

# Virological failure in children

Dr Lee Fairlie



# Case 1

- Thembi is a 34 year old female. She is HIV infected
- She lives in JHB and her 2 children, Lerato and Sipho live in Mpumalanga with Gogo
- They are both HIV +
- She was initiated on first line ART (3TC, TDF and NVP) 12 months ago. Her CD4 count when she started treatment was 150 cells/mm<sup>3</sup>
- She presents to the ART clinic for her routine visit and is found to be 5 months pregnant
- She has a VL done and the results show a Viral Load of 40 000 cps/ml. Her CD4 cell count is now 400 cells/mm<sup>3</sup>



# Dilemma?

- How should Tembi be managed further?
- What should you advise her regarding her new born baby regarding feeding?
- What prophylaxis should the baby be given?



# Continued....

- Thembi is changed to regimen 2 of AZT, 3TC and Aluvia. Siyathemba tests negative for HIV at her 6 week PCR test
- Thembi concerned about Lerato and Siphos who have now moved to Johannesburg
- Told at the clinic in Mpumalanga that both children are failing treatment and has been scolded by the staff who say that she is irresponsible because she hasn't been giving the ART
- In reality Thembi's mother, who was responsible for giving the ART was struggling to remember and had difficulty with giving the doses from the time she started developing cataracts.

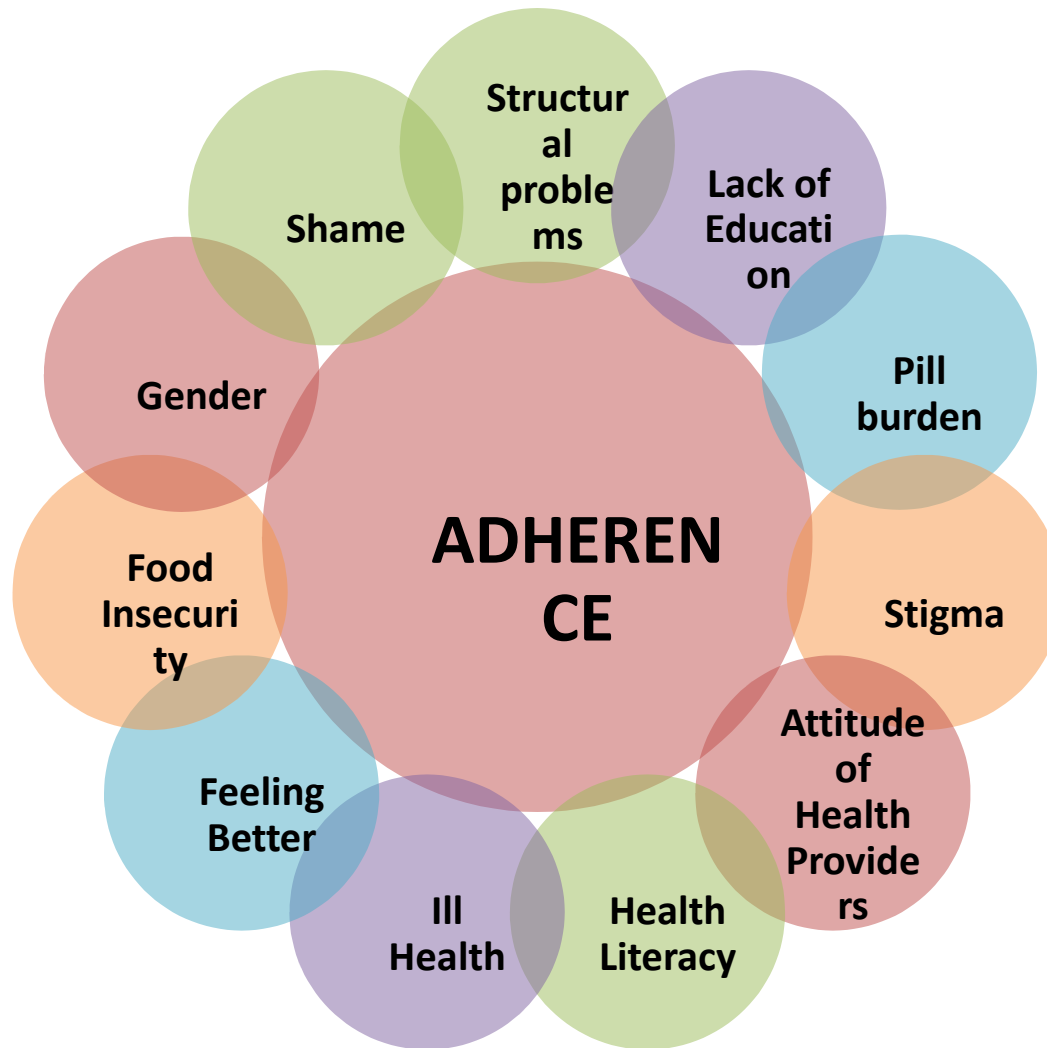


# Viral Load

- One log drop by 4 weeks
- Undetectable by 24 weeks(<50)
- Thereafter every 6 months
- Viral blips
- If above 1000 copies/ml confirm with a second test. Increase adherence counseling.



# Factors Affecting Adherence



# Adherence Challenges






# The mechanics of mutation

- Virion half-life = 30 minutes
- Daily production =  $10^9$  –  $10^{10}$  virions
- RT incorporates the wrong nucleotide once every 10,000 – 30,000 nucleotides

➔ Approximately 1 mutation per viral copy

- Every single point mutation occurs daily
- Higher viral replication ➔ more frequent mutations





# Nomenclature

Codon (position)  
PR = 1-99 amino acids  
RT = 1-560 amino acids



**M184V**



Wild-type  
amino acid  
(consensus)

