MDRTB and TB/HIV
Dr. Ed Wilkins
MDRTB and TB/HIV
Aims for today – 1

- What is MDRTB?
- The pitfalls in management:
  - Not suspecting and failing to make and early diagnosis
  - Failing to prevent hospital acquired infection
  - Not using an effective ant-TB regimen and not considering XDR-TB
Aims for today – 2

• The pitfalls with TB/HIV:
  • Not testing for HIV!
  • Delaying HIV treatment and not considering overlapping toxicities
  • Not checking on drug-drug interactions
  • Missing IRIS

• Challenges:
  • TDRTB
  • Local planning
What is MDRTB?
Normally straightforward
But over years sensitive TB has transitioned to MDRTB, XDRTB, & TDRTB
Definitions – drug resistance

- **Mono**: resistance to 1 first line drug (usually isoniazid) with susceptibility to the others
- **MDRTB**: resistance to R (rifampicin) and H (isoniazid)
- **XDRRTB**: MDR plus:
  - Resistance to **any quinolone** AND
  - Resistance to 2nd line injectable (kanamycin, amikacin, capreomycin)
- **TDRTB**: not clearly defined but resistance to all 1st and 2nd line drugs
Definitions: primary vs. acquired

- **Primary** drug resistance:
  - A person becomes infected with an organism that is already drug resistant

- **Acquired** drug resistance:
  - A person is infected with a drug susceptible organism and through drug pressure of inadequate treatment it becomes drug resistant
Pitfall 1
Not suspecting MDRTB
TB is a major problem in Myanmar

<table>
<thead>
<tr>
<th>No. cases</th>
<th>Prevalence</th>
<th>%</th>
<th>Mortality</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB (All)</td>
<td>811</td>
<td>43.8</td>
<td>222</td>
<td>27</td>
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<tr>
<td>-TBM</td>
<td>250</td>
<td>13.5</td>
<td>126</td>
<td>50</td>
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<tr>
<td>Anemia</td>
<td>191</td>
<td>10.3</td>
<td>4</td>
<td>2.1</td>
</tr>
<tr>
<td>GE</td>
<td>140</td>
<td>7.6</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Crypto M</td>
<td>95</td>
<td>5.1</td>
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<td>DILI</td>
<td>80</td>
<td>4.3</td>
<td>11</td>
<td>13.8</td>
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<tr>
<td>PJP</td>
<td>75</td>
<td>4</td>
<td>33</td>
<td>44.0</td>
</tr>
<tr>
<td>COL</td>
<td>50</td>
<td>2.7</td>
<td>18</td>
<td>36.0</td>
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<tr>
<td>Skin rash</td>
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<td>3</td>
<td>6.8</td>
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<tr>
<td>Toxo</td>
<td>37</td>
<td>2</td>
<td>5</td>
<td>13.5</td>
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<tr>
<td>Renal toxicity</td>
<td>35</td>
<td>1.9</td>
<td>13</td>
<td>37</td>
</tr>
<tr>
<td>Penicilliosis</td>
<td>35</td>
<td>1.9</td>
<td>3</td>
<td>8.6</td>
</tr>
<tr>
<td>MAC</td>
<td>29</td>
<td>1.6</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>sepsis</td>
<td>26</td>
<td>1.4</td>
<td>16</td>
<td>61</td>
</tr>
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</table>
Pitfall 1: not suspecting resistant TB

- Previous TB treatment
- History of poor adherence
- Contact with MDRTB/XDRTB
- Birth, travel or work in an area endemic for MDRTB
20% of cases diagnosed are relapsed in Myanmar

<table>
<thead>
<tr>
<th></th>
<th>New</th>
<th>%</th>
<th>Relapse</th>
<th>%</th>
<th>total</th>
<th>%</th>
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<tr>
<td>S(+)PTB</td>
<td>196</td>
<td>74</td>
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<td></td>
<td>270</td>
<td>19</td>
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<td>Clinical PTB</td>
<td>485</td>
<td>106</td>
<td></td>
<td></td>
<td>591</td>
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<td>Clinical EP</td>
<td>453</td>
<td>114</td>
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<td>567</td>
<td>40</td>
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<tr>
<td></td>
<td>1134</td>
<td>294</td>
<td>79.4</td>
<td>20.6</td>
<td>1428</td>
<td></td>
</tr>
</tbody>
</table>
Where MDRTB is prevalent, risk of primary TB being MDRTB is high
Pitfall 1: not suspecting resistant TB

