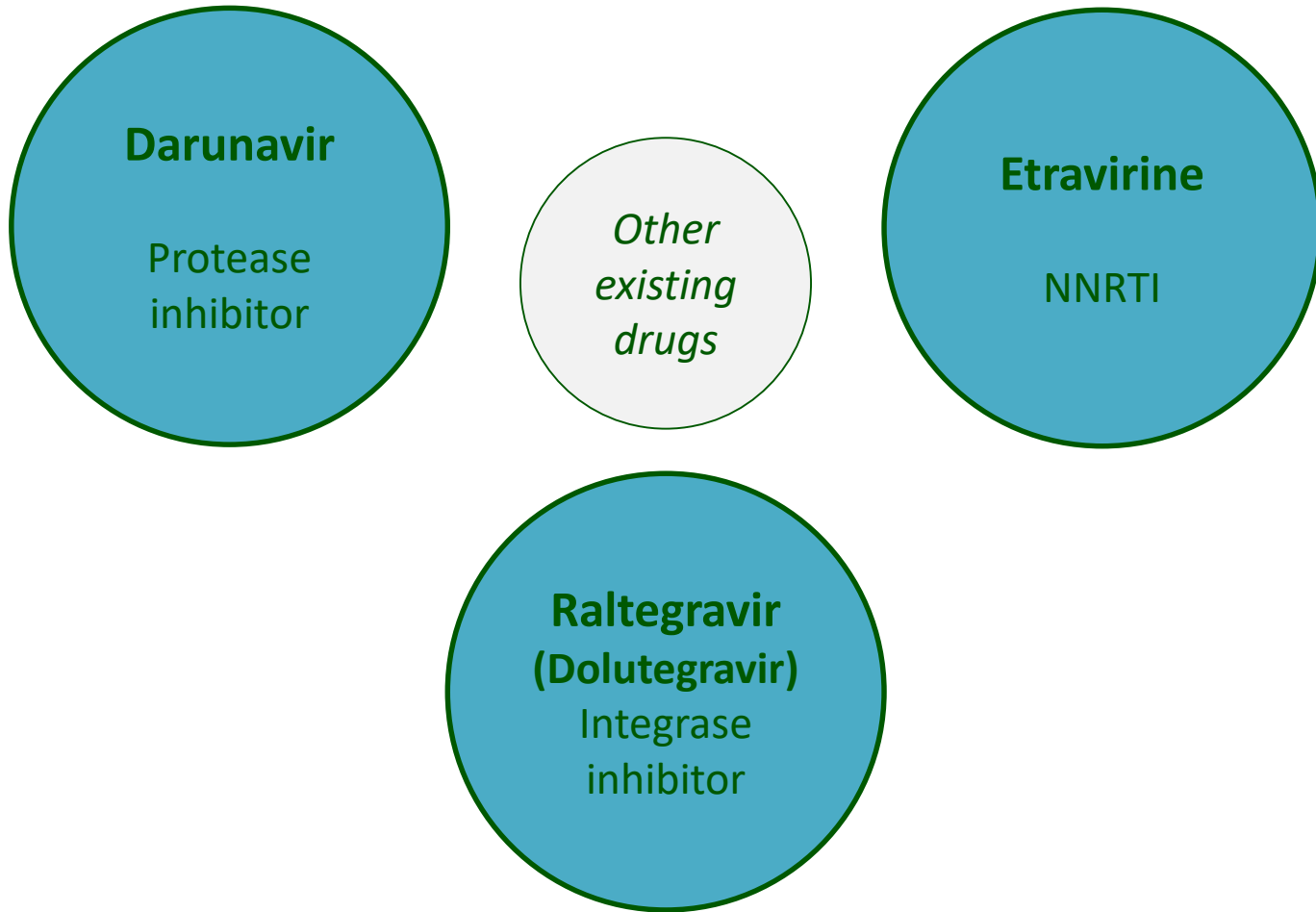
Conclusion : 2nd line resistance

- The minority (< 40%) of patients that FAIL second line therapy have drug resistance mutations. However, preliminary results suggest that KZN has the highest level of second line resistance in South Africa (see dashboard).
- Drug resistance testing for second line necessary to guide management. Second line surveys also necessary given the small number of studies and samples for management.
- It is important that national guidelines are followed and patients 2nd line ART are provided with drug resistance testing and specialized management.

