Regimen Design and Dosing for Children with Drug-Resistant TB: A Case-Based Discussion

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A three-year old child with fever, lethargy and difficulty walking

James Seddon
Jennifer Furin
Objectives

• Illustrate a pediatric case of MDR-TB
• Demonstrate when to suspect MDR-TB in a child and when to start treatment
• Understand how to construct MDR-TB treatment regimens in children
• Consider the dosage calculations of second-line TB drugs in children
• Review recent and future developments in the treatment of MDR-TB in children
Case History

• CC is a three-year-old boy who has been in the hospital for 4 weeks at the time of consultation.
• He was brought to the health center by his mother nearly 6 weeks ago when she noted he was febrile, lethargic, and seemed to have little interest in playing.
• At the center he was given some “antibiotics” and told to come back in one week.
Case History

• The following week his mother brought him back and she reported he was no better and that he seemed to want to be carried all the time
• He was given some vitamins and sent home
Case History

• Six days later, his mother brought him to the hospital when he could no longer stand on his own and she noticed a “lump” on his back
• At that time, she also noted he was coughing and losing weight and was barely eating anything
Questions

1) What is the most likely disease to consider in the differential diagnosis?

2) What additional information would you want to know?
Case History

- T=39 degrees
- Weight=8.2kg length=67cm
- Pale, listless, lymphadenopathy, tachypnea, crackles and wheezes bilaterally
- Absent ankle reflexes, no spontaneous leg movement
- Fully vaccinated, HIV status unknown, uncle living in house with TB
- CXR and spine MRI shown
Questions

3) What is the most likely cause of this x-ray appearance?
Case History

• Admitted to the hospital and started on therapy for presumed TB with HRZE
• Gastric aspirates were obtained and shown to have AFB, but cultures were not done on the specimens (as was standard care in the NTP at the time this child presented)
• He was also started briefly on corticosteroids, but these were stopped after a week, as his physicians decided he had Potts’ disease and not TB meningitis
Case History

• His condition, however, continued to deteriorate, and he eventually became bedbound, lying almost motionless in a crib with an oxygen mask over his face

• He was so malnourished, he began to develop pressure sores, including over the bridge of his nose where the oxygen mask was placed
Questions

4) What is the most likely cause of his deterioration?

5) What information would be most helpful to try and obtain?
Case History

- Upon further questioning, his mother reported that the uncle who lived with them was started on treatment for a form of “strong TB”
- Uncle had MDR-TB with resistance to isoniazid, rifampin, ethambutol, and streptomycin and was on a regimen of pyrazinamide-kanamycin-levofloxacin-ethionamide-and cycloserine
Case Discussion

6) What is the most important thing to do next?

7) What drugs would you put in the treatment regimen?
When to Suspect Drug-Resistant Tuberculosis in children
Child MDR-TB Suspect Criteria

- History of previous treatment within the past 6-12 months
- Close contact with a person known to have MDR-TB, including household and school contacts
- Close contact with a person who has died from TB, failed TB treatment, or is non-adherent to TB treatment
- Failure to improve clinically after 2-3 months of first-line TB treatment, including persistence of positive smears or cultures, persistence of symptoms, and failure to gain weight (radiological improvement is frequently delayed)

Yes

Clinical assessment and MDR-TB diagnostic work-up including sputum, rapid tests, fluid sampling, biopsy

Results of diagnostic workup available

Yes

MDR-TB confirmed
Treatment based on DST

Yes

Clinically stable without concerning signs or symptoms
Await diagnosis and monitor closely

Clinically unstable with concerning signs and symptoms present (Tm>40, hypoxia, respiratory distress, hemoptysis, indicators of meningeal or disseminated TB)
Consider empiric MDR-TB therapy while awaiting diagnosis

No

Continue evaluation for susceptible TB

No

DST-TB confirmed
First-line TB treatment

No diagnosis confirmed
Child MDR-TB Suspect Criteria

- History of previous treatment within the past 6-12 months
- Close contact with a person known to have MDR-TB, including household and school contacts
- Close contact with a person who has died from TB, failed TB treatment, or is non-adherent to TB treatment
- Failure to improve clinically after 2-3 months of first-line TB treatment, including persistence of positive smears or cultures, persistence of symptoms, and failure to gain weight (radiological improvement is frequently delayed)