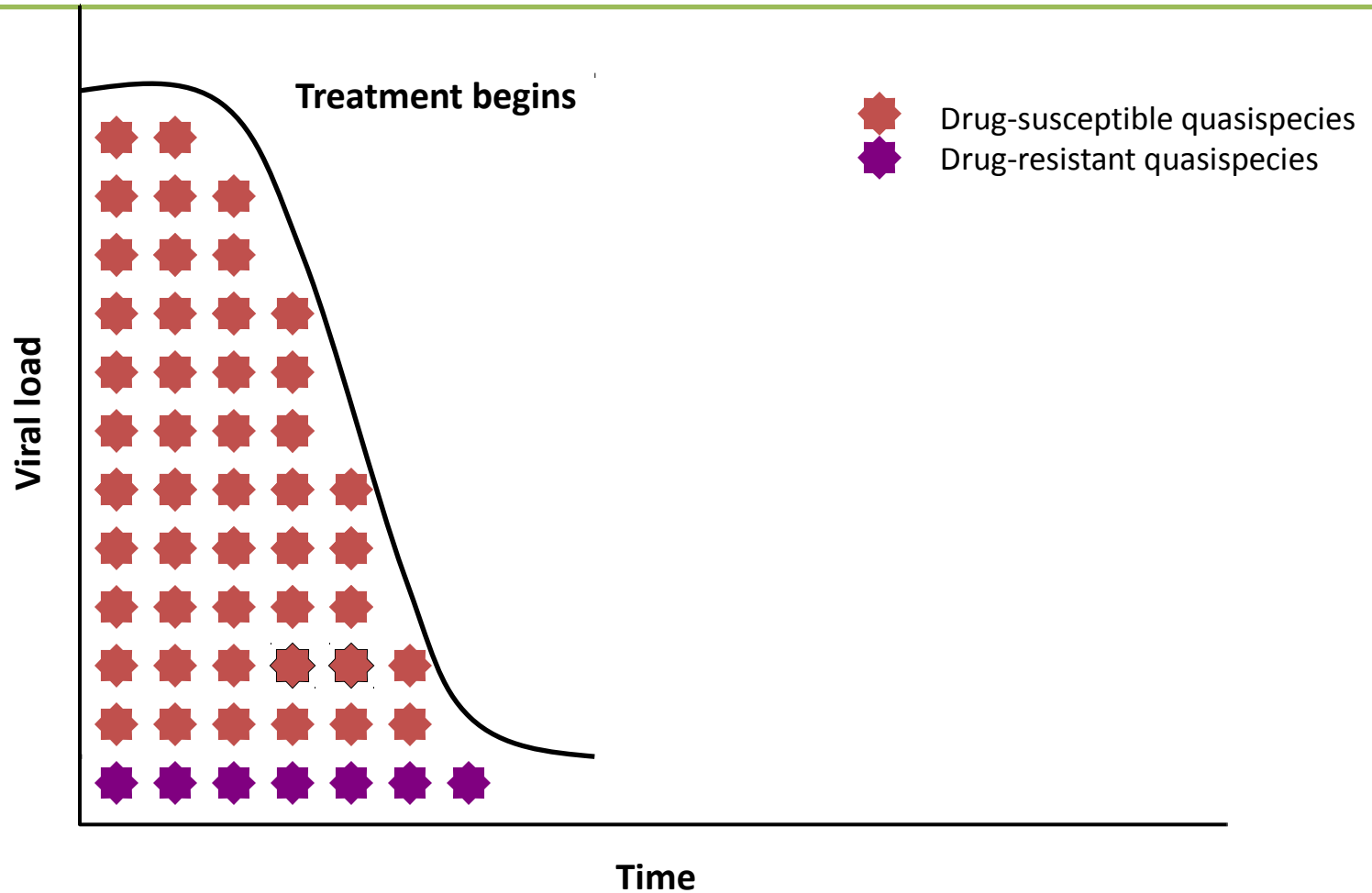


Mutant  
amino acid

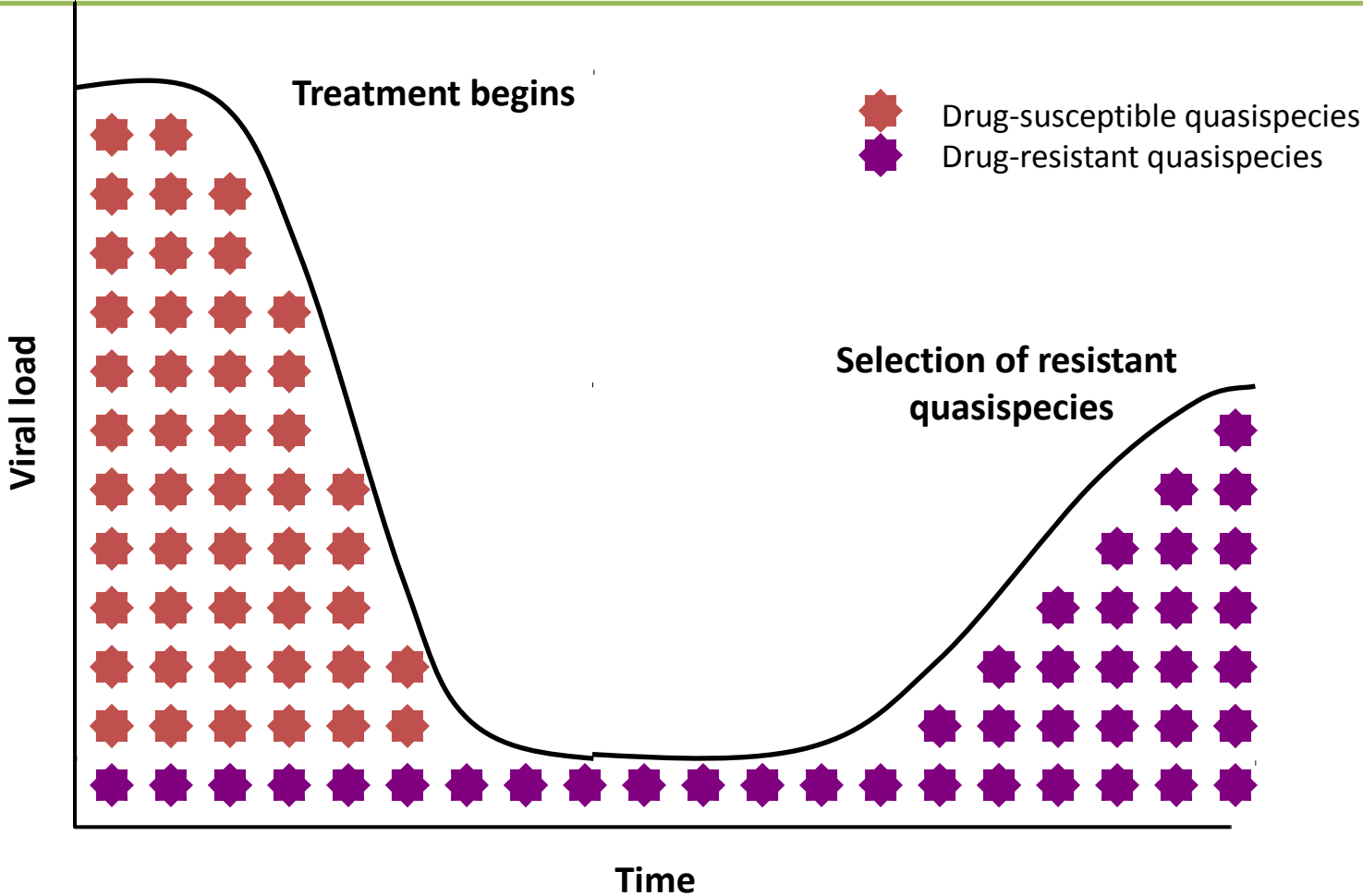
- If a patient is failing a regimen because of poor adherence there is no point in switching them to another regimen unless these issues have been sorted out
- Remember though the following cases:
  - NvP resistance through PMTCT
  - Not super-boosting lop/r with ritonavir