- Previous TB treatment
- History of poor adherence
- Contact with MDRTB/XDRTB
- Birth, travel or work in an area endemic for MDRTB

- No clinical improvement on standard therapy and/or sputum positive after 2m
- Specific at-risk groups
Percentage of new cases with MDRTB 2014

- 480,000 MDR cases per year globally
  - 190,000 deaths
- 5% TB cases are MDR
- New: 3.3%

Most recent data shown

Percentage of cases
- 0–2.9
- 3–5.9
- 6–11.9
- 12–17.9
- ≥18
- No data
- Subnational data only
- Not applicable
Percentage of previously treated TB cases with MDRTB 2014

- 480,000 MDR cases per year globally
  - 190,000 deaths
- 5% TB cases are MDR
- New: 3.3%
- Retreatment: 20.0%

Most recent data shown
Pitfall 2
Failing to make an early diagnosis

GreenShoots Foundation
Pitfall 2: Early diagnosis essential

Xpert MTB/RIF assay

GenoType MTBDRplus

- Conjugate Control (CC)
- Amplification Control (AC)
- M. tuberculosis complex (TUB)

- rpoB Locus Control
  - rpoB wild type probe 1 (rpoB WT1)
  - rpoB wild type probe 2 (rpoB WT2)
  - rpoB wild type probe 3 (rpoB WT3)
  - rpoB wild type probe 4 (rpoB WT4)
  - rpoB wild type probe 5 (rpoB WT5)
  - rpoB wild type probe 6 (rpoB WT6)
  - rpoB wild type probe 7 (rpoB WT7)
  - rpoB wild type probe 8 (rpoB WT8)
  - rpoB mutation probe 1 (rpoB MUT1)
  - rpoB mutation probe 2A (rpoB MUT2A)
  - rpoB mutation probe 2B (rpoB MUT2B)
  - rpoB mutation probe 3 (rpoB MUT3)

- katG Locus Control
  - katG wild type probe (katG WT1)
  - katG mutation probe 1 (katG MUT1)
  - katG mutation probe 2 (katG MUT2)

- inhA Locus Control
  - inhA wild type probe 1 (inhA WT1)
  - inhA wild type probe 2 (inhA WT2)
  - inhA mutation probe 1 (inhA MUT1)
  - inhA mutation probe 2 (inhA MUT2)
  - inhA mutation probe 3 (inhA MUT3)
  - inhA mutation probe 3A (inhA MUT3A)
  - inhA mutation probe 3B (inhA MUT3B)

- colored marker

Resistance
- R+I
- I
Gene-based assays associated with RIF and INH resistance

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin</td>
<td>rpo B</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Kat G, Inh A</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>emb B</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>rps L</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>pnc A</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>gyr A</td>
</tr>
</tbody>
</table>
## GeneXpert testing in Myanmar: CSF data

<table>
<thead>
<tr>
<th>Year</th>
<th>Total</th>
<th>Indian Ink</th>
<th>%</th>
<th>GeneXpert</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>2011</td>
<td>182</td>
<td>34</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>250</td>
<td>50</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2014</td>
<td>225</td>
<td>35</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>225</td>
<td>28</td>
<td>12</td>
<td>8/110</td>
<td>7</td>
</tr>
</tbody>
</table>
ABOUT THE XPERT MTB/RIF TEST
The rapid TB test – known as Xpert MTB/RIF – is a fully-automated diagnostic molecular test. It has the potential to revolutionize and transform TB care and control. The test:
• simultaneously detects TB and rifampicin drug resistance
• provides accurate results in less than two hours so that patients can be offered proper treatment on the same day
• has minimal bio-safety requirements and training needs, and can be housed in non-conventional laboratories.