Yes

Clinical assessment and MDR-TB diagnostic work-up including sputum, rapid tests, fluid sampling, biopsy

No

Continue evaluation for susceptible TB
Results of diagnostic workup available

Yes

MDR-TB confirmed
- Treatment based on DST

DS-TB confirmed
- First-line TB treatment

No diagnosis confirmed

Clinically stable without concerning signs or symptoms
- Await diagnosis and monitor closely

Clinically unstable with concerning signs and symptoms present (Tm>40, hypoxia, respiratory distress, hemaoptysis, indicators of meningeal or disseminated TB)
- Consider empiric MDR-TB therapy while awaiting diagnosis
The Treatment of Children with Drug-Resistant Tuberculosis Disease
DR-TB diagnosed

Use any Group 1 drugs to which the isolate has not been shown to be resistant
- Pyrazinamide
- Ethambutol
- Rifampin*

Add a drug from Group 2
- Amikacin
- Kanamycin
- Capreomycin
- Streptomycin**

Add a drug from Group 3
- Ofloxacin
- Levofloxacin
- Moxifloxacin

Add drugs from Group 4 until four active drugs prescribed
- Ethionamide (or prothionamide)
- Terizidone (or cycloserine)
- PAS

Add drugs from Group 5 until four active drugs prescribed
- High-dose isoniazid
- Clofazimine
- Linezolid
- Amoxicillin/clavulanate
- Imipenem/ cilastatin
- Thiacetazone (if confirmed HIV negative)
- Clarithromycin
HIV Co-Infection
Child diagnosed with DR-TB

Child:
- HIV positive and
- Already on HAART

Start DR-TB treatment ASAP

Child:
- Found to be HIV positive or
- Known to be HIV positive but not on HAART yet

Aim to start HAART two weeks after starting DR-TB treatment

Watch for signs of IRIS
- Worsening symptoms or signs (respiratory or lymphadenopathy)
- Fever
- Weight loss
- Abdominal pain

Treat with steroids if IRIS detected
If severe or life-threatening consider stopping HAART and restarting when DR-TB more established

Avoid if possible or monitor closely:
- D4T
- The combination of efavirenz and cycloserine/terizidone
- The combination of tenofovir and injectables
Drug Usage, Preparation and Dosing
<table>
<thead>
<tr>
<th>Group</th>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>Isoniazid</td>
<td>15-20mg/kg</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>30-40mg/kg</td>
</tr>
<tr>
<td></td>
<td>Ethambutol</td>
<td>20-25mg/kg</td>
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<tr>
<td>Group 2</td>
<td>Amikacin</td>
<td>15-20mg/kg</td>
</tr>
<tr>
<td></td>
<td>Capreomycin</td>
<td>15-30mg/kg</td>
</tr>
<tr>
<td>Group 3</td>
<td>Levofloxacin</td>
<td>15-20mg/kg</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin</td>
<td>7.5-10mg/kg</td>
</tr>
<tr>
<td>Group 4</td>
<td>Ethionamide</td>
<td>15-20mg/kg</td>
</tr>
<tr>
<td></td>
<td>Terizidone</td>
<td>15-20mg/kg</td>
</tr>
<tr>
<td></td>
<td>PAS</td>
<td>150mg/kg</td>
</tr>
<tr>
<td>Group 5</td>
<td>Linezolid</td>
<td>10mg/kg bd</td>
</tr>
<tr>
<td></td>
<td>Augmentin</td>
<td>15mg/kg tds</td>
</tr>
<tr>
<td></td>
<td>Clarithromycin</td>
<td>7.5mg/kg bd</td>
</tr>
</tbody>
</table>
### MDR-TB Weight-Based Dosing Chart for Children