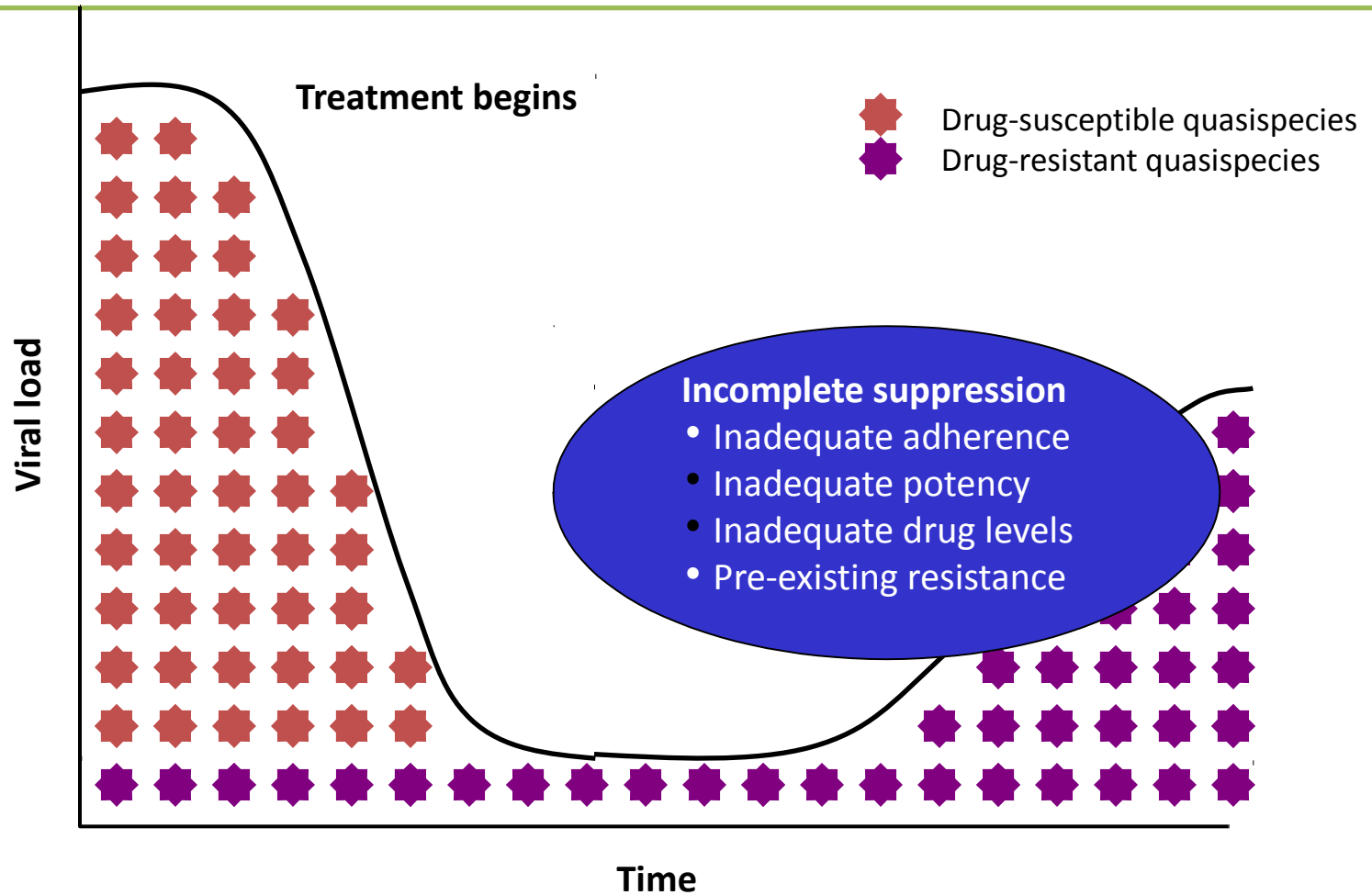
# Selective Pressure of Therapy



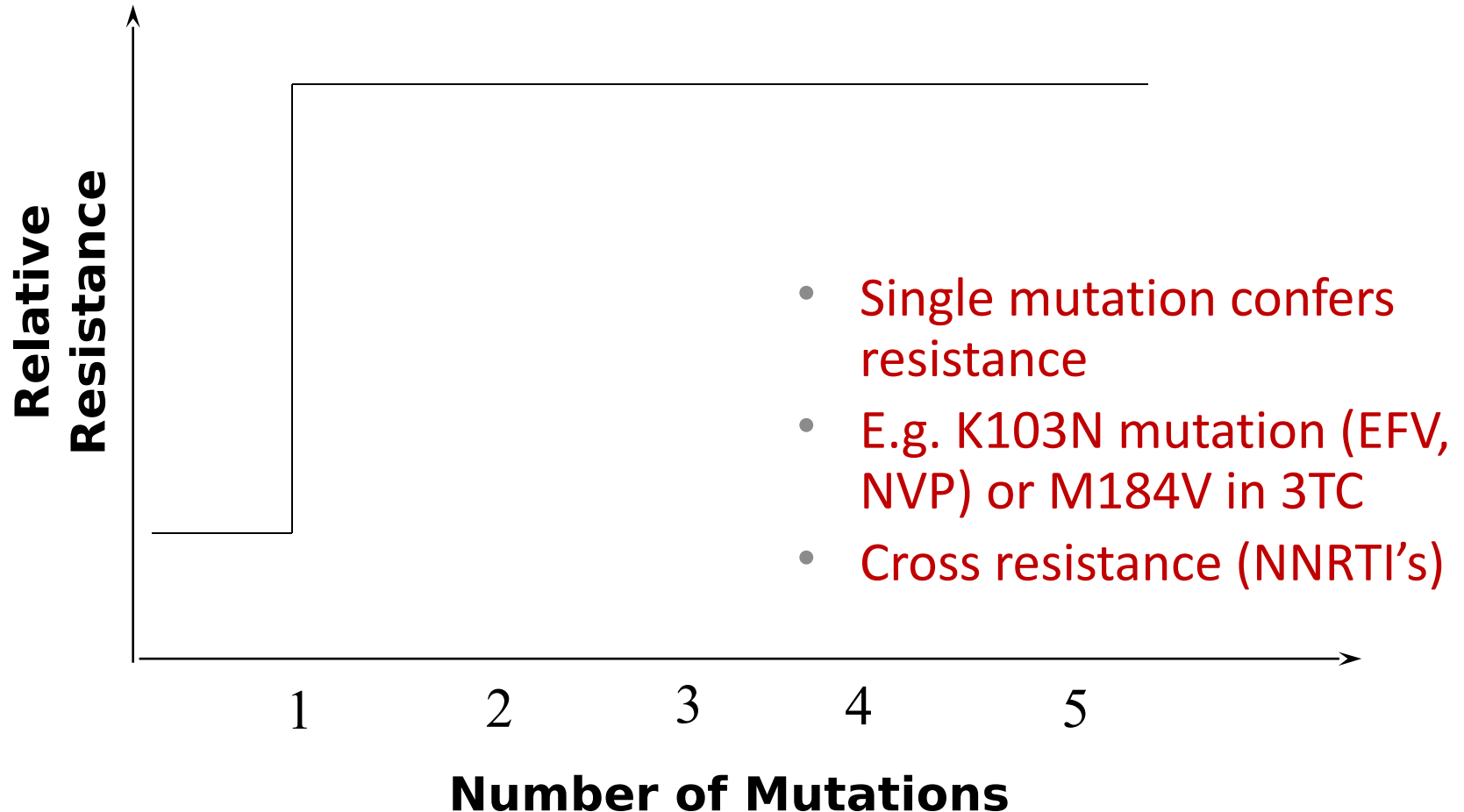
# Selective Pressure of Therapy



# Selective Pressure of Therapy

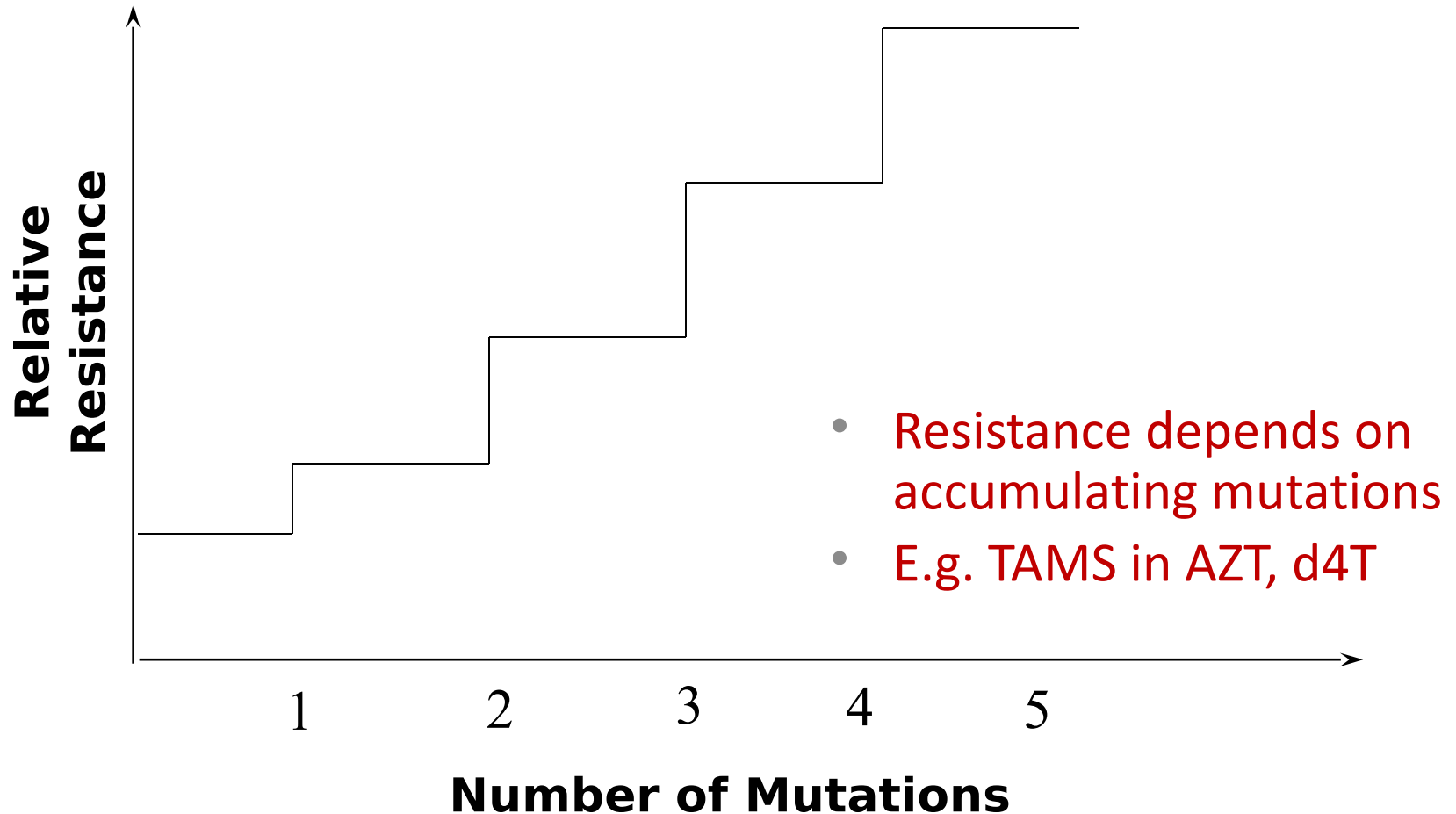


# “Low Genetic Barrier” for ARV resistance (3TC, NNRTIs)



# “High Genetic Barrier” for ARV resistance

(AZT, d4T, ddI, Kaletra)



# Sipho:

- 10 year old, 25 kg
- Treated with Efavirenz, 3TC and ABC, for 1 year
- TB treatment for 6 months before starting ART.
- Current CD4 is 400 cells/mm<sup>3</sup> and VL 23 000.
- Granny complains that recently he has become very naughty, always out playing with friends and isn't home on time to take treatment
- He doesn't take his ART unless it is exactly on time (7am and 7pm) as this is what the counsellor has instructed
- He keeps asking why he has to take his ART and says it looks similar to the treatment that Queen on Generations has to take





# Sipho...

- What are the issues here?
- How should these be addressed?
- How would you manage Sipho further?