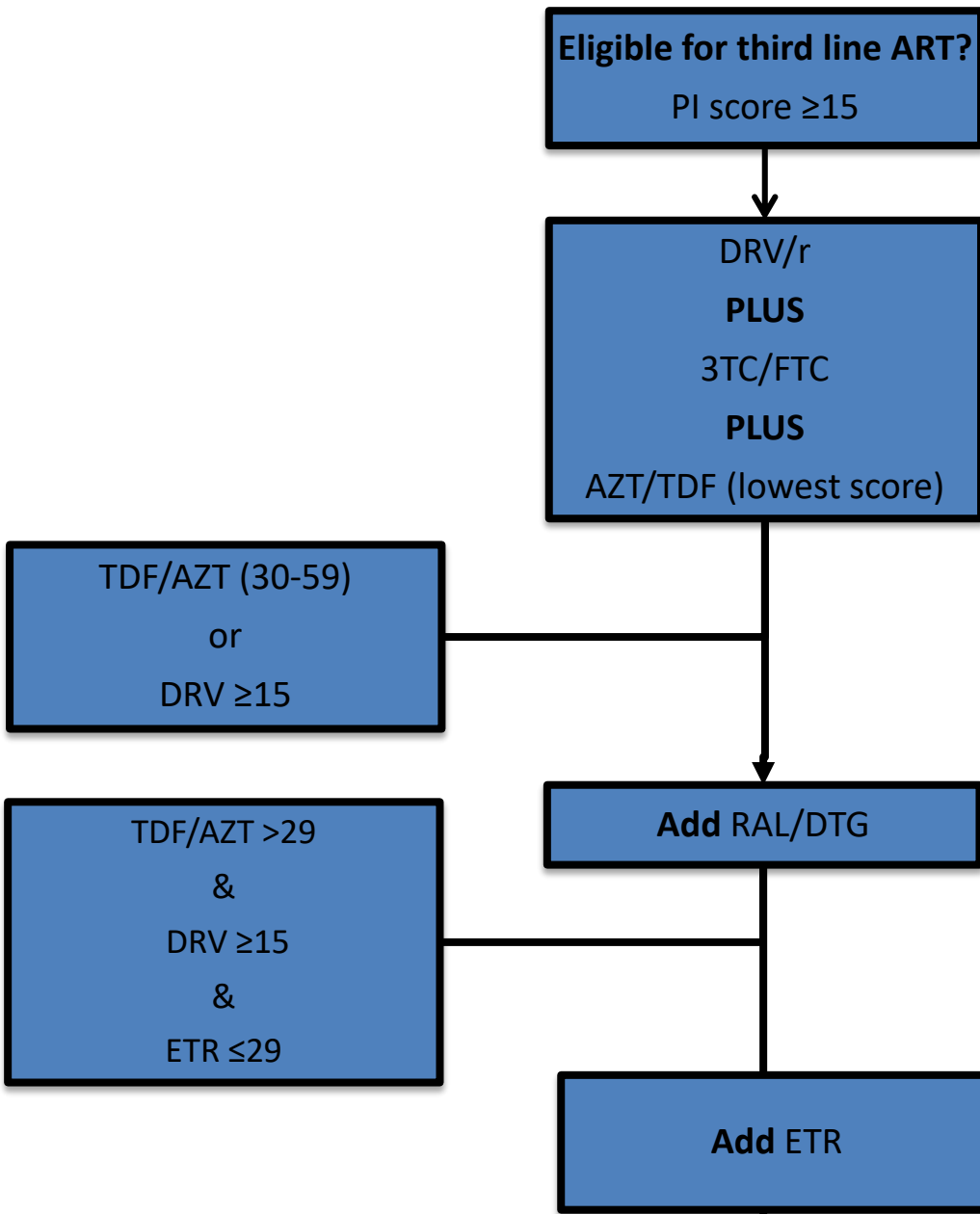
Figure 8: Algorithm for diagnosis of second-line treatment failure



Third-line options



Algorithm for choosing 3rd line agents



- Potential low level resistance: >10 to <15
- Low level resistance :>=15 to <30
- Intermediate level resistance:>=30 to <60
- High level resistance:>=60

DRV - Darunavir (Prezista®)