<table>
<thead>
<tr>
<th>Group 1: Oral first-line anti-TB drugs</th>
<th>Group 2: Injectable anti-TB drugs (injectable agents or parenteral agents)</th>
<th>Group 3: Fluoroquinolones</th>
<th>Group 4: Oral bacteriostasis agents</th>
<th>Group 5: Anti-TB drugs with unclear efficacy or unclear role in MDR-TB treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethambutol (15-25 mg/kg)</td>
<td>Levofloxacin (15-20 mg/kg)</td>
<td>Ofloxacin (15-20 mg/kg)</td>
<td>Cycloserine/ Terizidone (150-200 mg/kg)</td>
<td>PAS (100-200 mg/kg)</td>
</tr>
<tr>
<td>Pyrazinamide (30-40 mg/kg)</td>
<td>Moxifloxacin (7.5-10 mg/kg)</td>
<td></td>
<td></td>
<td>Protonamid/ Ethionamide (15-20 mg/kg)</td>
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<tr>
<td></td>
<td>Injectable anti-TB drugs (injectable agents or parenteral agents)</td>
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<td></td>
<td>Anti-TB drugs with unclear efficacy or unclear role in MDR-TB treatment</td>
</tr>
<tr>
<td>Available Formulations</td>
<td>Available Formulations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 mg tablet</td>
<td>250 mg tablet</td>
<td>250 mg capsule</td>
<td>1 capsule in 10 mL water</td>
<td>100 mg tablet</td>
</tr>
<tr>
<td>400 mg tablet</td>
<td>25 mg/mL suspension</td>
<td>200 mg tablet</td>
<td>Daily</td>
<td></td>
</tr>
<tr>
<td>500 mg tablet</td>
<td>400 mg tablet</td>
<td>250 mg capsule</td>
<td>Twice Daily</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>250 mg tablet</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Target Dose</strong></td>
<td><strong>Available Dose</strong></td>
<td><strong>Target Dose</strong></td>
<td><strong>Available Dose</strong></td>
<td><strong>Target Dose</strong></td>
</tr>
<tr>
<td>Wt (kg)</td>
<td>100 mg tablet</td>
<td>100 mg tablet</td>
<td>100 mg tablet</td>
<td></td>
</tr>
<tr>
<td>3-9</td>
<td>2 tabs 2 mL</td>
<td>.25 tab 2.5 mL</td>
<td>.25 cap 2.5 mL</td>
<td>.5 tab 3-3.5</td>
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<tr>
<td></td>
<td>.25 tab 2.5 mL</td>
<td>.5 tab 2.5 mL</td>
<td>.5 cap 2.5 mL</td>
<td>.5 cap 4-4.5</td>
</tr>
<tr>
<td></td>
<td>.25 tab 2.5 mL</td>
<td>.5 tab 2.5 mL</td>
<td>.5 cap 4-4.5</td>
<td>.5 tab 5-5.5</td>
</tr>
<tr>
<td>10</td>
<td>.25 tab 2.5 mL</td>
<td>.5 tab 2.5 mL</td>
<td>.5 cap 4-4.5</td>
<td>.5 cap 5-5.5</td>
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<tr>
<td>11-11</td>
<td>.25 tab 2.5 mL</td>
<td>.5 tab 2.5 mL</td>
<td>.5 cap 4-4.5</td>
<td>.5 cap 5-5.5</td>
</tr>
<tr>
<td>12-12</td>
<td>.25 tab 2.5 mL</td>
<td>.5 tab 2.5 mL</td>
<td>.5 cap 4-4.5</td>
<td>.5 cap 5-5.5</td>
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<tr>
<td>13-13</td>
<td>.25 tab 2.5 mL</td>
<td>.5 tab 2.5 mL</td>
<td>.5 cap 4-4.5</td>
<td>.5 cap 5-5.5</td>
</tr>
<tr>
<td>14-14</td>
<td>.25 tab 2.5 mL</td>
<td>.5 tab 2.5 mL</td>
<td>.5 cap 4-4.5</td>
<td>.5 cap 5-5.5</td>
</tr>
<tr>
<td>15-15</td>
<td>.25 tab 2.5 mL</td>
<td>.5 tab 2.5 mL</td>
<td>.5 cap 4-4.5</td>
<td>.5 cap 5-5.5</td>
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<td>16-16</td>
<td>.25 tab 2.5 mL</td>
<td>.5 tab 2.5 mL</td>
<td>.5 cap 4-4.5</td>
<td>.5 cap 5-5.5</td>
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<tr>
<td>17-17</td>
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<td>.5 tab 2.5 mL</td>
<td>.5 cap 4-4.5</td>
<td>.5 cap 5-5.5</td>
</tr>
<tr>
<td>18-18</td>
<td>.25 tab 2.5 mL</td>
<td>.5 tab 2.5 mL</td>
<td>.5 cap 4-4.5</td>
<td>.5 cap 5-5.5</td>
</tr>
<tr>
<td>19-19</td>
<td>.25 tab 2.5 mL</td>
<td>.5 tab 2.5 mL</td>
<td>.5 cap 4-4.5</td>
<td>.5 cap 5-5.5</td>
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<tr>
<td>20-20</td>
<td>.25 tab 2.5 mL</td>
<td>.5 tab 2.5 mL</td>
<td>.5 cap 4-4.5</td>
<td>.5 cap 5-5.5</td>
</tr>
<tr>
<td>21-21</td>
<td>.25 tab 2.5 mL</td>
<td>.5 tab 2.5 mL</td>
<td>.5 cap 4-4.5</td>
<td>.5 cap 5-5.5</td>
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<tr>
<td>22-22</td>
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<td>.5 tab 2.5 mL</td>
<td>.5 cap 4-4.5</td>
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<tr>
<td>23-23</td>
<td>.25 tab 2.5 mL</td>
<td>.5 tab 2.5 mL</td>
<td>.5 cap 4-4.5</td>
<td>.5 cap 5-5.5</td>
</tr>
<tr>
<td>24-24</td>
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<td>.5 tab 2.5 mL</td>
<td>.5 cap 4-4.5</td>
<td>.5 cap 5-5.5</td>
</tr>
<tr>
<td>25-25</td>
<td>.25 tab 2.5 mL</td>
<td>.5 tab 2.5 mL</td>
<td>.5 cap 4-4.5</td>
<td>.5 cap 5-5.5</td>
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<tr>
<td>26-26</td>
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<td>.5 tab 2.5 mL</td>
<td>.5 cap 4-4.5</td>
<td>.5 cap 5-5.5</td>
</tr>
<tr>
<td>27-27</td>
<td>.25 tab 2.5 mL</td>
<td>.5 tab 2.5 mL</td>
<td>.5 cap 4-4.5</td>
<td>.5 cap 5-5.5</td>
</tr>
<tr>
<td>28-28</td>
<td>.25 tab 2.5 mL</td>
<td>.5 tab 2.5 mL</td>
<td>.5 cap 4-4.5</td>
<td>.5 cap 5-5.5</td>
</tr>
<tr>
<td>29-29</td>
<td>.25 tab 2.5 mL</td>
<td>.5 tab 2.5 mL</td>
<td>.5 cap 4-4.5</td>
<td>.5 cap 5-5.5</td>
</tr>
</tbody>
</table>