# Issues

- Non-disclosure
- Pre-Adolescent
- Lifestyle: -ART times too rigid
  - Could take once daily ART
- TB??? Properly treated????
- Granny struggles to support



# How should Siphos be managed?

Viral load (VL)	Response	
< 400 copies/mL	-6 monthly viral load monitoring and routine adherence support	
400-1000 copies/mL	-Repeat viral load in 6 months -Begin step-up adherence package if VL still between 400 – 1000	
> 1 000 copies/mL	-Begin step-up adherence package -Repeat viral load in 3 months	-If < 400, return to routine 6-monthly monitoring -If between 400 and 1 000, continue step up adherence and repeat VL after 6 months -If > 1 000, despite stepped up adherence support, AND child is on a NNRTI-based regimen, switch to second-line therapy only if adherence is > 80%. -If > 1000 and child is on a PI-based regimen: <ul style="list-style-type: none"> <li>● Reinforce adherence (it is very difficult to fail a PI-based regimen unless the child ever received an unboosted PI)*</li> <li>● Switch to second-line therapy if VL &gt; 5000, only if adherence is &gt; 80% and consider drug resistance testing if available.</li> </ul> -If child received an unboosted PI (e.g. ritonavir alone) in the past, do resistance testing if available and change to second line if VL > 1000

# Sipho...

- After 3 months he claims that he has been very adherent to treatment
- He understands his illness and is much more settled living in Johannesburg with his mother
- Repeat VL is 25 000, CD4 420 cells/mm<sup>3</sup>. The counsellor shouts at him telling him “not to lie about taking his treatment as he can’t be if his VL is still elevated”



# Continued....

- Is this correct?
- Does he have resistance?
- To which drugs most likely?
- Further management?



# Does Siphon have resistance?

- Low genetic barrier to resistance for both EFV and 3TC
- Cross resistance NVP
- Most likely resistant to these
- ? ABC



## Regimens For Children

(DOH Guidelines)

	Less than 3years	>3 years (>10kg)
1st line	Abacavir (ABC) lamivudine(3TC) kaletra®	Abacavir (ABC) lamivudine(3TC) efavirenz (Stocrin®)

2

**PREVIOUS!!!!**

# What ART to start Children on?

First Line Regimen	
All infants and children under 3 years (or < 10kg)	ABC + 3TC + LPV/r
Children $\geq 3$ years (and $\geq 10\text{kg}$ ) <sup>∞</sup>	ABC + 3TC + EFV
Currently on d4T-based regimen	Change d4T to ABC if Viral Load is undetectable If Viral load >1000 copies/ml manage as treatment failure If Viral load between 50 – 1000 copies/ml – consult with expert for advise

<sup>∞</sup> Children  $\geq 3$  years and exposed to NVP for 6 weeks or longer (PMTCT) should be initiated on ABC + 3TC + LPV/r





# What ART to start Children on?

## Second Line Regimen

### Failed First line Protease Inhibitor (PI) based regimen

	<i>Recommended Second line regimen</i>
ABC + 3TC + LPV/r	Consult with expert for advice*
D4T + 3TC + LPV/r	
Unboosted PI based regimen	

### Failed First line NNRTI based regimen (discuss with expert before changing)

<i>Failed First line NNRTI Based regimen</i>	<i>Recommended Second line regimen</i>
ABC + 3TC + EFV (or NVP)	AZT + 3TC + LPV/r
d4T + 3TC + EFV (or NVP)	AZT + ABC + LPV/r

# Advice for the expert

## \*Recommended Second Line regimen under expert advice

ABC + 3TC + LPV/r	<p><u>No previous daily NVP for PMTCT</u> AZT + 3TC + EFV* + LPV/r * Use NVP if &lt; 3 years or &lt;10kg</p> <p><u>Previous Daily NVP for PMTCT</u> Treat with Third line regimen</p>
D4T + 3TC + LPV/r	<p><u>No previous daily NVP for PMTCT</u> AZT + ABC + EFV* + LPV/r * Use NVP if &lt; 3 years or &lt;10kg</p> <p><u>Previous Daily NVP for PMTCT</u> Treat with Third line regimen</p>
Previously on a regimen with <u>unboosted PI</u> (e.g. ritonavir alone), or with rifampicin while on LPV/r	Must be managed by an expert on basis of genotype resistance testing to confirm PI susceptibility.

# Advice for the expert

## Third line regimens

Failing any 2nd line regimen

Refer for specialist opinion – Regimen based on genotype resistance testing, expert opinion and supervised care. Access to third line ART will be managed centrally by the National Dept of Health.



# M184V

- Crippling effect on the virus
- Delays emergence of TAMS
- Overcome by an accumulation of TAMS or other mutations
- M184V alone not associated with reduced virologic response to ABC but with TAMS increased resistance
- Increased sensitivity to AZT and D4T
- 3TC monotherapy has been demonstrated to “hold” patient due to M184V



# More tips.....

- K65R mutation selected by DDI, ABC or stavudine
- Confers resistance to TDF
- Be cautious of using ABC and TDF in same second line regimen as select for same mutations
- Is DDI a good second line drug?
- 12.6-30 % patients failing ABC/3TC may have DDI resistance
- Difficult to take
- ABC, 3TC, Alluvia and DDI can all be given once daily





# PENPACT 1 (PENTA 9 / PACTG 390)



A phase II/III randomised, open-label trial of combination antiretroviral regimens and treatment-switching strategies in HIV-1-infected antiretroviral naïve children

A collaboration between PENTA and PACTG /  
IMPAACT



# Primary Objectives

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A long-term comparison in ART naïve children of:

- **PI-based versus NNRTI-based initial therapy**
- two different viral load criteria for switching from 1st to 2nd line therapy:  
**>1,000 versus >30,000 copies/ml**

ART naïve  
children

1st-line  
ART

Switch criteria:  
confirmed  
VL at/after week 24  
(or CDC-C)

2nd-line  
ART  
("strongly  
encouraged")

**R  
A  
N  
D  
O  
M  
I  
S  
E**

**PI  
+  
2  
NRTIs**

**PI  
+  
2  
NRTIs**

**NNRTI  
+  
2  
NRTIs**

**NNRTI  
+  
2  
NRTIs**

Switch  
when  
VL>1,000  
c/ml

Switch  
when  
VL>30,000  
c/ml

Switch  
when  
VL>1,000  
c/ml

Switch  
when  
VL>30,000  
c/ml

**NNRTI  
+  
2 new  
NRTIs**

**NNRTI  
+  
2 new  
NRTIs**

**PI  
+  
2 new  
NRTIs**

**PI  
+  
2 new  
NRTIs**

**Minimum  
follow-up:**  
  
4 years  
  
**Primary  
Endpoint:**  
  
Change  
in VL from  
baseline  
to 4 years



Preliminary Results

Cumulative Resistance at end of follow-up

	PI 1,000	PI 30,000	NNRTI 1,000	NNRTI 30,000	P- value
<b>Total children</b>	66	65	68	64	
Number expected to have tests	24	17	21	21	
Number with tests	21	11	17	19	
<b>NRTI resistance</b>					0.01*
1 or 2 mutations	8 (12%)	5 (8%)	10 (15%)	9 (14%)	
3+ mutations	1 (2%)	1 (2%)		7 (11%)	
3+ mutations group					