- Highly potent protease inhibitor
- Dose 600mg bd + ritonavir 100mg bd
- Retains activity in the presence of resistance to other protease inhibitors (e.g. LPV/r and ATV/r)
- Drug interaction with rifampicin
- Important adverse effects: diarrhoea, rash, hepatitis



RAL - Raltegravir (Isentress®)

- Integrase inhibitor
- Dose 400mg bd
- Potential drug interaction with rifampicin
- Important adverse effects: rash, hepatitis
- New drug class so should not be any resistance at baseline



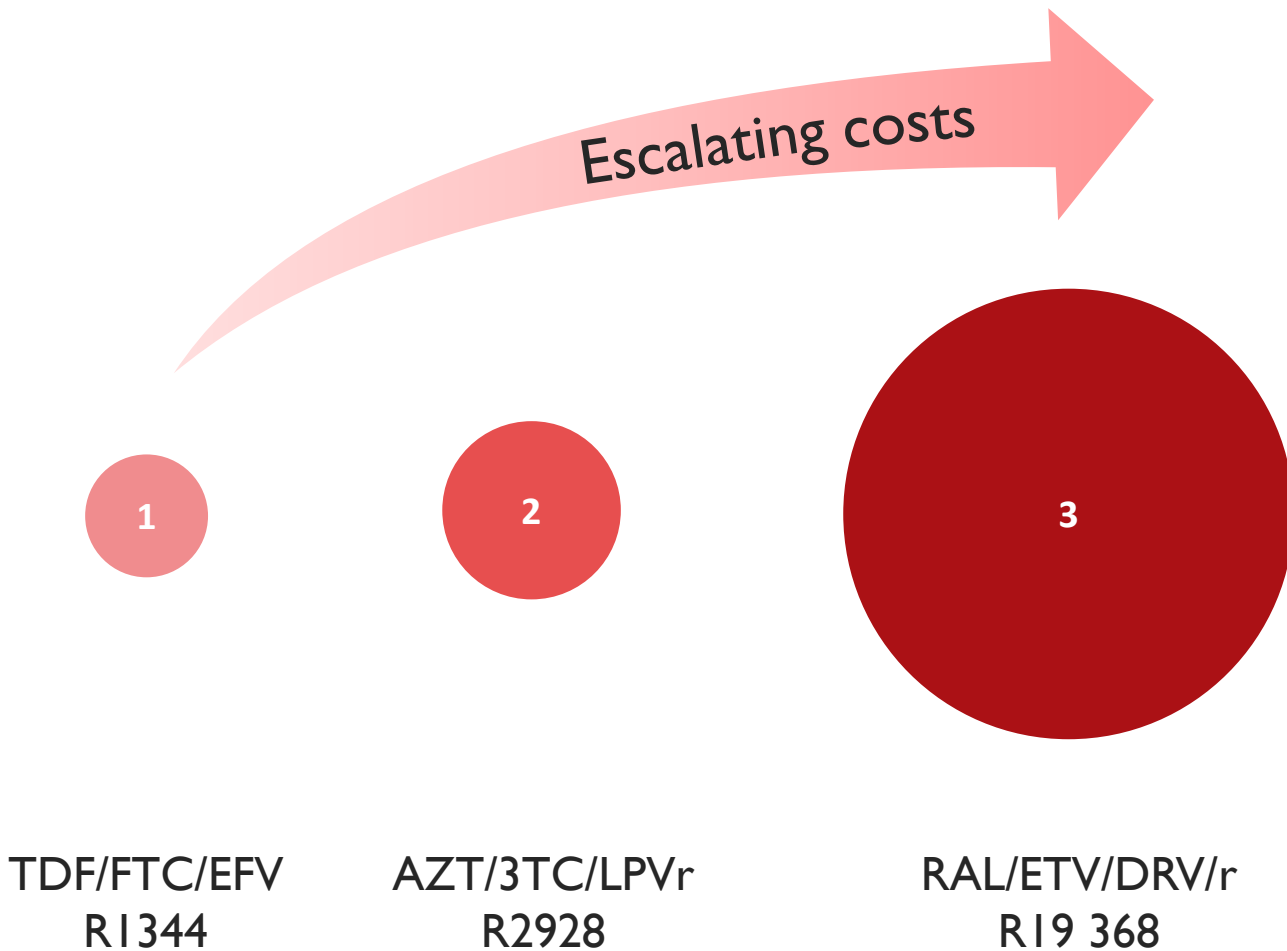
Dolutegravir

- Integrase inhibitor
- Dose 50mg daily
- Potential drug interaction with rifampicin (\downarrow DTG levels)
- Needs to be adequately evaluated in patients on treatment for TB (INSPIRING study)
- Important adverse effects: insomnia and headache
- mean rise in Cr of $\sim 10\mu\text{mol/L}$ due to inhibition of tubular secretion and does not affect GFR
- New drug class – no resistance at baseline

