

# HIV Resistance Case Presentation 1

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# Siyanda

- 12 yr old male
- Known HIV positive on ART since 2010 currently on a 3<sup>rd</sup> line regimen
- Presented with 1 month history of:
  - Progressive abdominal swelling
  - Associated cough and night sweats

# ART History - 2010

- Admitted to a Peripheral hospital with –
- Suspected TB – suggestive CXray
- HIV positive:
  - Started - ABC / 3TC / EFV – 2 weeks later
- Baseline (9/12/2010)
  - CD4 count: 7 (0.72%)
  - Viral Load: 1 400 000 c/ml (6.15 log)

# 2011

- Completed 6 months of TB treatment
- Step-up adherence
- Repeat Bloods: (13/06/2011)
  - CD4: 10 (0.47%)
  - VL: 201 399 c/ml (5.30 log)

# 2012/13

	01/12	04/12	11/12	04/13	6/13	10/13
CD4	79	10			4	4
CD4%	4.5%	0.49%			0.2%	0.8%
VL	529450	431244	382984	1674976	549738	1576299
VL log	5.72	5.63	5.58	6.22	5.82	6.18



# How would you manage Siyanda

A: Do HIV DR Test

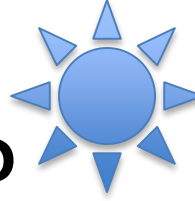
B: Check adherence  
and keep on same  
regimen

C: Change to  
AZT/3TC/LPV/rtv

D: Change to  
AZT/ABC/LPV/rtv

# 2014

- 02/2014:
  - VL: 375 307 (5.57 log)
- Changed to second line:
  - AZT / 3tc / Lopinavir/rtv
- 08/2014:
  - CD4: 116 (6.03%)
  - VL: 1 283 127 (6.11 log)



# What do you think is happening?

A: Non-adherent to all  
meds

B: New opportunistic  
infection

C: Intermittent  
adherence

D: Not taking the  
LPV/rvt



# 2015

- Same old, same old.....just a new regimen
- 06/2015 VL: 175 096 c/ml (5.24 log)
- 08/2015 referred to ID:
  - VL: 304818 c/ml
  - Identified and addressed adherence/non-compliance
  - Disclosure was done
  - Resistance test performed

# Resistance Test

- NRT Mutations
  - D67N , T69N , K70R , L74I
  - Y115F , M184V, T215F, K219Q
- NNRTI Mutations
  - L100I, K103N, H221Y
- PI Mutations
  - M46I, I54V , V82A
  - L10V, K43T

## Drug Resistance Interpretation: PR

PI Major Resistance Mutations: M46I, I54V, V82A  
PI Minor Resistance Mutations: L10V, K43T  
Other Mutations: None

### Protease Inhibitors

atazanavir/r (ATV/r)	High-level resistance
darunavir/r (DRV/r)	Susceptible
fosamprenavir/r (FPV/r)	Intermediate resistance
indinavir/r (IDV/r)	High-level resistance
lopinavir/r (LPV/r)	High-level resistance
nelfinavir (NFV)	High-level resistance
saquinavir/r (SQV/r)	Intermediate resistance
tipranavir/r (TPV/r)	Intermediate resistance