Analysis assumes those without tests were not resistant

# PENPACT 1 Trial Summary

- **PI- or NNRTI**
- switch at viral load **1,000** or **30,000** c/ml
- Children on ART had excellent clinical/CD4 outcomes:
  - >70% on first-line ART at ~5 years
  - >80% VL <400c/ml at 4 years
  - No difference in adverse events
- No difference in NNRTI or PI resistance switching at **1,000** v **30,000** c/ml
- More children accumulated NRTI resistance mutations over 5 years in **NNRTI** group switching at **30,000** c/ml



# Bottom line.....

- Need to switch children on NNRTI based regimen early at a lower VL to prevent the accumulation of TAMS



# SA HIV Clinicians Society...

- Adherence adherence adherence
- Failing ABC/3TC/EFV
  - LPV/r + AZT/3TC (if less than 12 years)
  - LPV/r + TDF/3TC (> 12 years and meet criteria)
- Failing D4T/3TC/EFV or NVP
  - LPV/r + AZT/3TC



# Guidelines for Tenofovir use in Adolescents

- TDF 300mg daily  $\geq 15$  years **and** over 35 kg if eGFR is  $\geq 80$  mL/min per 1.73 m<sup>2</sup>

**eGFR in adolescents <16 years :**

**height(cm)X40**

**Creatinine( $\mu$ mol/l)**

- Can switch those on ABC if meet criteria
- Newly diagnosed with Hepatitis B
- Failing ART with limited other options (don't switch 1 drug)
- Monitoring
- eGFR 1 month, 3 months and then 6 monthly.



# Lerato

- 2 year old. She weighs 9.5 kg and is receiving 1.5 ml bd kaletra; 3TC 4 ml bd; ABC 4 ml bd
- She is on continuation phase of TB treatment
- She was started on ART 9 months ago
- Received SD NVP and AZT 6 weeks as neonate
- Clinically well
- CD4 count is 1000 cells/mm<sup>3</sup> (30%); her viral load is 6523 copies/ml (done 3 months previously)



- How should she be managed?
- Why is her viral load elevated?
- Does she have resistance?
- To which drugs is she most likely to be resistant?
- Should her regimen be changed?
- To what?



# Why is her VL elevated?

- Adherence
- Her kaletra has not been “super-boosted” or doubled since she is on TB treatment
- ? Ongoing TB/MDR: less likely as she is responding to TB treatment clinically



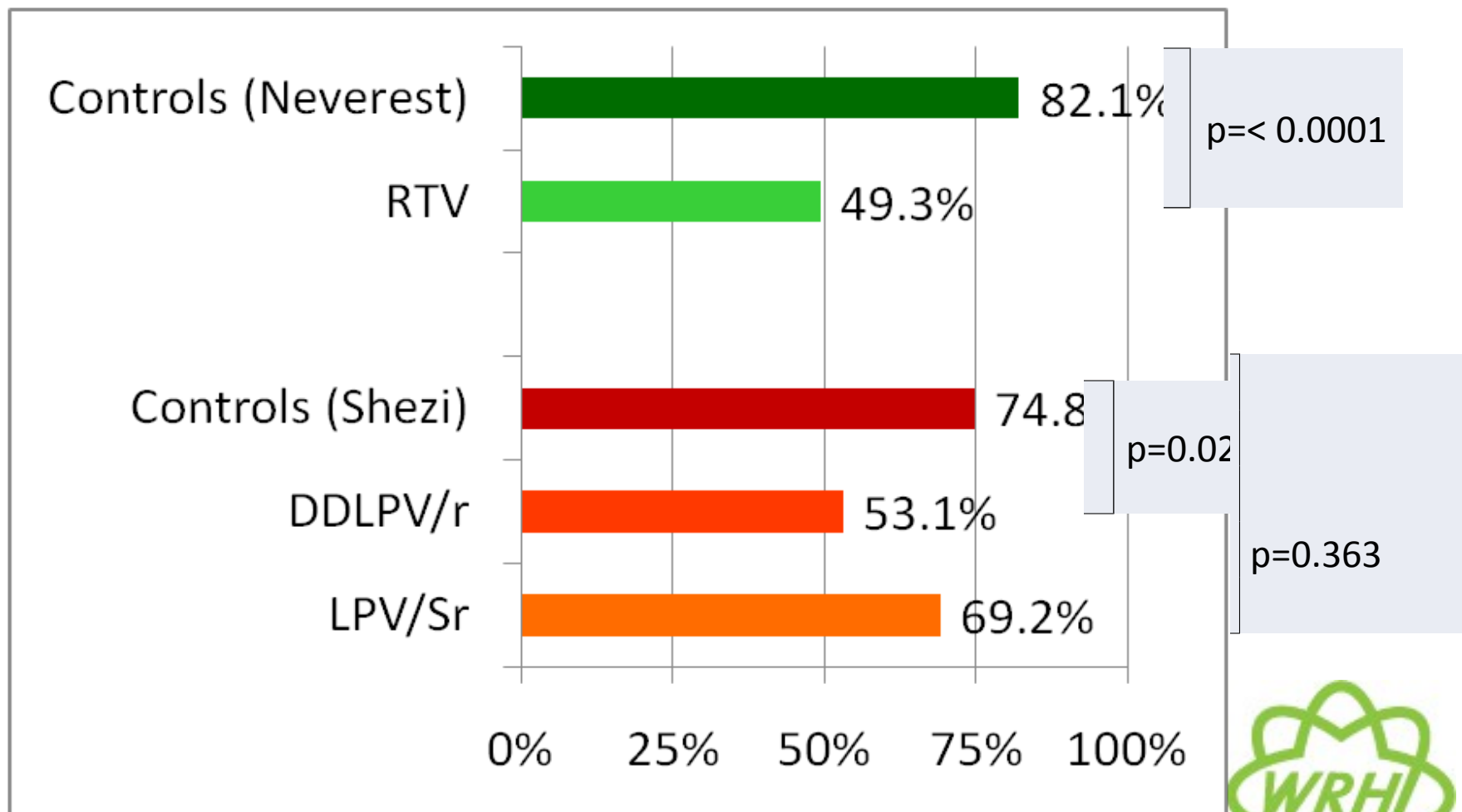


# TB and HIV co-treatment

- 18 young children (median 1.25 and 1.59)
- Compared those on lop/r only vs those on lop/r (low double dose 230 mg/m<sup>2</sup>) and TB Rx
- Pre-dose lop concentration; c<sub>max</sub> and AUC all significantly lower in children on TB Rx
- Lacked the power to correlate clinically
- Concern about double dosing lop/r especially at a lower dose



