Southern African HIV Clinicians Society

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Johannesburg

Our Issues, Our Drugs, Our Patients

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NDOH PAEDIATRIC 3rd LINE ART PROGRAM

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What's in the Bucket? Difference bet. the Paeds and Adult

Twenty Two year old Failing a PI Based regimen

Difference between the Paeds and Adult

Two year old Failing a PI Based regimen

Both are not on licensed in SA

Daurinavir – only >3yrs

Dolutegravir – FDA approval >12 yrs (6-12 yrs pending)

Formulation Matters

4 yr old with:

Drug Resistance Interpretation: PR

PI Major resistance mutations	M46I	I54V	L76V	V82A
PI Minor resistance mutations	L10F	L10I		

Protease Inhibitors:	
Atazanavir/r (ATV/r)	Intermediate resistance
Darunavir/r (DRV/r)	Low-level resistance
Fosamprenavir/r (FPV/r)	High-level resistance
Indinavir/r (IDV/r)	High-level resistance
Lopinavir/r (LPV/r)	High-level resistance
Nelfinavir/r (NFV)	High-level resistance
Saquinavir/r (SQV/r)	Intermediate resistance
Tipranavir/r (TPV/r)	Low-level resistance

Drug Resistance Interpretation: RT

NRTI resistance mutations	M184V
NNRTI resistance mutations	None

Nucleoside RTI:	
Lamivudine (3TC)	High-level resistance
Abacavir (ABC)	Low-level resistance
Zidovudine (AZT)	Susceptible
Stavudine (D4T)	Susceptible
Didanosine (DDI)	Potential low-level resistance
Emtricitabine (FTC)	High-level resistance
Tenofovir (TDF)	Susceptible
Non-Nucleoside RTI:	
Efavirenz (EFV)	Susceptible
Etravirine (ETR)	Susceptible
Nevirapine (NVP)	Susceptible

Optimal regimen
Darunavir/r +
Raltegravir +
AZT/3tc
(+/- Etravirine)

How to give this to a child who can't swallow tablets!!!