Etravirine (Intelence®)

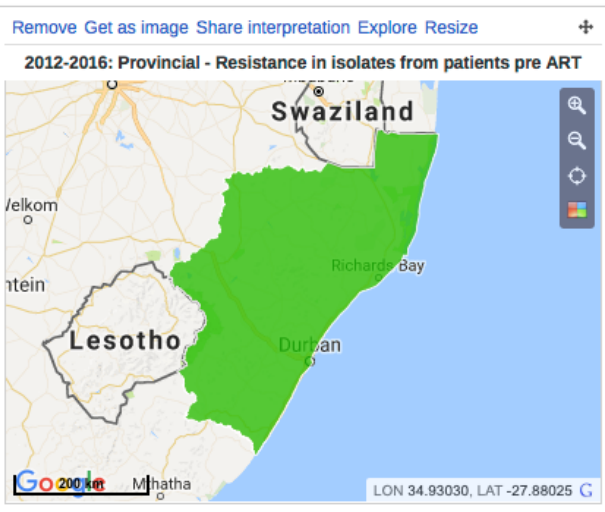
- Next-generation NNRTI
- Dose 200mg bd
- Retains activity in the presence of resistance to EFV/NVP
- Potential drug interaction with rifampicin
- Important adverse effects: rash



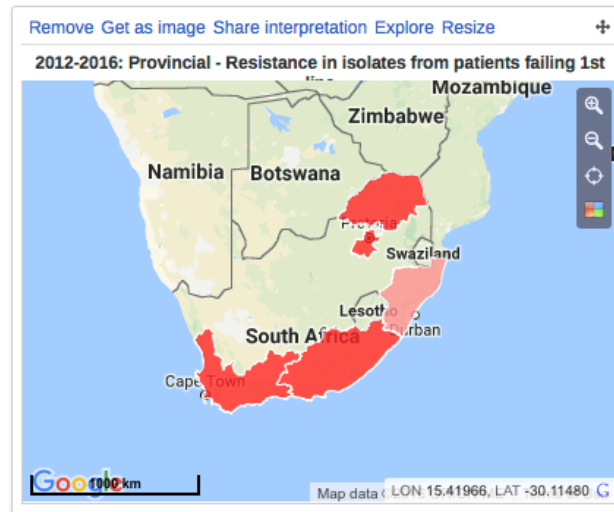


Source: Department of Health ARV tender 2015-2018

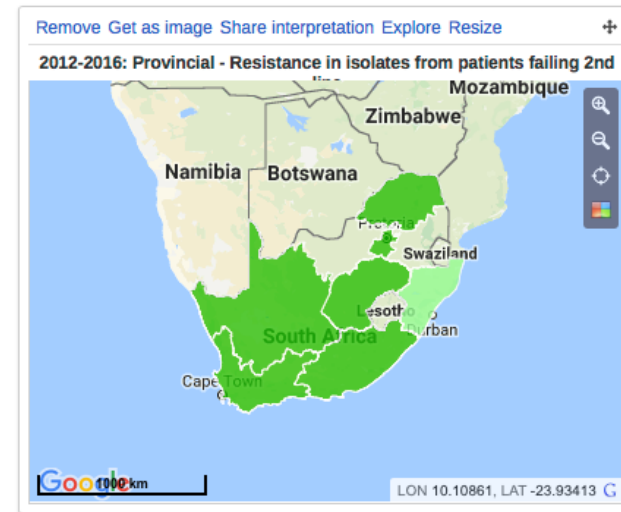
KwaZulu-Natal, preliminary results in comparison with other provinces:



KZN has the highest transmitted resistance (> 10%)



KZN has high level 1st line resistance (79%) in patients failing ART. Other provinces have levels > 90%.