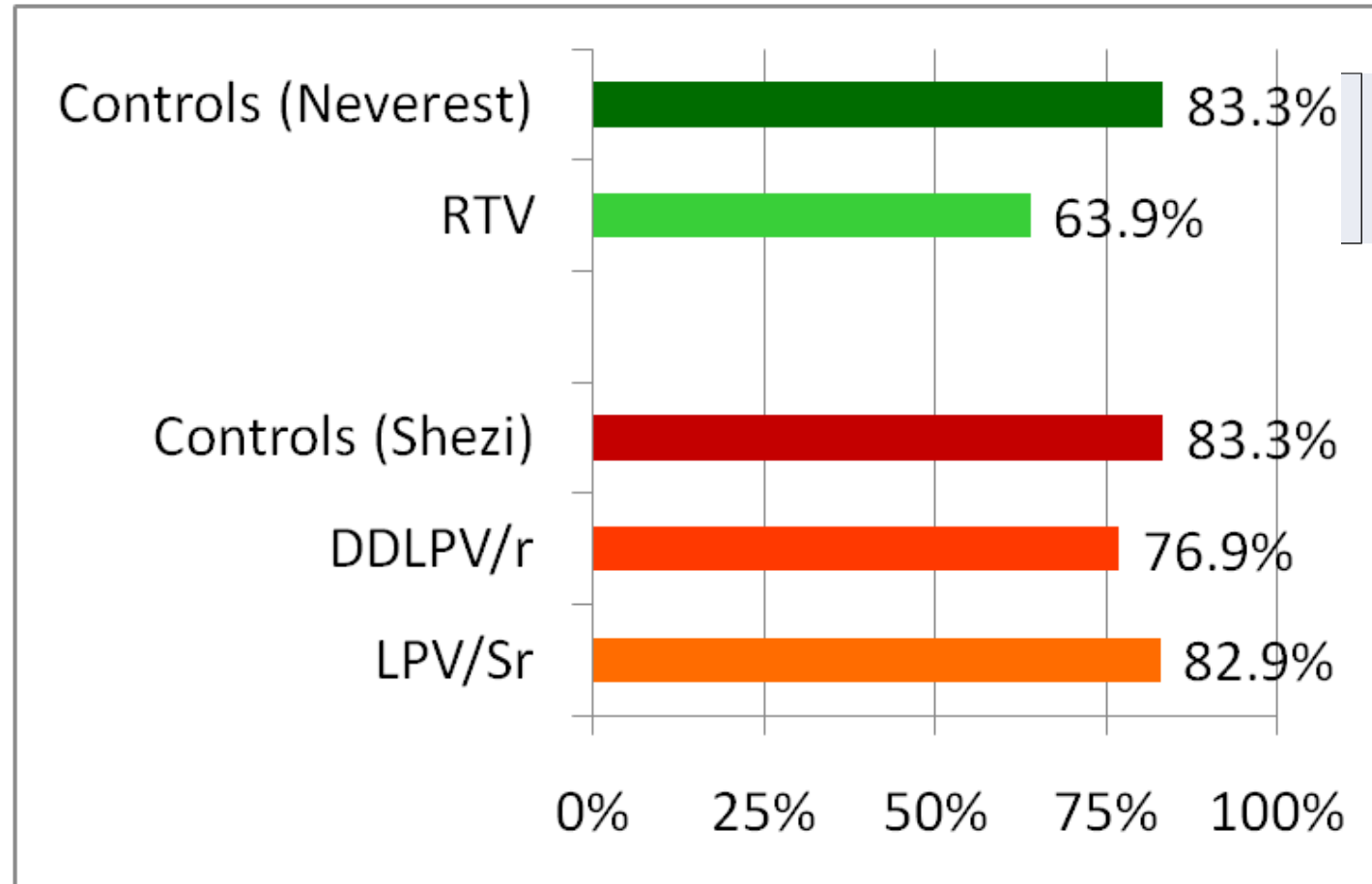
# HIV viral suppression rates at 6 months



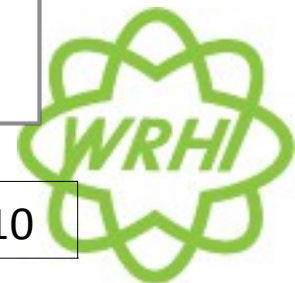
Moodley et al CROI 2010



# HIV Viral suppression rates at 12 months



Moodley et al CROI 2010



# Does she have resistance?

- 17 % patients had major PI resistance mutations
- All RTV as single PI
- Median age 36 months
- Also all had M184V
- 50% had VL between 1000 and 5000 copies/ml
- +- a third had TAMS



# Further management.....

- Lerato may have PI resistance due to suboptimal dosing
- Most likely has resistance to 3TC +/- ABC
- Lerato had SD NVP and AZT
- Resistance testing very helpful in this case
- She is still on treatment for TB
- Adherence has been good recently but previously problematic



# What ART to start Children on?

## Second Line Regimen

### Failed First line Protease Inhibitor (PI) based regimen

	<i>Recommended Second line regimen</i>
ABC + 3TC + LPV/r	Consult with expert for advice*
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d4T + 3TC + EFV (or NVP)	AZT + ABC + LPV/r

# Advice for the expert

## \*Recommended Second Line regimen under expert advice

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# Nevirapine Resistance

## NVP Resistance Detected Post single Dose NVP for PMTCT

- ~25-40% women
- ~40-90% babies

## Implications for future NVP-Based Treatment Regimen

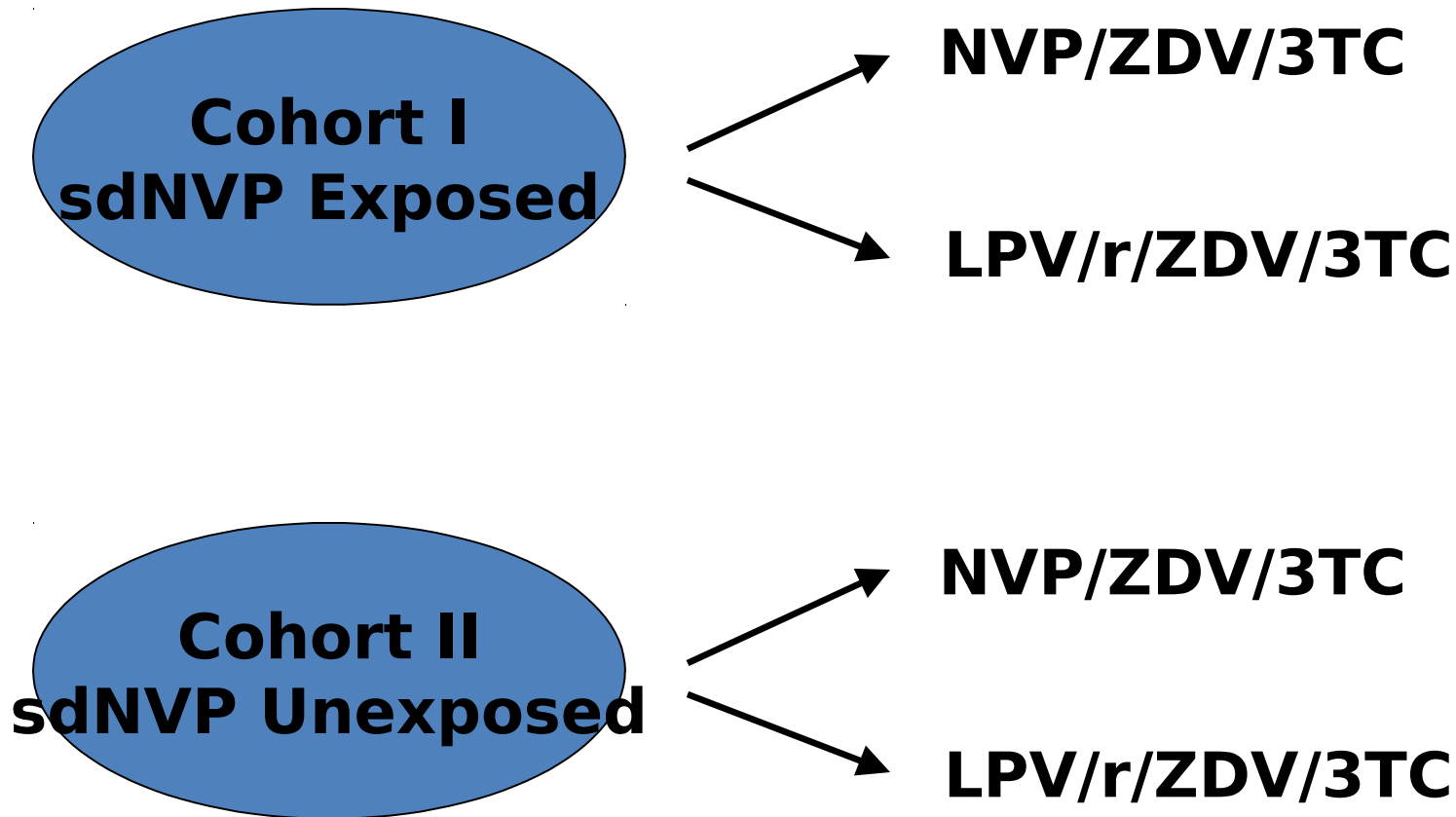
- women > 6 months post delivery → viral suppression (Mashi Plus)
- < 6 months post delivery ↑ risk of virological failure NVP arm (Lockman et al Mashi Plus Study, Botswana 2005)
- Neverest 1

## Data Required for Infants

- Mashi Plus study -15 children each in non-NVP vs NVP treatment arms → significant ↑ risk virological failure in NVP arm
- Neverest (Coronation Hospital, Johannesburg)
- PACTG 1060 (see next slide)