## Drug Resistance Interpretation: RT

**NRTI Resistance Mutations:** D67N, T69N, K70R, L74I, Y115F, M184V, T215F, K219Q

**NNRTI Resistance Mutations:** L100I, K103N, H221Y

**Other Mutations:** None

### Nucleoside RTI

lamivudine (3TC) High-level resistance

abacavir (ABC) High-level resistance

zidovudine (AZT) High-level resistance

stavudine (D4T) High-level resistance

didanosine (DDI) High-level resistance

emtricitabine (FTC) High-level resistance

tenofovir (TDF) High-level resistance

### Non-Nucleoside RTI

efavirenz (EFV) High-level resistance

etravirine (ETR) Intermediate resistance

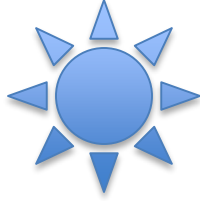
nevirapine (NVP) High-level resistance

rilpivirine (RPV) High-level resistance

## Mutation Scoring

PR	ATV/r	DRV/r	FPV/r	IDV/r	LPV/r	NFV	SQV/r	TPV/r
M46I	<u>10</u>	<u>0</u>	<u>10</u>	<u>10</u>	<u>10</u>	<u>20</u>	<u>5</u>	<u>5</u>
I54V	<u>15</u>	<u>0</u>	<u>10</u>	<u>15</u>	<u>15</u>	<u>20</u>	<u>15</u>	<u>20</u>
V82A	<u>15</u>	<u>0</u>	<u>15</u>	<u>30</u>	<u>30</u>	<u>30</u>	<u>15</u>	<u>0</u>
L10V	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>
K43T	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>10</u>
I54V+V82A	10	-	10	10	10	10	10	-
V82A+M46I	10	-	10	10	5	10	-	-
<b>Total:</b>	60	0	55	75	70	90	45	35

RT	3TC	ABC	AZT	D4T	DDI	FTC	TDF	EFV	ETR	NVP	RPV
D67N	<u>0</u>	<u>5</u>	<u>15</u>	<u>15</u>	<u>5</u>	<u>0</u>	<u>5</u>	-	-	-	-
T69N	<u>0</u>	<u>0</u>	<u>5</u>	<u>5</u>	<u>10</u>	<u>0</u>	<u>0</u>	-	-	-	-
K70R	<u>0</u>	<u>10</u>	<u>30</u>	<u>15</u>	<u>10</u>	<u>0</u>	<u>10</u>	-	-	-	-
L74I	<u>0</u>	<u>30</u>	<u>0</u>	<u>0</u>	<u>60</u>	<u>0</u>	<u>0</u>	-	-	-	-
Y115F	<u>0</u>	<u>45</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>	<u>15</u>	-	-	-	-
M184V	<u>60</u>	<u>15</u>	<u>-10</u>	<u>-10</u>	<u>10</u>	<u>60</u>	<u>-10</u>	-	-	-	-
T215F	<u>5</u>	<u>15</u>	<u>45</u>	<u>45</u>	<u>15</u>	<u>5</u>	<u>15</u>	-	-	-	-
K219Q	<u>0</u>	<u>5</u>	<u>10</u>	<u>10</u>	<u>5</u>	<u>0</u>	<u>5</u>	-	-	-	-
L100I	-	-	-	-	-	-	-	<u>45</u>	<u>30</u>	<u>45</u>	<u>60</u>
K103N	-	-	-	-	-	-	-	<u>60</u>	<u>0</u>	<u>60</u>	<u>0</u>
H221Y	-	-	-	-	-	-	-	<u>10</u>	<u>10</u>	<u>10</u>	<u>10</u>
M184V+Y115F	-	-	-	-	-	-	10	-	-	-	-
D67N+K70R+K219Q	10	10	10	10	10	10	10	-	-	-	-
L74I+M184V	-	15	-	-	-	-	-	-	-	-	-
<b>Total:</b>	75	150	105	90	125	75	60	115	40	115	70



# What Regimen would you recommend?

A: AZT/3TC/LPV/rtv

B:

AZT/3TC/DRV/rtv/RAL

C:

AZT/3TC/DRV/rtv/RAL/  
ETV

D:

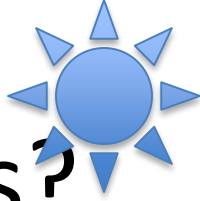
AZT/3TC/DRV/rtv/DTG

# 11/2015: Wt:23kg

- Was started on:
  - Darunavir – 450mg BD (3x 150mg Tab)
  - Ritonavir – 100mg BD (1x 100mg Tab)
  - Raltegravir – 150mg BD (1½ 100mg Tab)
  - AZT/3TC (300/150mg) 1 tab BD
  
  - Total burden: 6½ tabs BD = 13 tabs/day

- Now presents 5 months later with:
  - Progressive abdominal swelling
  - Cough / Night Sweats
- On examination:
  - Pyrexial, Generalised Lymphadenopathy
  - Extensive bilateral chest signs with wheeze
  - Significant Ascites