UPDATED WHO RECOMMENDATIONS
AS OF OCTOBER 2013

Strong recommendation:
• Xpert MTB/RIF should be used as the initial diagnostic test in adults and children presumed to have MDR-TB or HIV-associated TB
No molecular tests performed

No RIF/INH probe

Culture RIF/INH/EMB resistant = MDRTB

Amikacin/moxifloxacin resistant = XDR-TB

2nd line analogue

Amikacin ototoxicity

PZA/PRO/CYC/LYN/AZI/PAS/CO-AMOX

Bedaquilline added

FIGURE 1 Schematic diagram showing the treatment course in this case of extensively drug-resistant tuberculosis. MDR-TB: multidrug-resistant tuberculosis; WHO: World Health Organization; PAS: para-amino salicylic acid; P: positive sputum culture; N: negative sputum culture.
Pitfall 3
Failing to prevent hospital acquired infection
Pitfall 3: failure to prevent hospital acquired infection
Risk to patients and staff from hospital transmission

<table>
<thead>
<tr>
<th></th>
<th>HCW</th>
<th>General Population</th>
<th>Odds Ratio (95% C.I.)*</th>
</tr>
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<tbody>
<tr>
<td>Annual DRTB Inc./100,000</td>
<td>70.5/100,000</td>
<td>11.7/100,000</td>
<td>5.84 (3.07-11.33)</td>
</tr>
<tr>
<td>Annual MDRTB Inc./100,000</td>
<td>63.2 /100,000</td>
<td>10.7/100,000</td>
<td>5.73 (2.93-11.50)</td>
</tr>
<tr>
<td>Annual XDRTB Inc./100,000</td>
<td>7.4/100,000</td>
<td>1.04/100,000</td>
<td>7.08 (4.55-10.91)</td>
</tr>
</tbody>
</table>
Establish good infection control practice
Isolation/FP2 mask

TB WARD
KEEP DOORS CLOSED
AND WEAR MASK
AT ALL TIMES
Pitfall 4
Not using an effective anti-TB treatment regimen
Not using an effective regimen

- The best current antituberculous drugs are rifampicin (R) and isoniazid (H)

- Second line treatment is less effective, more toxic, requires parenteral therapy and takes longer, compared with first line treatment.
Principles of MDRTB treatment

- Promptly suspect AND initiate appropriate therapy early
- Assume resistance if therapy given previously
- Resistance prevalence in country of birth/residence MUST be taken into consideration
- Tailor drugs to past treatment if available
- DO NOT rely on any drug being fully active
- Give AT LEAST 4 active drugs while awaiting sensitivities
- Drugs chosen in a stepwise manner
Step 1

Begin with any First line agents to Which the isolate is Susceptible

First-line drugs

- Pyrazinamide
- Ethambutol
- (Rifampicin)
- (Isoniazid)

- Most potent and best tolerated
- All MUST be used if MDRTB suspected but unconfirmed
- MUST not rely on and assume resistance is present and therefore add in additional drugs
- If RIF resistance then Rifabutin likely to be resistant
- If INH resistance then may be PRO/ETH resistant
Step 1

Begin with any 
First line agents to 
Which the isolate is 
Susceptible

Add a 
Fluoroquinolone

Use any available 
PLUS 
One of 
these

<table>
<thead>
<tr>
<th>First-line drugs</th>
<th>Fluoroquinolones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrazinamide</td>
<td>Levofloxacin</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Moxifloxacin</td>
</tr>
<tr>
<td>(Rifampicin)</td>
<td>Ofloxacin</td>
</tr>
<tr>
<td>(Isoniazid)</td>
<td></td>
</tr>
</tbody>
</table>

• All patients should receive a quinolone unless resistance very likely.
• Ciprofloxacin should NO longer be used to treat TB
• Most potent: Moxifloxacin > Levofloxacin > Ofloxacin
• MOX/LEVO may have activity against CIP/OFL resistant strains
• GAT is associated with SERIOUS glucose imbalance and should NOT be used
Step 1

Begin with any First line agents to Which the isolate is Susceptible
Add a Fluoroquinolone And an injectable Drug based on

Use any available

PLUS

One of these

PLUS

One of these

First-line drugs
- Pyrazinamide
- Ethambutol

Fluoroquinolones
- Levofloxacin
- Moxifloxacin
- Ofloxacin

Injectable agents
- Amikacin
- Capreomycin
- Kanamycin

• All patients with possible MDRTB MUST receive an injectable agent
• All patients SHOULD receive Amikacin or Kanamycin
• Streptomycin should not be used as likely resistance
• Hearing should be monitored with AMIK/KAN
• AMIK and KAN usually X-resistant
• If an isolate is resistant to AMIK/KAN, capreomycin should be used
Step 1