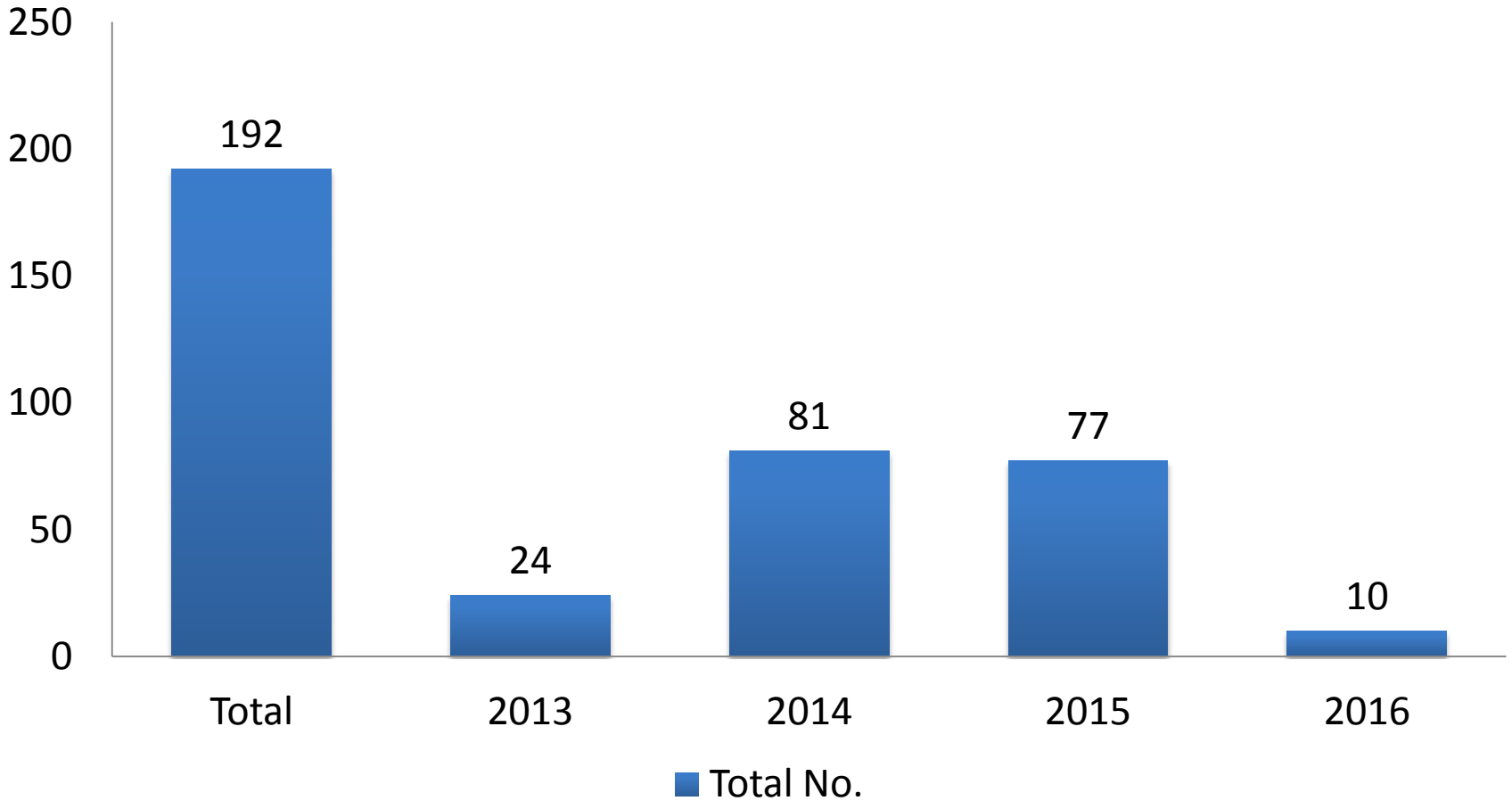
Clinical Case – 19 yr old

- Started D4t/3TC/EFV - ? 7yrs of age
- Changed to AZT/3TC/LPV/rtv – 13 yrs of age
- Changed to LPV/rtv + Ral – 17 yrs