# What is your differential diagnosis?

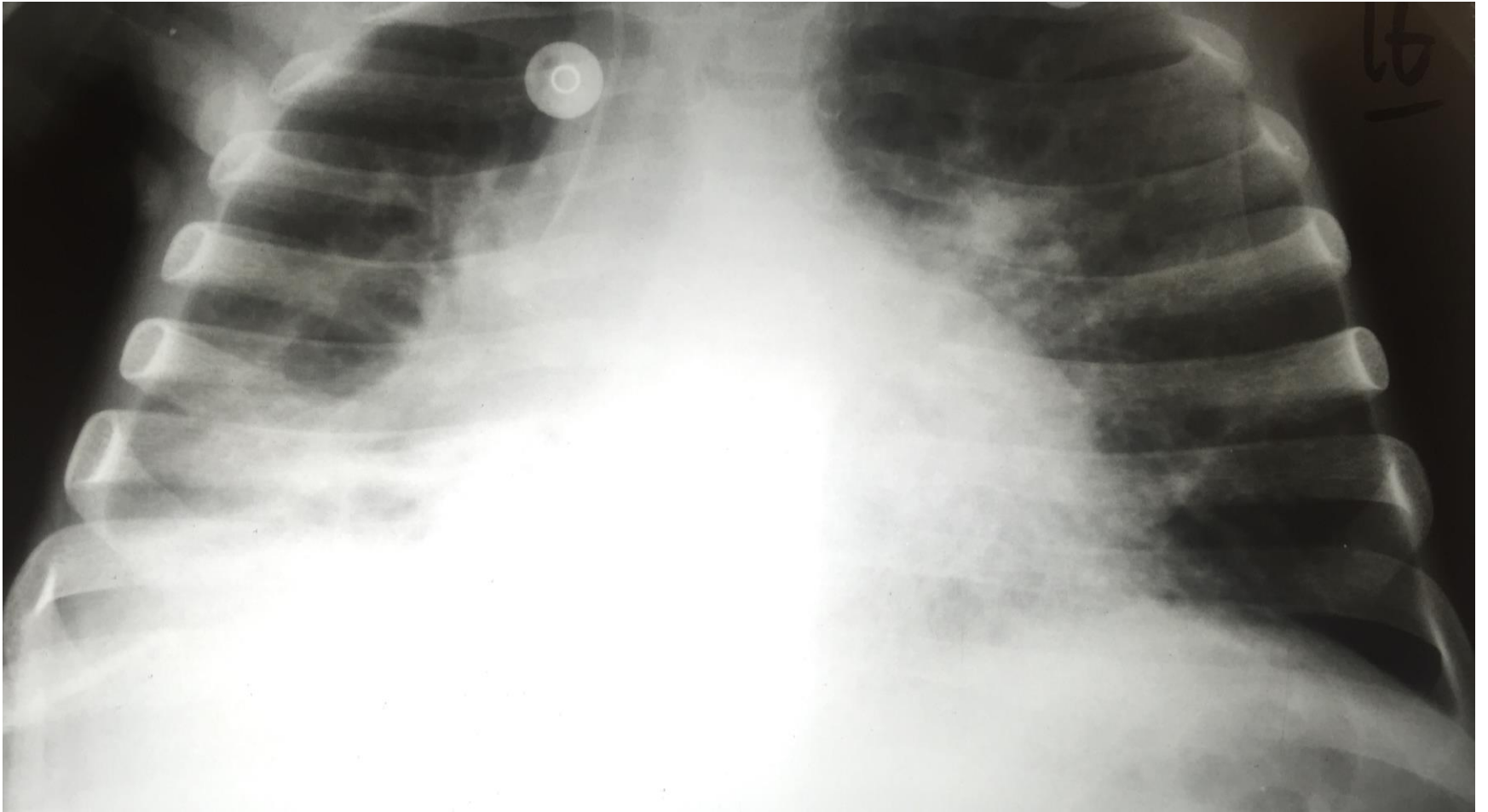
A: New Opportunistic  
Infection

B: Malignancy

C: TB IRIS

D: Treatment Failure

# C Xray



- Sputum: GeneXpert Negative
- FBC: wbcc: 5.63 / hb:9.5 / plt: 515
- LFT: 79/33/180/25/20
- ESR: >140
  
- Ascitic Tap:
  - Exudate ( LDH:635 / Protein:46)
  - AFB neg / GeneXpert Neg

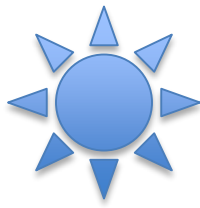
- CD4: 255 (10.1%)
- VL: 237 c/ml

Diagnosis:

Unmasking TB IRIS

- Pulmonary TB
- Abdominal TB

In view of the ART regimen how would you manage?