KZN has the highest level (>20%) of 2nd line resistance in patients failing ART. Other provinces have lower level.

Conclusion:

- **The preliminary results suggest that KZN has the highest level of transmitted resistance (i.e. 1/10 of patients starting ART are likely to be resistance to first line regimen).**
- **Individuals on 1st fail for long, which may cause the increase in transmitted resistance.**
- **Preliminary results suggest that KZN has the highest level of second line resistance in South Africa. It is important to note that new surveys and more data is necessary to confirm these results.**
- **National drug guidelines are appropriate (genotypes for second line failure and pregnant women). However, there is a need to effectively implement viral load monitoring and appropriate switching patients. Need to increase surveillance.**

Next Steps SATuRN and CAPRISA ACC

Training:

- Large SATuRN and CAPRISA workshop (400 clinicians and nurses) as part of AWACC, ICC, 8-9 Oct. 2016.
- Publish HIV & TB Drug Resistance and Clinical Management case book

Operational research:

- Implementation of national guidelines for drug resistance testing system in KZN
- Develop and apply a surveillance protocol for transmitted and second line resistance.
- Keep populating the dashboard with new data
- Publish manuscripts on the results of the analysis
- Provision of quaternary reports to CAPRISA ACC and provincial NDoH

SATuRN: Newsletter

Vol. 5, Num. 1
Jan- Mar 2016

Southern Africa Treatment and Resistance Network



Foreword:

The concept behind this newsletter is that anyone with 15 minutes to spare can learn about the work of SATuRN.

In this first 2016 issue of our newsletter we have included interesting news, blogs, reports, tweets, publications and training information produced by our network.

We hope you enjoy it and find it informative. We welcome any feedback about content or format.

Produced by: Tulio de Oliveira, Richard Lessells, Justen Manasa, Jennifer G, Benjamin Chimukangara, Jennifer Giandhari, Nicolette Crozier

Highlights:

News: SATuRN and CAPRISA Advanced Clinical Care Workshop, 6-7 July 2016

Publication: Global epidemiology of drug resistance after failure of WHO recommended first-line regimens for adult HIV-1 infection

Publication: Increasing HIV-1 drug resistance between 2010 and 2012 in adults participating in population-based HIV surveillance in rural KwaZulu-Natal South Africa

Publication: Understanding Specific Contexts of Antiretroviral Therapy Adherence in Rural South Africa

Web Resource: BioAfrica and ViralZone HIV-1 proteome resource: summarizes all HIV protein functions and drug resistance mutations!

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NHLS/UKZN virology department

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NHLS Tygerberg/Stellenbosch Univ.

Funding:

CAPRISA ACC CDC program

South African Medical Research Council.

More info & Open Access manuscripts:

SATuRN newsletter

www.bioafrica.net/saturn

Summary of studies on HIV-1 primary resistance in KwaZulu Natal

Study year	Province	Study participants	Facility/ Region	N	CD4 cells/mm ³	PI resistance (%)	NRTI resistance (%)	NNRTI resistance (%)	Any drug resistance mutation (%)	References
2001	KwaZulu-Natal	Treatment naïve patients	Durban, Ulundi, Hlabisa, Tongaat and Phoenix.	72	N/A	0.0	0.0	2.8	2.8	Gordon et al., (2003) ³
2005	KwaZulu-Natal	ANC Survey	ANC clinics in KZN	40	≤200	ND	0.0	2.5	2.5	Hunt et al., (2012) ⁸
2007	KwaZulu-Natal	ANC Survey	ANC clinics in KZN	35	≤200	0.0	0.0	0.0	0.0	Hunt et al., (2012) ⁸
2008*	KwaZulu-Natal	ANC Survey	ANC clinics in KZN	37	≤200	2.9	5.4	8.1	13.5	Hunt et al., (2012) ⁸
2008	KwaZulu-Natal	Treatment naïve patients	Durban	405	≤200	1.5	1.8	1.8	4.4	Matthews et al., (2008) ¹⁰
2009	KwaZulu-Natal	ANC Survey	ANC clinics in KZN	48	≤200	0.0	2.2	6.5	6.2	Hunt et al., (2012) ⁸
2009	KwaZulu-Natal	ANC Survey	Folweni, Hlengi- sizwe, Inanda Community Health Centre, Kwadabeka and Kwamashu clinic	56	≤200	1.8	0.0	1.8	3.6	Parboosing et al., (2011) ¹¹
2010	KwaZulu-Natal	HIV surveillance	Hlabisa subdistrict	72	≤350	0.0	1.4	1.4	1.4	Manasa et al., (2012) ¹²
2010	KwaZulu-Natal	HIV surveillance	uMkhanyakude	67	≤350	0.0	0.0	0.0	0.0	Manasa et al., (2016) ¹⁴
2011	KwaZulu-Natal	HIV surveillance	uMkhanyakude	381	≤350	0.6	1.3	4.5	5.2	Manasa et al., (2016) ¹⁴
2012	KwaZulu-Natal	HIV surveillance	uMkhanyakude	253	≤350	0.0	2.0	6.0	7.1	Manasa et al., (2016) ¹⁴
2014	KwaZulu-Natal	HIV surveillance	Umgungundlovu	708	≤500	0.6	4.1	11.9	13.7	N/A
2015	KwaZulu-Natal	HIV surveillance	Umgungundlovu	470	≤500	1.9	6.4	9.4	14.3	N/A