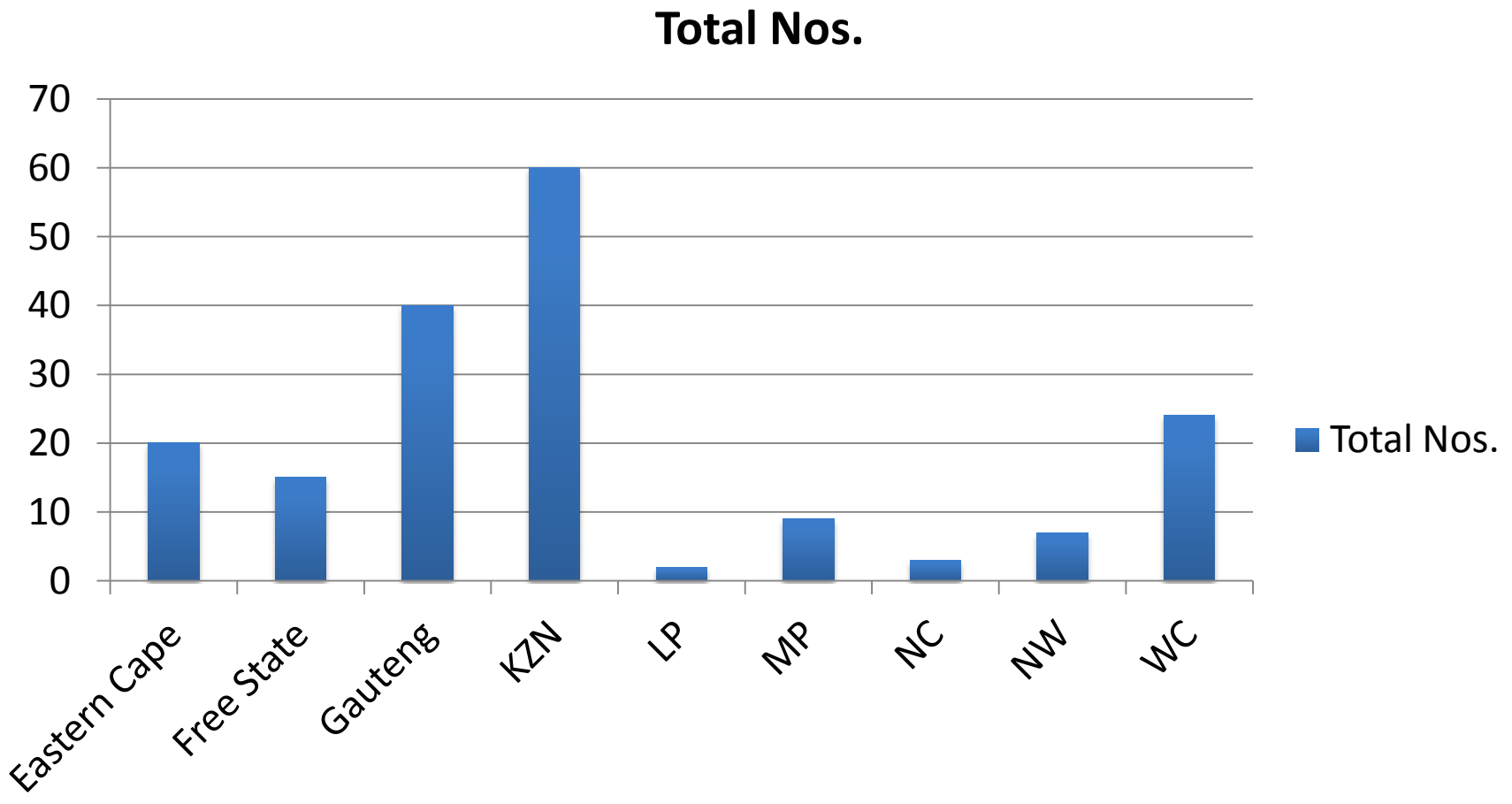
- Current bloods at 19yrs:
- CD4 count: 1 cells/ul
- VL: 136 366 copies/ml
- Resistance test: Extensive resistance to NRTI/NNRTI/Pis and ?Integrase inhibitors

Review of NDOH 3rd Line Applications

Total Number of Applications 2013 - 2016



Applications per Province



- Age:
  - Ave: 8.5 yrs
  - Min:1 yr – Max:17yrs
- Weight:
  - Ave: 23 kg
  - Min: 7.8 kg – Max: 55kg

Duration on Treatment:

Ave: 75.7 months

Min: 1.7 months – Max: 210 months)

Sex:

Females: 36%

Males: 61%

Western Cape DOH Experience

- In October 2014 – Management of applications for genotyping and 3rd line ART in the Western Cape was dissolved to the Provincial DOH

Applications for Genotyping to Western Cape DOH (Oct 2014 – Oct 2015)

Paediatric	36 / 92
Applications Approved	22
Genotype Provided	14

Compiled by Jackqueline Voget and James Nuttal

Third line ART

Paediatric	36
ART Approved	18
- Holding regimens	6
- Definitive regimen	12
Deceased	1
Sequencing incomplete	1
Genotype Not done yet	3
ART not approved (no PI mutations)	13

Compiled by Jackqueline Voget and James Nuttal

3rd line Review Protocol

Indications for genotyping

- Any newly diagnosed child <2 years of age whose mother was receiving PI-based cART during pregnancy and/or during breastfeeding

- Patients on a PI regimen with virological non-suppression defined as at least 3 viral load measurements of ≥30 000 copies/ml (≥log 4.5) at least 8-12 weeks apart:
  - Children (<15 years of age): receiving PI regimen for at least 1 year
  - Adults & adolescents ≥15 years of age: receiving PI regimen for at least 2 years

Eligibility criteria for 3rd line cART

- Accessing cART through public sector
- Lopinavir (LPV) or atazanavir (ATV) mutation score ≥15 (Stanford)