A: Rifampicin/INH/PZA

B:

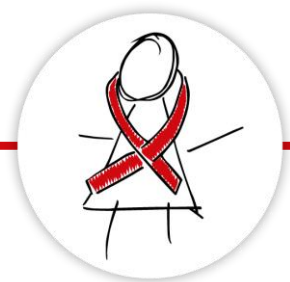
Rifampicin/INH/PZA/Ethambutol

C:

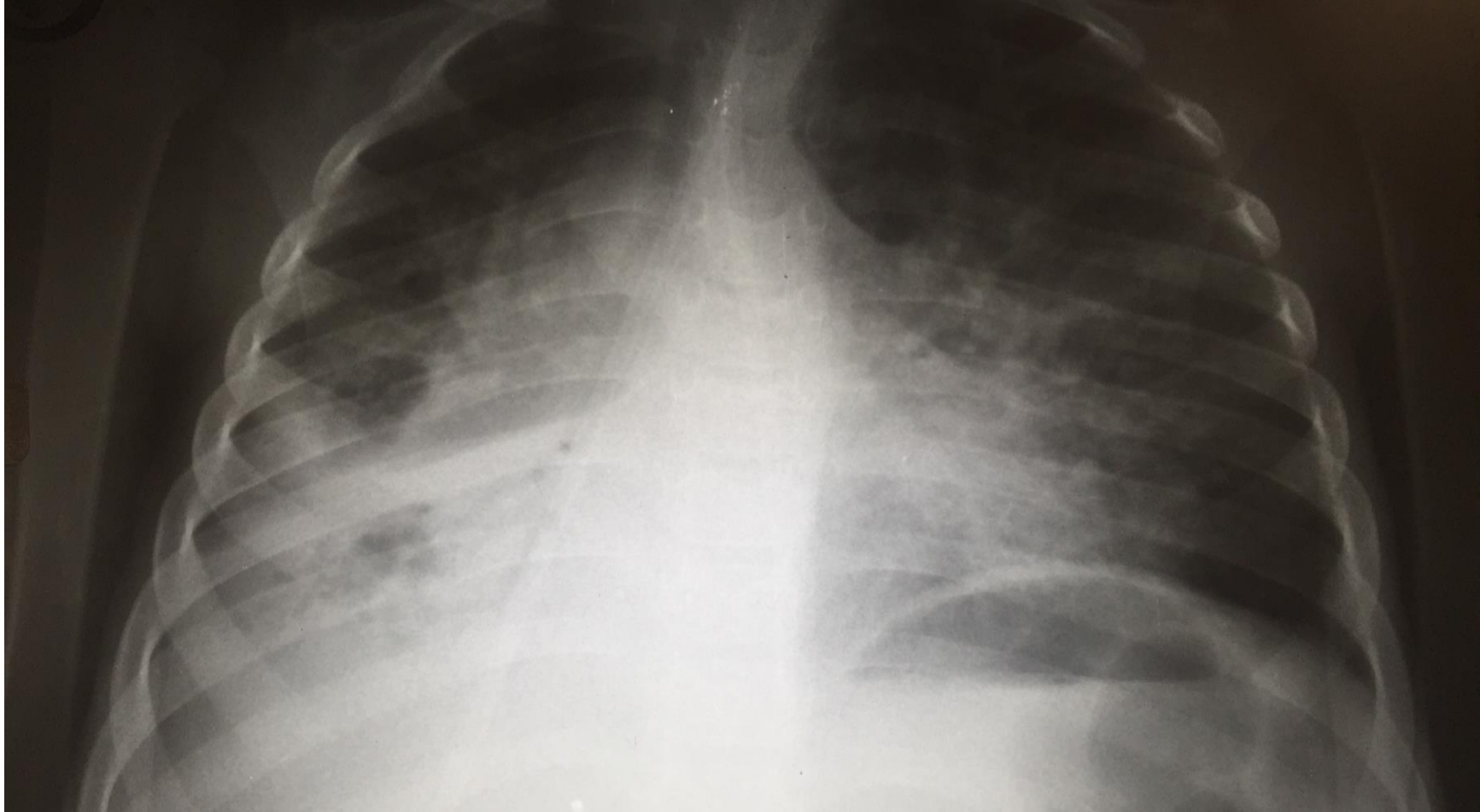
Rifabutin/INH/PZA/Ethambutol

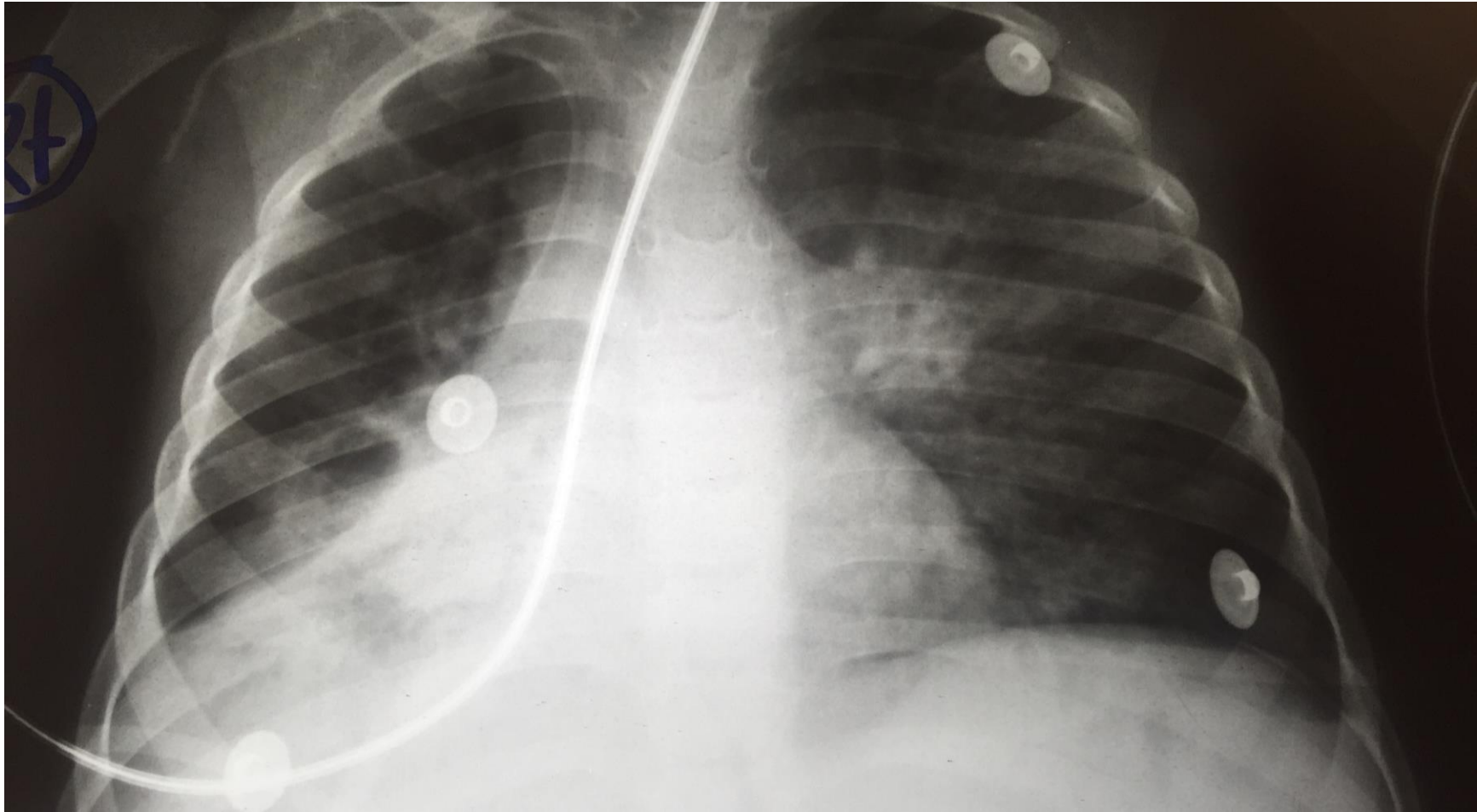
D:

Rifabutin/INH/PZA/Ethionamide



- Rifabutin – 300mg dly – 2 tabs dly
- Isoniazid – 300mg dly – 2 tabs dly
- Pyrazinamide – 1g dly – 2 tabs dly
- Ethambutol – 600mg dly – 1 ½ tabs dly
  
- Pill count:
  - TB meds: 7 ½ tabs/day
  - ARVs: 13 tabs/day
  - Total: 20 ½ tabs/day







# HIV Resistance Case Presentation 2

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King Edward VIII Hospital / UKZN  
Paediatric Infectious Diseases Unit



# Sihle



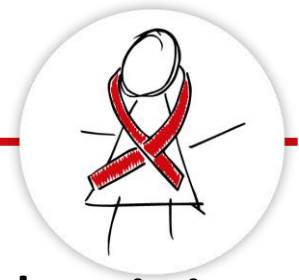
- History:
- 19yr old male was referred – initially treated at a private health care facility.
- Sihle’s mother received PMTCT during pregnancy in Private– unsure of regimen used
- He was started on an EFV based regimen by a General Practitioner in early 2000s while under the care of his mother.

# 2009



- In 2009 (13 years old) – referred to a Paediatrician because of treatment failure as per verbal history – no results available.
- Caregiver changed to the father
- Changed to:
  - Zidovudine / Lamivudine / Lopinavir/rtv
- No results available

# 2013



- 
- At age 17yrs – was seen by an adult physician due to treatment failure.
  - Viral Load: 64 773 copies/ml
  - CD4 Count: Abs: 66 cells/ul
  - HIV resistance test ordered
  - Diagnosed with PTB

# Resistance Test

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- NRT Mutation:
  - D67N, K70R, M184V, T215Y
- NNRTI Mutations:
  - K103N, A98G, V106I, E138K
- PI Mutations:
  - No major or minor mutations

# Stanford Database



## HIVdb: Genotypic Resistance Interpretation Algorithm

Date: 28-Jun-2016 11:05:07 UTC

### Drug Resistance Interpretation: RT

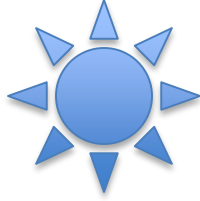
**NRTI Resistance Mutations:** D67N, K70R, M184V, T215Y  
**NNRTI Resistance Mutations:** A98G, K103N, V106I, E138K  
**Other Mutations:** None

Nucleoside RTI		Non-Nucleoside RTI	
lamivudine (3TC)	High-level resistance	efavirenz (EFV)	High-level resistance
abacavir (ABC)	Intermediate resistance	etravirine (ETR)	Low-level resistance
zidovudine (AZT)	High-level resistance	nevirapine (NVP)	High-level resistance
stavudine (D4T)	High-level resistance	rilpivirine (RPV)	Intermediate resistance
didanosine (DDI)	Intermediate resistance		
emtricitabine (FTC)	High-level resistance		
tenofovir (TDF)	Low-level resistance		



## Mutation Scoring

RT	3TC	ABC	AZT	D4T	DDI	FTC	TDF	EFV	ETR	NVP	RPV
D67N	<u>0</u>	<u>5</u>	<u>15</u>	<u>15</u>	<u>5</u>	<u>0</u>	<u>5</u>	-	-	-	-
K70R	<u>0</u>	<u>10</u>	<u>30</u>	<u>15</u>	<u>10</u>	<u>0</u>	<u>10</u>	-	-	-	-
M184V	<u>60</u>	<u>15</u>	<u>-10</u>	<u>-10</u>	<u>10</u>	<u>60</u>	<u>-10</u>	-	-	-	-
T215Y	<u>5</u>	<u>15</u>	<u>45</u>	<u>45</u>	<u>15</u>	<u>5</u>	<u>15</u>	-	-	-	-
A98G	-	-	-	-	-	-	-	<u>10</u>	<u>10</u>	<u>30</u>	<u>15</u>
K103N	-	-	-	-	-	-	-	<u>60</u>	<u>0</u>	<u>60</u>	<u>0</u>
V106I	-	-	-	-	-	-	-	<u>0</u>	<u>0</u>	<u>0</u>	<u>0</u>
E138K	-	-	-	-	-	-	-	<u>10</u>	<u>10</u>	<u>10</u>	<u>30</u>
<b>Total:</b>	65	45	80	65	40	65	20	80	20	100	45



