TB and HIV

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Case 1

Themba is a 11 month old child who is admitted to the ward with a chronic cough.

His mother has been recently started on Anti-TB treatment (Sputum positive) and she has been recently diagnosed as HIV positive.

Themba is severely malnourished (<60th centile), clinically WHO stage 4.

HIV DNA PCR done on a previous admission is found to be positive

Is Themba eligible for HAART?

Will you start Themba on TB prophylaxis?

Should Themba have been started on Primary TB Prophylaxis?

Should you start his HAART first or the TB treatment first?

How long should you wait between starting TB Treatment and HAART?

Co-treatment of TB in the Child with HIV Infection

- There are two major considerations in HIV-infected children who develop tuberculosis
  - Treatment of the tuberculosis
  - Treatment of HIV infection
    - Immediate
    - 2 - 8 week deferral
    - 6 month deferral-to complete treatment of tuberculosis

- Treatment of TB in a child with HIV infection can be complicated by a number of factors:
  1. Pharmacokinetic issues:
     1. Drug-drug interactions
     2. Malabsorption
  2. Adherence with multiple medications
  3. Overlapping drug toxicities
  4. Paradoxical reactions (Immune reconstitution events)

1. Drug-Drug Interactions

- Rifamycins induce the activity of the isoenzyme CYP3A4 (3A) of the cytochrome P450 system
  - Substantially decrease serum concentrations of PIs and NNRTIs
    - Rifampicin is the most potent
    - Rifapentine is intermediate
    - Rifabutin is the least potent
  - Rifabutin is also a substrate for CYP3A4 and its concentration is increased by inhibition of CYP3A4 by PIs and NNRTIs
    - Other rifamycins are not 3A substrates and, therefore, serum concentrations are not affected

Rifampicin markedly decreases blood levels of all protease inhibitors

PI	Rifampicin
Saquinavir	↓ 80%
Ritonavir	↓ 35%
Indinavir	↓ 90%
Nelfinavir	↓ 82%
Amprenavir	↓ 81%
Lopinavir/ritonavir	↓ 75%

Rifampicin & Non-nucleoside reverse transcriptase inhibitors

	Dose Change		Comments
Efavirenz	⇑ to 800 mg/day*	None (600 mg/day)	Efavirenz AUC ⇓ by 22%; no change in rifampicin concentration. *May ⇓ to 600 mg/day if 800 mg dose not easily tolerated.
Nevirapine	200 mg twice-daily	None (600 mg/day)	Nevirapine AUC ⇓ 37-58% and Cmin ⇓ 68% with 200 mg 2x/day dose (***14-17***). Limited, though favorable, data for efficacy of 200 mg BID dose, although should only be used if no other options exist and clinical and virologic monitoring possible. May consider 300 mg BID only if close biochemical monitoring feasible; however, no clincal, pharmacokinetic, or safety data available for 300 mg BID dose.
Delavirdine	Rifampin and delavirdine should not be used together.		Delavirdine AUC ⇓ by 95%.

Dose Adjustments:

- NRTIs are not affected and therefore do not require dose adjustments.
- NNRTI – EFV AUC decreased by 20-25% - currently no dose change if using Paediatric WHO dosage table
- PI – All Pis affected by Rifampicin:
  - Kaletra/Alluvia – add extra ritonavir to regimen : Dose of extra RTV = 0.75 X dose of Kaletra (ml)

Adjusted dosing of Lopinavir/Ritonavir (Kaletra®) for children on TB treatment (with Rifampicin)

Dose:
Prescribing **additional Ritonavir** to give a 1:1 ratio (mg) for Lopinavir/Ritonavir is currently recommended
(NOT double-dosing of Kaletra® as previously recommended)

N.B. The increased dose of Ritonavir is required to counteract the enhanced metabolism of Kaletra® due to induction of liver enzymes by rifampicin (TB treatment)

Frequency:
12 hourly

Formulation:
Syrup - 80mg/ml
(at room temperature for 30 days only - otherwise refrigerate)
Capsules - 100mg

Wt (in kg)	Single dose by weight	
	Kaletra®	Ritonavir
5 – 5,9	1,0 ml	0,8 ml
6 – 6,9	1,5 ml	1,2 ml
7 – 7,9	1,5 ml	1,2 ml
8 – 8,9	2,0 ml	1,5 ml
9 – 9,9	2,0 ml	1,5 ml
10 – 10,9	2,0 ml	1,5 ml
11 – 11,9	2,0 ml	1,5 ml
12 – 13,9	2,0 ml	1,5 ml
14 – 16,9	2,0 ml	1,5 ml
17 – 19,9	2,5 ml or 1½ capsules*	2,0 ml or 1½ capsules*
20 – 24,9	3 ml or 2 capsules	2,5 ml or 2 capsules
25 – 29,9	3,5 ml or 2 capsules	2,8 ml or 2½ capsules°
30 – 34,9	4 ml or 3 capsules	3,0 ml or 2½ capsules°
35 – 39,9	5 ml or 3 capsules	3,8 ml or 3 capsules
> 40	5 ml or 3 capsules	3,8 ml or 3 capsules