PR	ATV/r	DRV/r	FPV/r	IDV/r	LPV/r	NFV	SQV/r	TPV/r
M46I	10	0	10	10	10	20	5	5
I54V	15	0	10	15	15	20	15	20
V82A	15	0	15	30	30	30	15	0
L10F	0	5	10	10	5	10	0	0
L24I	10	0	10	10	10	10	10	-5
A71V	0	0	0	0	0	0	0	0
L24I+V82A	-	-	-	10	10	-	-	-
I54V+V82A	10	-	10	10	10	10	10	-
V82A+L10F	-	-	10	-	-	-	-	-
V82A+M46I	10	-	10	10	5	10	-	-
Total:	70	5	85	105	95	110	55	20

RT	3TC	ABC	AZT	D4T	DDI	FTC	TDF	EFV	ETR	NVP	RPV
M41L	5	10	15	15	10	5	10	-	-	-	-
D67N	0	5	15	15	5	0	5	-	-	-	-
K70T	10	10	0	10	10	10	10	-	-	-	-
T215Y	5	15	45	45	15	5	15	-	-	-	-
K219Q	0	5	10	10	5	0	5	-	-	-	-
K103N	-	-	-	-	-	-	-	60	0	60	0
T215Y+M41L	-	10	10	10	10	-	10	-	-	-	-
Total:	20	55	95	105	55	20	55	60	0	60	0

Holding Regimen

- **Is the child eligible for a holding regimen?**
  - CD4 count ≥350 (≥5 years age) / ≥25% (<5 years of age)
  - In the interests of the child to delay switch to 3rd line cART due to serious adherence issues or poor drug tolerance
- **If yes, consider using**
  - Lamivudine (3TC) monotherapy (once daily) if AZT OR ABC OR TDF mutation score is <30
  - AZT + 3TC + ABC if AZT AND ABC AND TDF mutation scores are all ≥30
- **Monitoring while on holding regimen**
  - CD4 count & percentage: 3 monthly
  - WHO clinical stage: 3 monthly
  - VL monitoring not required
- **When to consider starting 3rd line cART**
  - CD4 count drops to <350 / <25%
  - WHO clinical stage deteriorates
  - 3rd line cART may be started before the CD4 or clinical criteria are met provided adherence issues have been resolved as far as possible
- **If no, start 3rd line cART**

Children <3 years of age or <10kg (Darunavir (DRV) not approved <3 years or <10kg)

If child meets above criteria for 3rd line cART, choice of 3rd line cART should be decided by committee at time of application

Is child eligible for a holding regimen?

CD4 count ≥25%	In the interests of the child to delay switch

If yes, consider using

Lamivudine (3TC) monotherapy (once daily)	Consider using AZT + 3TC + ABC

Monitoring while on holding regimen

CD4 count & percentage: 3 monthly	WHO clinical stage: 3 monthly	VL monitoring not required