# What Regimen would you recommend?

A: AZT/3TC/LPV/rtv

B:

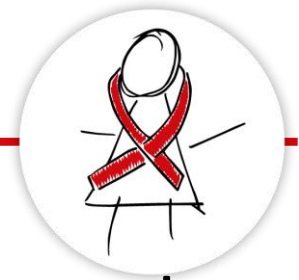
AZT/3TC/DRV/rtv/RAL

C: TDF/3TC/DRV/rtv

D: TDF/3TC/LPV/rtv



# 2013



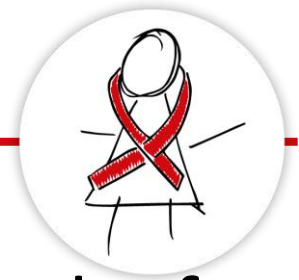
- Diagnosed with Pulmonary TB and started on anti-TB treatment – treated for 6 months
- Changed to:
  - Lopinavir/Rtv (Alluvia Tablet) + Raltegravir
  - No history provided regarding superboosting or double dose Alluvia

# 2014



- Repeat bloods 6 months post change in regimen:
  - VL: 401 998 copies/ml (5.6 log)
  - CD4 count: Abs: 8 cells/uL (1.03%)

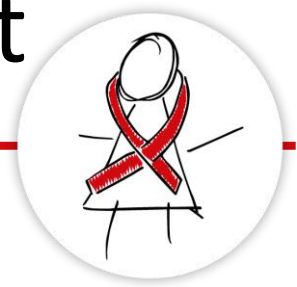
# 2015



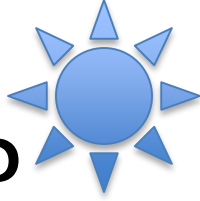
- Referred to the public sector due to lack of funds:
- CD4 count: Abs 1 cell/uL
- VL: 136 366 copies/ml (5.13 Log)
- Clinically wasted (BMI 11.6), PPE
- No evidence of a new OI

# Immediate Management

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- OI Prophylaxis:
  - Cryptococcus
  - PJP
- Adherence/Compliance assessment
  - Father extremely concerned/supervises every dose
  - Sihle – quiet and dejected
- HIV Resistance testing



# What do you think is happening?

A: Non-adherent to all  
meds

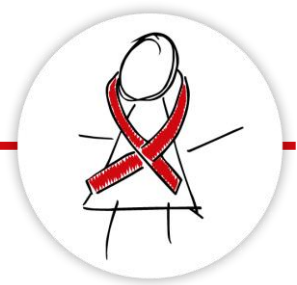
B: New opportunistic  
infection

C: Intermittent  
adherence

D: Not taking the  
LPV/rvt

# What was the problem

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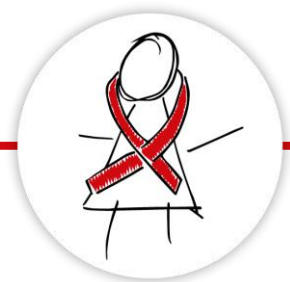


- Unable to swallow the Alluvia tablet – crushing the tablet





- On discussion with Sihle – he was unable to swallow any tablets – would feel the tablet going down and would immediately start retching.
- No difficulty with ingestion of food or liquids.
- On physical examination – no anatomical defects were identified to explain the symptoms

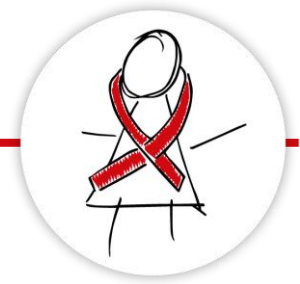


Q: How would you manage Sihle's inability to tolerate tablets?