* conducted as ANC survey, but the number of participants analyzed was insufficient to classify TDR based on the WHO method.

Question 3: Will individuals with resistance to 1/3 drugs on fixed dose combination suppress on ART?

A) Yes

B) No

C) More research need to see the long term effects

D) A & C

Summary of studies on HIV-1 resistance in patients failing 1st line ART KwaZulu Natal

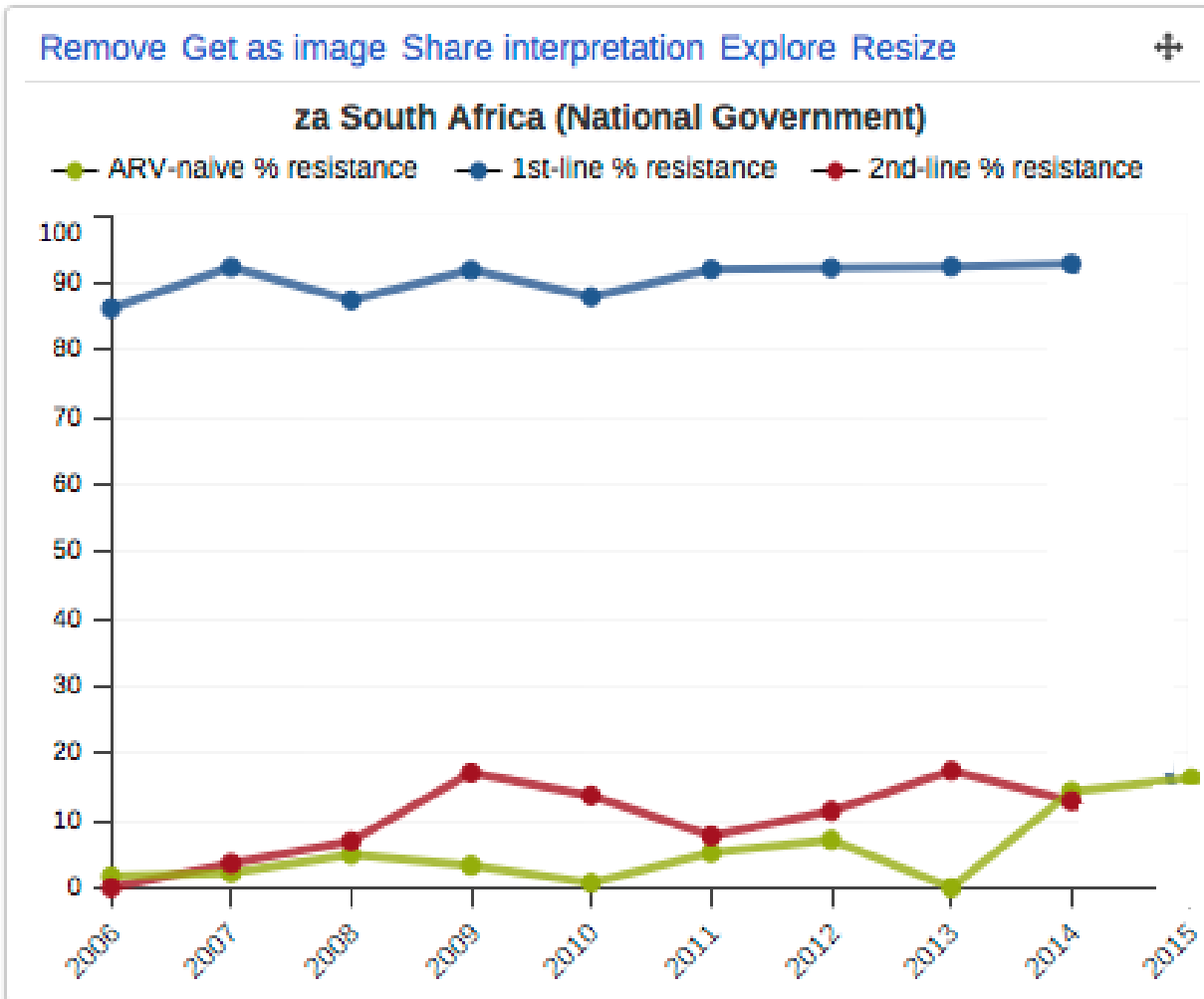
Study Period	Site	Criteria for failure	N		Median Duration of ART (months)	ART Regimen (%)	≥1 DRM (%)	NNRTI (%)	M184V (%)	Any TAM (%)	TAM ≥3 (%)	K65R (%)	Ref
Dec 2010 – Mar 2012	Hlabisa (17 rural clinics)	1 × VL >1000	222	42		d4T/3TC/EFV (51) d4T/3TC/NVP (24) AZT/3TC/EFV (8) TDF/3TC/EFV (11) Other (6)	86.0	83.0	78.0	40.0	18.0	6.0	Manasa et al. [34]
Sep 2010 to Mar 2011	Urban clinic	1 × VL >1000	33	5.7		TDF/3TC/EFV (89)	>97.0	97.0	27.3	15.2	NR	70.0	Sunpath et al. [33]
NR	Durban (urban hospital)	1 × VL >5000	43	29		d4T/3TC/EFV (51) AZT/3TC/EFV (29) AZT/3TC/NVP (9) Other (10)	95.0	95.0	87.0	55.0	NR	NR	Singh et al. [32]
Aug 2004 to Aug 2006	Urban Clinics	1 × VL >1000	141	NR		D4T/3TC/EFV (43) D4T/3TC/NVP (6) AZT/3TC/EFV (27) AZT/3TC/NVP (12) OTHER (11)	86.5	NR	NR	NR	NR	5.0	Murphy et al. [31]