Consult with a clinician experienced in pediatric MDR-TB prescribing for neonates (<28 days of age) and infants weighing <3 kg.

For preventive regimens, consult with experts regarding optimal regimen construction.

The doses of isoniazid, ethambutol, and fluoroquinolones for preventive regimens are the same as in this dosing chart.

<table>
<thead>
<tr>
<th>Group 2</th>
<th>Steptomycin</th>
<th>Amikacin</th>
<th>Kanamycin</th>
<th>Capreomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily Dose</td>
<td>20-40 mg/kg once daily</td>
<td>15-20 mg/kg once daily</td>
<td>15-20 mg/kg once daily</td>
<td>15-20 mg/kg once daily</td>
</tr>
<tr>
<td>Maximum Dose</td>
<td>1000 mg</td>
<td>1000 mg</td>
<td>1000 mg</td>
<td>1000 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 5</th>
<th>Clofazimine (CFZ)</th>
<th>Amoxicillin-clavulanate (AMX-CLV)</th>
<th>Meropenem (MPN)</th>
<th>Linezolid (LZD)</th>
<th>Clarithromycin (CLR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily Dose</td>
<td>2-3 mg/kg once daily; if the child is &lt;25 kg give 100 mg every second day</td>
<td>85 mg/kg in two divided doses based on the amoxicillin component</td>
<td>20-40 mg/kg IV every 8 hours</td>
<td>10 mg/kg dose twice daily for children &lt;10 years of age or 300 mg daily for children &gt;10 years of age (also give vitamin B6)</td>
<td>7.5 mg/kg twice daily</td>
</tr>
<tr>
<td>Maximum Dose</td>
<td>200 mg</td>
<td>4000 mg amoxicillin and 500 mg clavulanate</td>
<td>6000 mg</td>
<td>600 mg</td>
<td>1000 mg</td>
</tr>
</tbody>
</table>