# Resistance Test

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- NRT Mutation:
  - D67N, K70R, M184V, T215Y
  - **NONE**
- NNRTI Mutations:
  - K103N, A98G, V106I, E138K
  - **K103N, V106I**
- PI Mutations:
  - No major or minor mutations
  - **Major: M46I, L76V, I84V    Minor: A71V, L10I**

# Resistance Test

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- Integrase Mutations
  - L74M, T97A, Y143R

## **Integrase Inhibitors:**

- |                      |                             |
|----------------------|-----------------------------|
| ■ Raltegravir (RAL)  | High-level resistance       |
| ■ Elvitegravir (EVG) | Intermediate resistance     |
| ■ Dolutegravir (DTG) | Potential low-level resist. |



## Drug Resistance Interpretation: PR

PI Major Resistance Mutations: M46I, L76V, I84V  
PI Minor Resistance Mutations: L10I, A71V  
Other Mutations: None

### Protease Inhibitors

atazanavir/r (ATV/r)	High-level resistance
darunavir/r (DRV/r)	Intermediate resistance
fosamprenavir/r (FPV/r)	High-level resistance
indinavir/r (IDV/r)	High-level resistance
lopinavir/r (LPV/r)	High-level resistance
nelfinavir (NFV)	High-level resistance
saquinavir/r (SQV/r)	High-level resistance
tipranavir/r (TPV/r)	Intermediate resistance



## Drug Resistance Interpretation: RT

NRTI Resistance Mutations: D67N, K70R, M184V, T215Y

NNRTI Resistance Mutations: A98G, K103N, V106I, E138K

Other Mutations: None

### Nucleoside RTI

lamivudine (3TC)	High-level resistance
abacavir (ABC)	Intermediate resistance
zidovudine (AZT)	High-level resistance

### Non-Nucleoside RTI

efavirenz (EFV)	High-level resistance
etravirine (ETR)	Low-level resistance
nevirapine (NVP)	High-level resistance

stavudine (D4T)	High-level resistance
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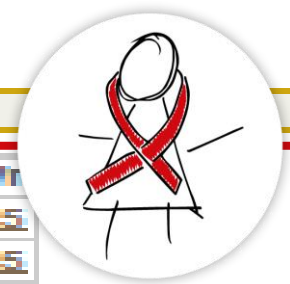
rilpivirine (RPV)	Intermediate resistance
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didanosine (DDI)	Intermediate resistance
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emtricitabine (FTC)	High-level resistance
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tenofovir (TDF)	Low-level resistance
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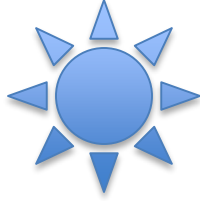
## Mutation Scoring



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
L76V	-5	20	60	30	30	0	-5	-5
I84V	60	15	60	60	30	60	60	30
L10I	0	0	0	0	0	0	0	0
A71V	0	0	0	0	0	0	0	0
L76V+M46I	-	-	-	10	10	10	-	-
Total:	65	35	130	110	80	90	60	30

RT	3TC	ABC	AZT	D4T	DDI	FTC	TDF	EFV	ETR	NVP	RPV
D67N	0	5	15	15	5	0	5	-	-	-	-
K70R	0	10	30	15	10	0	10	-	-	-	-
M184V	60	15	-10	-10	10	60	-10	-	-	-	-
T215Y	5	15	45	45	15	5	15	-	-	-	-
A98G	-	-	-	-	-	-	-	10	10	30	15
K103N	-	-	-	-	-	-	-	60	0	60	0
V106I	-	-	-	-	-	-	-	0	0	0	0
E138K	-	-	-	-	-	-	-	10	10	10	30
Total:	65	45	80	65	40	65	20	80	20	100	45

IN	DTG	EVG	RAL
Y143R	0	10	60
L74M	5	10	10
T97A	5	10	15
L74M+Y143R	-	5	-
T97A+Y143R	-	5	-
Total:	10	40	85



# What Regimen would you recommend?

A: AZT/3TC/LPV/rtv

B:

AZT/3TC/DRV/rtv/DTG

C:

TDF/3TC/DRV/rtv/DTG

D: TDF/3TC/LPV/rtv