When to consider starting 3rd line cART

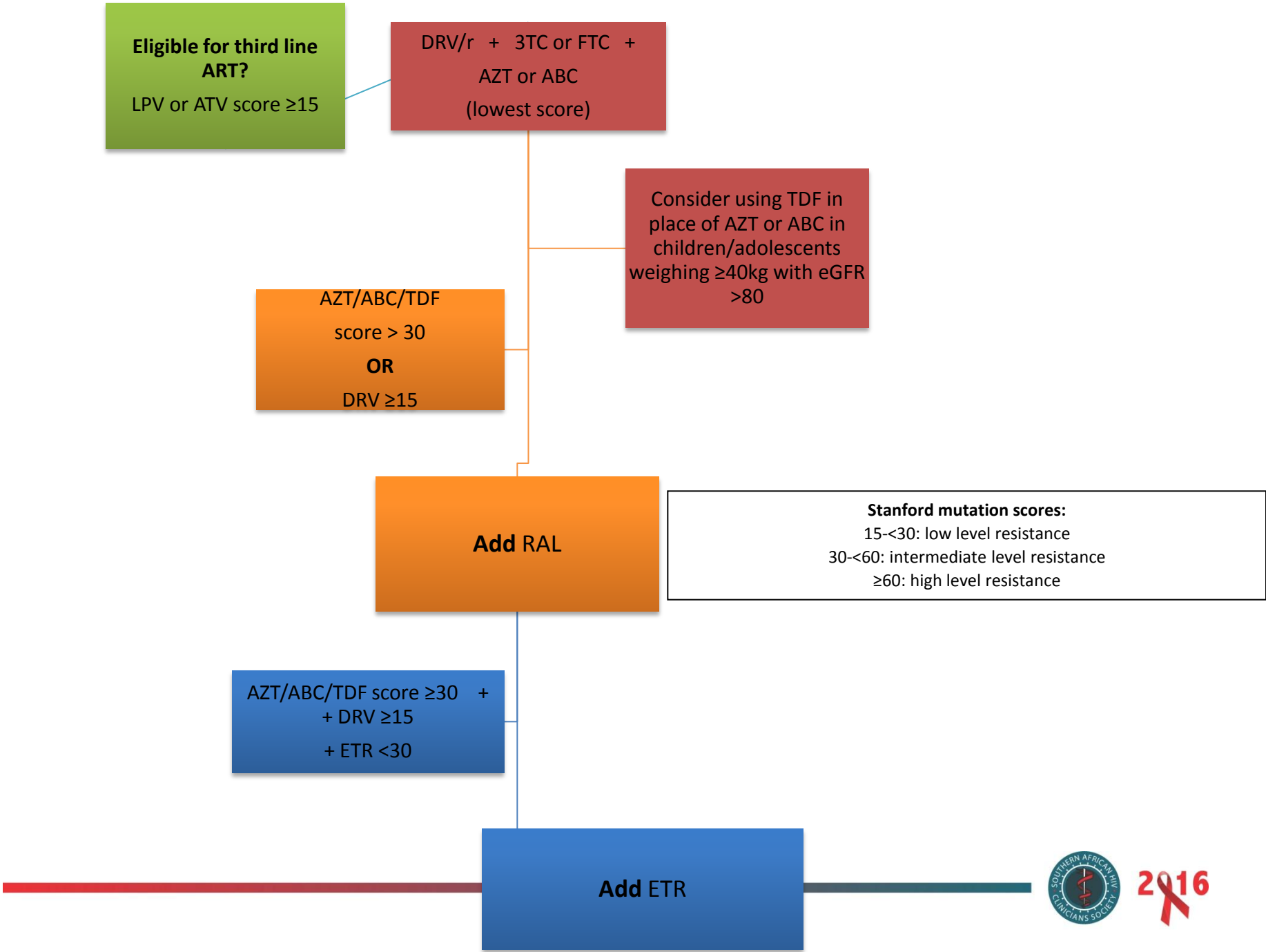
When child reaches ≥3 years of age	CD4 count drops to <25%	WHO clinical stage deteriorates	Maybe started sooner

If still <3yrs or < 10kg, consider off-label use of 3rd line cART

2016

Children ≥3 years of age and ≥10kg

- All get DRV/r
- All get 3TC or Emtricitabine (FTC)
- Plus either AZT OR ABC whichever has the lowest score. Consider using TDF in place of AZT OR ABC in children/adolescents weighing ≥40kg with eGFR >80
- Add Raltegravir (RAL) if
  - The AZT OR ABC OR TDF mutation score is ≥30 OR
  - The DRV mutation score is ≥15
- Add Etravirine (ETR) in addition to RAL if
  - AZT OR ABC OR TDF mutation score is ≥30 AND
  - DRV mutation score is ≥15 AND
  - ETR score is <30


Eligible for third line ART?
LPV or ATV score ≥15
DRV/r + 3TC or FTC + AZT or ABC (lowest score)
Consider using TDF in place of AZT or ABC in children/adolescents weighing ≥40kg with eGFR >80
AZT/ABC/TDF score > 30 OR DRV ≥15
Add RAL
Stanford mutation scores:
15-<30: low level resistance
30-<60: intermediate level resistance
≥60: high level resistance
AZT/ABC/TDF score ≥30 + + DRV ≥15 + ETR <30
Add ETR
2016

Summary:

- 3rd Line committee should NOT be seen as a dictatorship
  - Queries regarding the regimen (with a rationale) / management or relevant clinical information always welcome.
  - Increasing use of standardized algorithms – improves transperancy

- Willingness to devolve the responsibility to Provincial structures – provided available resources