For further information, visit the Sentinel Project website: [http://sentinel-project.org](http://sentinel-project.org)
Example

• Prescribing for a 6kg child with XDR-TB:

  – Pyrazinamide (6x35=210) Tablet 500mg
  – Ethambutol (6x25=150) Tablet 400mg
  – Moxifloxacin (6x10=60) Tablet 400mg
  – Ethionamide (6x20=120) Tablet 250mg
  – Terizidone (6x20=120) Capsule 250mg
  – PAS (6x150=900) Sachet 4000mg
  – Linezolid (6x10=60) Tablet 600mg
Strategies for Administration of Second-Line Drugs in Children

- Depend on age of child
- Injectable is painful: consider mixing with lignocaine, using hot compresses
- Pills can be difficult to swallow: consider mixing with palatable and nutritious foods and beverages
- Nasogastric tube administration may be necessary as a temporary measure
- Compounding may be needed for some drugs and ages
- Involve children and families in adherence measures and administration
- Cutting and crushing of tablets should be done by health providers wherever possible to reduce risk of errors
- If tablets cannot be crushed or cut or compounded, could try giving higher doses every other day (i.e. with CFZ)
Review of MDR-TB treatment studies in children
Treatment outcomes for children with multidrug-resistant tuberculosis: a systematic review and meta-analysis

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of patients</th>
<th>Number of events</th>
<th>Proportion (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drobac et al (2005)</td>
<td>Peru</td>
<td>38</td>
<td>36</td>
</tr>
<tr>
<td>Granich et al (2005)</td>
<td>USA</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Feja et al (2008)</td>
<td>USA</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>Lemaire et al (2009)</td>
<td>Latvia</td>
<td>76</td>
<td>70</td>
</tr>
<tr>
<td>Fairlie et al (2011)</td>
<td>South Africa</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Seddon et al (2011)</td>
<td>South Africa</td>
<td>111</td>
<td>88</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Percentage*
Vs.

MDR-TB treatment Cape Town

- 149 children
- Median age: 36 months (IQR: 16-66)
- Male gender: 69 (46.3%)
- HIV-infected 32 of 146 tested (21.9%)

Thorax 2014; 69: 458-464
## Treatment and Outcome

<table>
<thead>
<tr>
<th></th>
<th>Severe disease (n=45)</th>
<th>Non-severe disease (n=104)</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital admission</td>
<td>42 (93.3)</td>
<td>61 (58.7)</td>
<td>9.87 (2.64-36.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Injectable TB drug use</td>
<td>39/41 (95.1)</td>
<td>55/101 (54.5)</td>
<td>16.3 (3.27-81.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median duration of injectable drug</td>
<td>6 (4-6)</td>
<td>4 (3-5)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median total duration of therapy</td>
<td>18 (18-20)</td>
<td>12 (10-16)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mortality</td>
<td>3 (6.7)</td>
<td>0</td>
<td></td>
<td>0.008</td>
</tr>
</tbody>
</table>

*Thorax 2014; 69: 458-464*
Case Discussion

- CC was started on an empiric treatment regimen based on the DST pattern of his uncle, since he was most likely exposed to him in the home.
- This regimen included PZA-Kanamycin-Levofloxacin-ethionamide-cycloserine.
- Plan to treat for 24 months given extent of disease with injectable given for 6 months.
- A gastric aspirate was also obtained that day and sent for culture.
Case Discussion

• After 1.5 months of empiric MDR-TB treatment, the gastric aspirate done at the time of initiation of his MDR-TB treatment regimen showed that CC had resistance to HRES, KM, CM, and AMK.