Jan 2005 – Aug 2006	Durban (two urban hospitals)	1 × VL >1000	115	10.8		d4T/3TC/EFV (49) d4T/3TC/NVP (5) AZT/3TC/EFV (26) AZT/3TC/NVP (11) Other (8)	83.5	78.3	64.3	32.2	13.0	2.6	Marconi et al. [30]

Summary of studies on HIV-1 resistance in patients failing 2nd line ART in KwaZulu-Natal

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Study year	Province	Study participants	PI resistance (%)	References
2001	KwaZulu-Natal	Treatment naïve patients	0.0	Gordon et al., (2003)
2008	KwaZulu-Natal	ANC Survey	2.9	Hunt et al., (2012)
2008	KwaZulu-Natal	Treatment naïve patients	2.2	Matthews et al., (2008)
2009	KwaZulu-Natal	ANC Survey	1.8	Parboosing et al., (2011)
2011	KwaZulu-Natal	HIV surveillance	0.6	Manasa et al., (2016)
2012	KwaZulu-Natal	Patients failing second-line therapy	4.8	Zanoni et al., (2012)
2014	KwaZulu-Natal	Patients second-line therapy	5.8	Pillay et al., (2014)
2014	KwaZulu-Natal	HIV surveillance	0.6	N/A
2015	KwaZulu-Natal	HIV surveillance	2.4	N/A
2015	KwaZulu-Natal	Patients failing second-line therapy	39.0	N/A

Summary of resistance over time (National, n=13,140 genotypes)



Blue: Majority patients fail first line with resistance

Green: Increasing trends of Transmitted resistance (*2013 no data)

Red: minority of patients On 2nd line with resistance