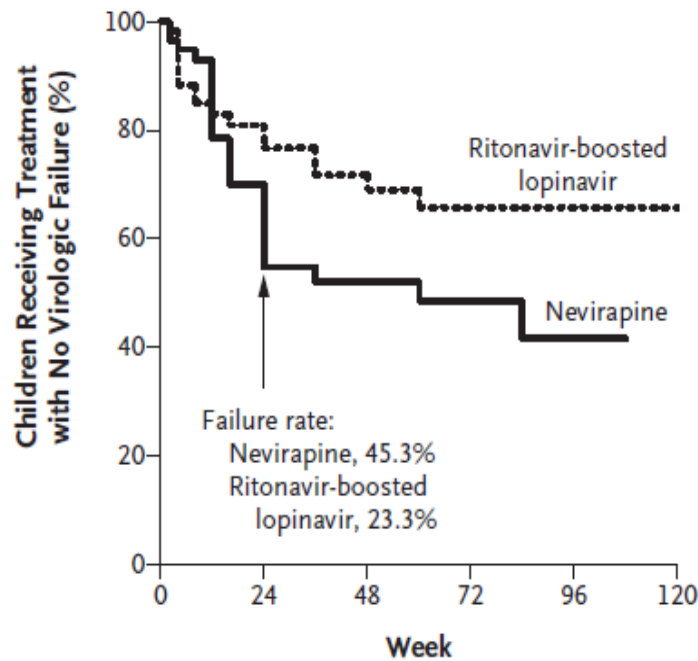


# P1060 Study Design



Thanks to the P1060 team

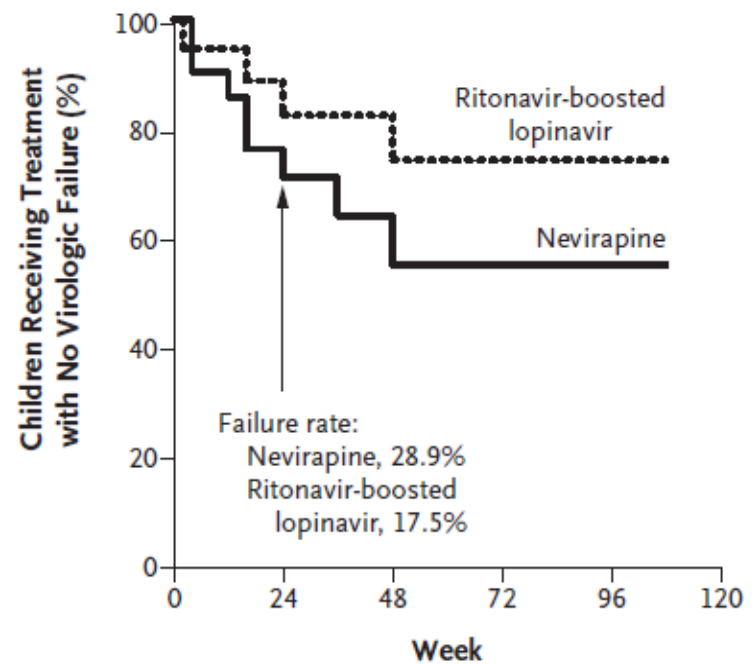
**A Time to Virologic Failure or Discontinuation, Age <12 Mo**



**No. at Risk**

Nevirapine	60	32	18	9	2
Ritonavir-boosted lopinavir	63	38	26	10	3

**B Time to Virologic Failure or Discontinuation, Age ≥12 Mo**



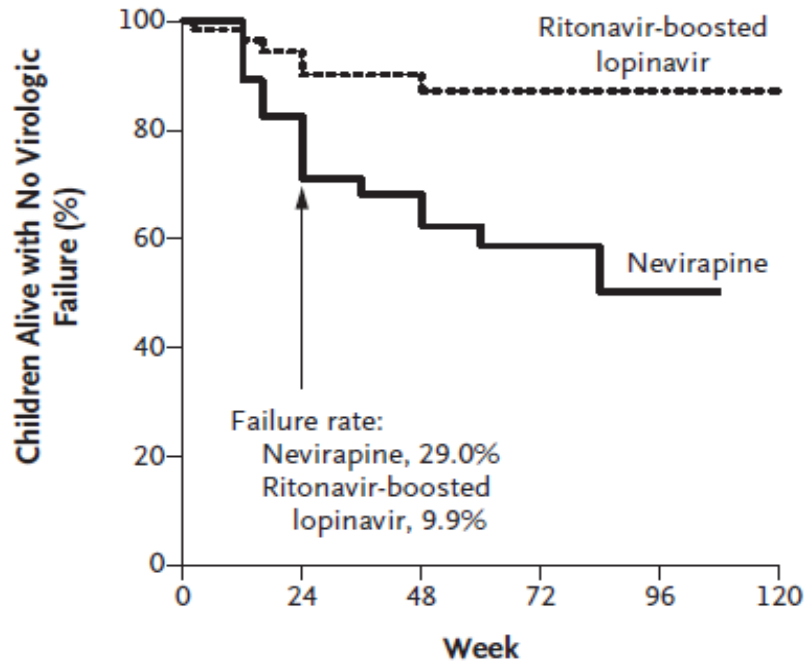
**No. at Risk**

Nevirapine	22	15	7	5	2
Ritonavir-boosted lopinavir	19	14	10	6	5

**Figure 1. Times to Primary End Point and to Virologic Failure, According to Treatment and Age Stratum.**

The time to the primary end point of virologic failure or discontinuation of treatment by study week 24 is shown among children 6 to less than 12 months of age (Panel A) and among children 12 months of age or older (Panel B) ( $P=0.52$  for interaction of age stratum with treatment at week 24); the time to virologic failure or death is also shown among children in the two age groups (Panels C and D, respectively) ( $P=0.65$  for interaction of age stratum with treatment at week 24).

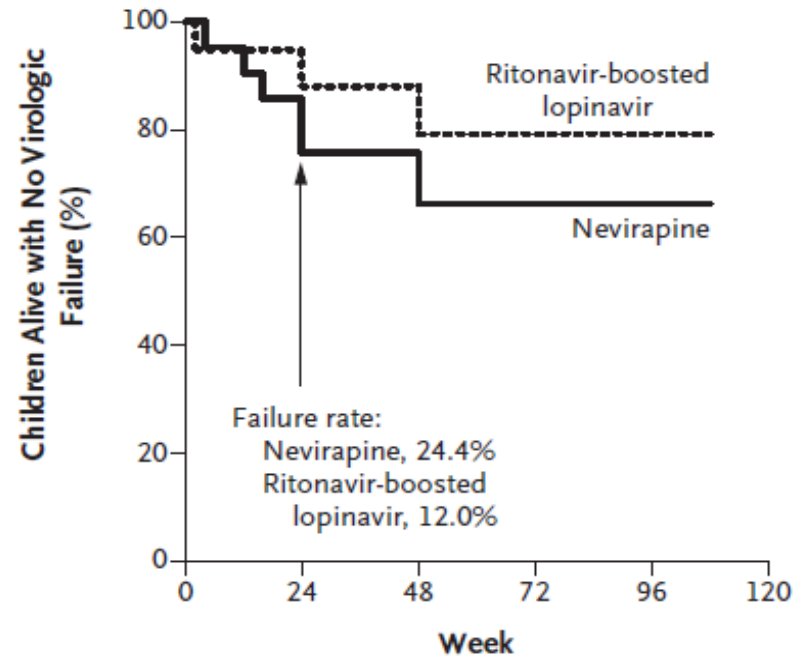
**C Time to Virologic Failure or Death, Age <12 Mo**