• His KM was changed to CM and the rest of his regimen continued
Questions

8) If CC were being treated today, what might be some strategies for him?
The Future

- Re-tooling existing drugs
- New PK data on second-line drugs
- New drugs
- New regimens
- Host-directed therapies
Retooling existing agents

- Clofazimine
- Thioridazine
- Fluoroquinolones
- Linezolid
- Beta Lactams
- Co-trimoxazole
- Metronidazole
- Tetracyclines
- Disulfiram

Two Pediatric Cases of Multidrug-Resistant Tuberculosis Treated With Linezolid and Moxifloxacin

**Linezolid-containing regimens for the treatment of drug-resistant tuberculosis in South African children**

**REVIEW**

Linezolid for the treatment of drug-resistant tuberculosis in children: A review and recommendations

**Linezolid for Treatment of Chronic Extensively Drug-Resistant Tuberculosis**

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**MEROPENEM/CLAVULANATE AND LINEZOLID TREATMENT FOR EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS**

**Linezolid in the Treatment of Multidrug-Resistant Tuberculosis**
PK data in children

- Efficacy can be determined from adult studies
- Specific issues around
  - Toxicity and tolerability
  - Formulations
  - Pharmacokinetics

*Thee et al. AAC 2011; 55: 4595-4600
New Drugs

![Diagram showing the stages of drug development: Discovery, Preclinical, Clinical (Phase 1, Phase 2, Phase 3).]

Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone

The Diarylquinoline TMC207 for Multidrug-Resistant Tuberculosis

Delamanid for Multidrug-Resistant Pulmonary Tuberculosis
Short, Highly Effective, and Inexpensive Standardized Treatment of Multidrug-resistant Tuberculosis

Armand Van Deun¹,², Aung Kya Jai Maug³, Md Abdul Hamid Salim³, Pankaj Kumar Das³, Mihir Ranjan Sarker³, Paul Daru³, and Hans L. Rieder¹,⁴

<table>
<thead>
<tr>
<th>Regimen (sequence)</th>
<th>Intensive Phase</th>
<th>Continuation Phase 1</th>
<th>Continuation Phase 2</th>
<th>Patients Enrolled</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Number</td>
</tr>
<tr>
<td>1</td>
<td>3(+) KCOEHZP</td>
<td>12 OEHZP</td>
<td>6 EP</td>
<td>59</td>
</tr>
<tr>
<td>2</td>
<td>3(+) KCOEHZP</td>
<td>12 OHEZP</td>
<td></td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>3(4) KCOEZP</td>
<td>12 OEZP</td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>3(+) KCOEHZP</td>
<td>12 OHEZ</td>
<td></td>
<td>45</td>
</tr>
<tr>
<td>5</td>
<td>3(+) KCOEHZP</td>
<td>12 OHEZC</td>
<td></td>
<td>38</td>
</tr>
<tr>
<td>6</td>
<td>4(+) KCGEHZP</td>
<td>5 GEZC</td>
<td></td>
<td>206</td>
</tr>
<tr>
<td>Total number of patients enrolled</td>
<td>427</td>
<td>100.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1+2: Oflo-based, Pth plus INH throughout
3: Oflo-based, Pth throughout, no INH
4: Oflo-based, Pth intensive phase, INH throughout
5: Oflo-based, Pth intensive phase, INH and Clo throughout
6: Gati-based, Pth and INH intensive phase, Clo throughout

Van Deun et al. AJRCCM 2010; 182(5): 684-692
Nutrition

Creative adherence strategies
- Mobile phones
- Alternative DOT
- Rewards/incentives

Vitamin D

New formulations
- Dispersible tablets
- Sprinkles
- Melts
- Aerosol
- Nebulisers
- Depot injections

Helminth treatment

cART

New formulations

Creative adherence strategies

Vitamin D

Helminth treatment

cART
Case Resolution

• CC was eventually cured of his MDR-TB and made a full recovery
• He received a total 6 months of injectable therapy and 24 months of total drugs
• Today he is finishing secondary school and living a full and happy life
• He has had no long-term effects from his MDR-TB therapy, except his plan to become a doctor and “help other sick kids”
Summary

• Suspect MDR-TB in children if unwell with clinical TB and contact with an MDR-TB source case
• Attempt to obtain microbiological specimens for culture and susceptibility testing
• Initiate treatment (empiric if necessary) with at least four drugs felt to be effective against the likely strain
• Be aware that re-purposed drugs, new drugs and new regimens are likely to be available soon
Questions?
This presentation has been developed by the TB CARE II project and is made possible by the generous support of the American people through the United States Agency for International Development.