* best achieved by giving: 1 capsule in the morning and 2 capsules at night

° best achieved by giving: 2 capsules in the morning and 3 capsules at night

Simple alternative method for calculating additional dose of Ritonavir:

When using syrup, the additional dose of Ritonavir is 0.75 times the volume of the Kaletra dose
e.g. if the Kaletra dose is 2ml 12 hourly,
then the additional Ritonavir dose will be 0.75 x 2 = 1.5ml 12 hourly

APPENDIX VII: SIMPLIFIED PAEDIATRIC DRUG DOSING FOR RESOURCE POOR SETTINGS: First Line (Regimen 1)

Weight (kg)	D4T Twice daily Suspension (1 mg/ml) or Capsules (20 mg)	3TC Twice daily Syrup (10 mg/ml) or Tablets (150 mg)		EFAVIRENZ (Stocrin®) Once daily Capsules (50 mg & 200 mg)	KALETRA (LPV/RNV) Twice daily Syrup (80/20 mg) or Capsules (133/33 mg)		Intensive TB Treatment (first 2 months) Mon - Fri, daily RHZ 60/30/150 Rimcure Paed 3FDC tablets	Maintenance TB Treatment (last 4 months) Mon - Fri, daily RH 60/30 Rifanah Sachets	Additional RITONAVIR (if on TB Rx) Twice daily Syrup (80mg/ml) or Capsules (100 mg)		Bactrim (PCP Prophylaxis) Daily Syrup, or Tablets	Multivitamins (Remember to give Vitamin A) Daily Vidaylin drops, Syrup, or Tablets
2 – 2,9	2,5 ml	1 ml			0,4 ml		½ tab	½ tab	0,3 ml		1,6 ml	0,6 ml Vidaylin
3 – 3,9	3,5 ml	1,4 ml			0,5 ml		½ tab	½ tab	0,4 ml		2 ml	0,6 ml Vidaylin
4 – 4,9	5 ml	1,8 ml			0,7 ml		½ tab	½ tab	0,5 ml		3 ml	0,6 ml Vidaylin
5 – 6,9	6 ml	2 ml			5-5,9 kg 1 ml 6-6,9 kg 1,5 ml		1 tab	1 tab	0,8 ml 1,2 ml		5 ml	2,5 ml syrup
7 – 9,9	10 ml	3 ml			7-7,9 kg 1,5 ml 8-9,9 kg 2 ml		1½ tabs	1½ tabs	1,2 ml 1,5 ml		5 ml	2,5 ml
10 – 11,9	10 ml	4 ml		200 mg	2 ml	1 caps	2 tabs	2 tabs	1,5 ml		7,5 ml	5 ml
12 – 14,9	15 ml	5 ml		200 mg	2 ml	am: 1 pm: 2	2 tabs	2 tabs	1,5 ml		7,5 ml	5 ml
15 – 16,9	15 ml	6 ml		200 mg + 50 mg	2 ml	am: 1 pm: 2	3 tabs	3 tabs	1,5 ml		10 ml	5 ml
17 – 19,9	20 mg	7 ml	½ tab	200 mg + 50 mg	2,5 ml	am: 1 pm: 2	3 tabs	3 tabs	2 ml	am: 1 pm: 2	10 ml or 1½ tabs	5 ml
20 – 24,9	20 mg	9 ml	am: ½ pm: 1	200 mg + 2 x 50 mg	3 ml	2 caps	4 tabs	4 tabs	2,5 ml	2 caps	15 ml or 2 tabs	1 tab
25 – 29,9	20 mg	11 ml	1 tab	200 mg + 3 x 50 mg	3,5 ml	2 caps	5 tabs	5 tabs	2,7 ml	2 caps	2 tabs	1 tab
30 – 34,9	20 mg	13 ml	1 tab	200 mg + 3 x 50 mg	4 ml	3 caps	6 tabs	6 tabs	3 ml	am: 2 pm: 3	2 tabs	1 tab
35 – 40	20 mg	15 ml	1 tab	200 mg + 200 mg	5 ml	3 caps	Use adult dose 2 Rifafour	Use adult dose 2 Rimactizid 150/75	3,8 ml	3 caps	2 tabs	1 tab