**No. at Risk**

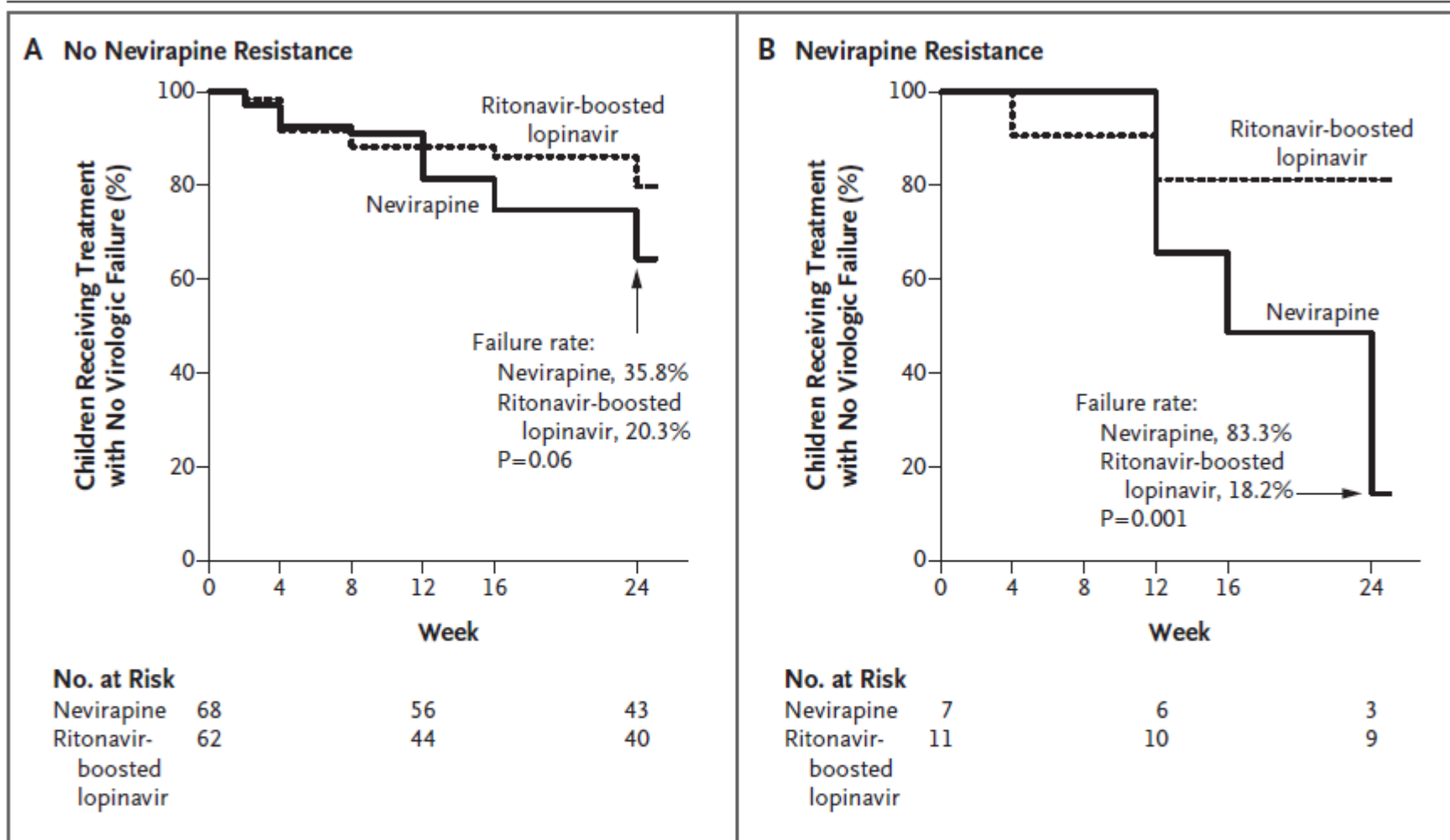
Nevirapine	60	36	23	10	2
Ritonavir-boosted lopinavir	63	44	30	14	4

**D Time to Virologic Failure or Death, Age ≥12 Mo**



**No. at Risk**

Nevirapine	22	17	8	6	3
Ritonavir-boosted lopinavir	19	14	10	6	5



**Figure 2. Time to Primary End Point, According to Treatment and Resistance or Nonresistance to Nevirapine at Baseline.**

The primary end point was virologic failure or discontinuation of treatment by study week 24. P=0.02 for interaction between treatment and baseline resistance to NNRTIs.

**New drugs.....**  
**Protease inhibitors**



# Remember....

- Most important factor is adherence!!!
- Unless addressed may risk losing 2nd and 3rd line regimens



	Atazanavir	Darunavir	Tipranavir	Fosemprenavir
ART naïve	6 years upwards	3 years upwards	2 years upwards	2 years upwards
ART experienced	> 25 kg	Yes	Yes	6 years upwards
Dose	Weight-banded	Weight-banded	14 mg/kg bd	30 mg/kg unboosted 18 mg/kg boosted
Ritonavir	Yes	Yes	Yes	Changes dose
Side effects	<ul style="list-style-type: none"> <li>↑ In Br</li> <li>↑ PR interval</li> <li>Metabolic SE</li> <li>Transaminitis</li> </ul>	<ul style="list-style-type: none"> <li>Skin rash</li> <li>Hepatotoxicity</li> <li>G/E SE</li> <li>Metabolic</li> </ul>	<ul style="list-style-type: none"> <li>Intracranial haemorrhage</li> <li>Skin rash</li> <li>G/E SE</li> <li>Metabolic</li> </ul>	<ul style="list-style-type: none"> <li>G/E SE</li> <li>Skin rash (SJS)</li> <li>Headache</li> <li>Metabolic</li> <li>Nephrolithiasis</li> </ul>
Response in those failing PI	Insufficient data in < 25 kg	56% VL< 50 c/ml 24 weeks but 88% < 400	45.6 % at 48 weeks VL< 400	57% at 24 weeks 43% at 48 weeks
Limitations for 3rd line	No data in young children, not registered SA	Not registered in SA	Increased pill burden Serious SE	Not registered



# Darunavir dosing table

Body Weight, kg	DRV dose, mg b.i.d.	DRV dose, mL b.i.d.	Ritonavir dose, mg b.i.d.	Ritonavir dose, mL b.i.d.
10 – 10.9	250	2.6	33	0.4
11 – 11.9	275	2.8	36	0.4
12 – 12.9	300	3.0	38	0.5
13 – 13.9	325	3.4	43	0.5
14 – 14.9	350	3.6	46	0.6
≥ 15 – 29.9	375	3.8	50	0.6
≥ 30 – 39.9	450	4.6	60	0.7
≥ 40*	600	6.0	100	1.25



# NNRTI's

	Etravirine	Rilpivarinine
Approved in children	6-18 years	No
Registered in SA (children)	No	No
Dose	5.2 mg/kg/dose (max 200mg)	Not available
Side effects	Nausea Rash including Stevens Johnson Syndrome HSRs	Insomnia Depression, mood change Headache Rash
Resistance profile	Better than other NNRTIs Failing an NNRTI for prolonged period with > 3 mutations increases ETR resistance	Use with caution if VL > 100 000 copies as increased risk of virologic failure



# Integrase inhibitors: Raltegravir

- Advantage: new class of drug
- Registered by FDA > 2 years; > 10 kg
- Dose 6 mg/kg
- SE: G/E; Headache, fever, muscular effects

	2-5 years	6-11 years	12-18 years
Virologic suppression (12 weeks)	86%	78%	80%
Virologic suppression (24 weeks)	71 %	56%	



# Fusion and entry inhibitors

## **Enfuvirtide:**

- Expensive, twice daily subcutaneous injection
- SE: Local injection site (98%), bacterial pneumonia, HSR
- Uncommonly used

## **Maraviroc:**

- Not approved < 16 years
- HIV tropism assay, only use on patients with CCR5-tropic virus



# Wish list for 3rd line.....

- Darunavir
- Raltegravir
- Etravirine
- Lower dose tenofovir
- Atazanavir for lipaemic control
- [JamalK@health.gov.za](mailto:JamalK@health.gov.za)

*Guidelines for the Use of Antiretroviral Agents in Pediatric Infection 2011  
Violari et al CROI 2011; Nachman et al CROI 2011; Wiznia et al CROI 2011;  
Chadwick et al CROI 2007  
Eley BS, Meyers T. Pediatr drugs 2011*



# When To Change Treatment

- **Toxicity**
  - Short-term side-effects
  - Longterm side-effects
- **Treatment failure**
  - Clinical
  - Virological (Resistance)
  - Immunological
- **Drug interactions**



# So what should we do for Lerato?

- SD NVP
- DRV on compassionate use? Dose?
- Backbone: AZT and 3TC
- ? Add NVP
  
- Lerato is too young for 3TC monotherapy or a holding regimen
- She has TB as well which is a concern



# SA Clinicians Society

- Adherence adherence adherence!!!!
- Holding strategy????? In this case?
- Genotyping guiding ART
- If no genotyping:
  - Full dose RTV: DRV or lop/r /EFV or ETR/2 NRTI's
  - No RTV: lop/r/Efv/2NRTI's
  - Daily NVP: DRV/r/ral/2NRTI's or high dose lop/r + NNRTI + 2NRTI's





# Things to remember.....

- NEVER change 1 drug in a failing regimen
- Resistance testing is ideal but if unavailable choose wisely
- And PHONE A FRIEND!!!!
- See expert advice and group discussion
- Holding regimens can work but they are not to be taken lightly