Compiled for KwaZulu-Natal ARV Clinics – Dr Kimesh Naidoo (Updated November 2008)

If treating HIV & TB

- Rifamycins should not be excluded from TB regimen because of fear of interactions as exclusion may delay sputum conversion, prolong duration of therapy and ultimately is associated with worse outcome
- NRTI's and NtRTI's (TDF) – no significant interactions and no dose adjustment necessary
- Rifampin can be used with EFV, ritonavir and Saq/r
- May wish to substitute Rifabutin for Rifampin if necessary to use Kaletra, will need dose adjustment of Rifabutin

2. Adherence to Multiple Medications

- Combination of TB treatment and HAART increases the pill burden: For an 18kg old child increases pill burden from 8 tab/day to 11 tab/day

- Extra effort is needed to ensure adherence to both treatment regimens

3. Overlapping Toxicities

Side Effects	Anti-TB Drugs	ARV Drugs
Skin rash	PZA, RIF,RBT, INH	NVP, DLV, EFV,ABC
Nausea, vomiting	PZA, RIF,RBT, INH	ZDV, RTV, AMP, IDV
Hepatitis	PZA, RIF,RBT, INH	NVP, all Pis, immune reconstitution
Leukopenia, anemia		ZDV

Burman. AmJRespCCM 2001;164:7

- Themba is initiated on D4T/3TC/Kaletra - 2 weeks after starting TB treatment.
- 2 weeks later his mother brings him to the clinic complaining of yellow eyes.
- A Liver Function Test was ordered:

GGT	359 - Grade 2
ALT	1245 - Grade 4

- How would you manage Themba?

Principles of management:

- Grade 4 LFT – Need to stop all potentially hepato-toxic drugs
- Viral Hepatitis Screen
- Repeat LFT until AST/ALT returns to normal or < 2 X ULN
- Reintroduce TB treatment first:
  - Start with the least hepatotoxic drugs first – starting with Ethambutol, repeat LFT a week later.
  - If remains ISQ – add INH then RIF (+/- PZA)
- Reintroduce ARV Treatment

4. Paradoxical Reactions - IRIS

Case 2

- Patient MM
- 7 month old female
- HIV positive – WHO Stage 4
  - HIV encephalopathy – delayed milestones / abn neurology (increased tone/brisk reflexes)
  - Marasmus – weight 52% of expected
- Started HAART 13/11/2007 – Stavudine / Lamivudine / Kaletra
- TB workup: No contact, CXRay not suggestive of TB, G/W negative
- Previous admission – Bronchopeumonia / GE

- Presented on 25/11/2007 (2 weeks after starting HAART) with:
  - Cough , Difficulty in breathing x 5 days
  - Feeding intolerance
  - Right Axillary swelling

- Examination:
  - Irritable, Pyrexial, Oeophageal candidiasis
  - Weight had decreased
  - Generalized LAD/ Rt Axillary mass – indurated, 3 X 4cm, fluctuant
  - BCG scar – ulcerated
  - Brisk reflexes bilaterally/ Central/Peripheral Hypertonicity

- Diagnosis:
  - Acute Bronchopneumonia- ? Bacterial / ?TB with suspected meningitis.

- Treatment:
  - Ceftriaxone IVI
  - High dose Bactrim IVI
  - IV Fluids / Oxygen / Feeds
  - Continue Antiretroviral therapy

- Investigations:
  - Chest Xray: Right hilar lymphadenopathy with bilateral patchy infiltrates.
  - Lumbar puncture: normal
  - CT Brain: normal
  - U/S Abd: No intra-abd LAD noted
  - FNA L/n: Sent for MCCS / AFB / Culture
  - Gastric Washings: AFB / Culture

- Both Gastric Washings and FNA L/N – 2 week culture positive

- Differential:
  - IRIS – BCG or MTB
  - Disseminated BCG disease
  - Dual BCG/MTB

Management

A: Regional BCG IRIS with no dissemination

Observe, regular follow-up for progression.

Report as vaccine-related adverse event to EPI.

B: Local or regional disease:

Treat medically:

INH 15-20 mg/kg/day

Rifampicin 20mg/kg/day

PZA 20-25mg/kg/day (2months or until TB excluded)

Ethambultol 20-25mg/kg/day

Ofloxacin 15mg/kg/day or ciprifloxacin 30mg/kg/day

Consider therapeutic aspiration if node fluctuant 2-4 weekly follow-up: if no improvement or deterioration of adenitis consider excision biopsy.

B: Suspected or confirmed distant or disseminated disease:

- Treat medically as above.
- Consider expedited HAART initiation.
- Monitor for drug toxicity
- Report as vaccine-related adverse event to EPI.