Begin with any First line agents to Which the isolate is Susceptible

Add a Fluoroquinolone And an injectable Drug based on susceptibilities

First-line drugs

Pyrazinamide
Ethambutol

Fluoroquinolones

Levofloxacin
Moxifloxacin
Ofloxacin

Injectable agents

Amikacin
Capreomycin
Kanamycin

Step 2

Pick one or more of these

Oral second line drugs

Cycloserine
Ethionamide/
prothionamide
PAS

• Generally more side effects & bacteriostatic
• Ethionamide = prothionamide for activity: ETH/PRO X-resistant
• ETH/PRO resistant then X-reactivity with INH resistance so also cannot rely on as fully active drug
• CYC + PRO or PAS common combination (check TSH)
• All neurotoxic – give high dose PYR
Myanmar MDR-TB Regimen

First-line
- Isoniazid
- Rifampicin
- Ethambutol
- Pyrazinamide

Second-line
- Group 1: First line oral
  - Isoniazid
  - Rifampicin
  - Ethambutol
  - Pyrazinamide
- Group 2: Injectable
  - Streptomycin
  - Kanamycin
  - Amikacin
  - Capreomycin
- Group 3: Quinolone
  - Ciprofloxacin
  - Ofloxacin
  - Levofloxacin
  - Moxifloxacin

Third-line
- Group 4: Bacteriostatic 2nd-line drugs
  - Ethionamide
  - Cycloserine
  - PAS
- Group 5: Limited data of efficacy
  - Clofazimine
  - Linezolid
  - AMX/CLV
  - High dose INH

6 Am-Lfx-Eto-Cs-Z / 18 Lfx-Eto-Cs-Z
Principles of MDR+ treatment

- When possible, give pyrazinamide (PZA), ethambutol, and moxifloxacin once per day as thought high peaks may be more efficacious.
- Prothionamide, Cycloserine and PAS usually split because decreases side effects
- If you can monitor levels of Amikacin/Kanamycin/Cycloserine as may be needed for up to six months
- The minimum length of treatment for XDR-TB will be 18 months after culture conversion = usually 2y in total
- PZA can be used for full course of treatment
- Consider surgery if localised disease
Pitfall 5
Not considering XDRTB
Countries reporting at least 1 case of XDR-TB

- Globally 9.7% (95% CI 7.4-12.0) of MDRTB is XDR
  - Belarus 29%
  - Lithuania 25%
  - Latvia 19%
  - Georgia 15%
Outcome of XDR-TB treatment 2011 worse: less than half cured
### Step 1

Use any available

**First-line drugs**

- Pyrazinamide
- Ethambutol

**Fluoroquinolones**

- Levofloxacin
- Moxifloxacin
- Ofloxacin

**Injectable agents**

- Amikacin
- Capreomycin
- Kanamycin

### Step 2

Pick one or more of these

**Oral second line drugs**

- Cycloserine
- Ethionamide
- PAS

### Step 3

Consider use of these

**Third line drugs**

- Imipenem
- **Linezolid**
- Macrolides
- Amoxicillin/Clavulanic A
- High-dose INH
- Meropenem
- Clofazimine
- Thiacetazone
But these drugs..

- Efficacy often uncertain
  - Imipenem/Meropenem
  - Co-Amoxiclav
  - Linezolid
- Or weak and bacteriostatic
  - Clofazamine
  - Azithromycin/clarithromycin
  - Thioacetazone (NOT IN HIV)
- Expensive & may require IV admin
- High-dose INH can be considered if low level R
Step 3

If there are not 4-6 drugs available consider 3rd line

Consider use of these

Third line drugs

- Imipenem
- Linezolid
- Macrolides
- Amoxicillin/Clavulanic acid
- High-dose INH
- Meropenem
- Clofazimine
- Thiacetazone

Step 4

Consider use of these

HELP

Expanded access drugs

- Bedaquilline
- Delamanid
Countries that had used bedaquilline by 2014
WHO Policies available

The use of bedaquiline in the treatment of multidrug-resistant tuberculosis
Interim policy guidance

2013

The use of delamanid in the treatment of multidrug-resistant tuberculosis
Interim policy guidance

2014
Pitfall 6
Not testing for HIV
Not considering HIV: estimated HIV prevalence in TB
HIV prevalence in key populations: Myanmar 2014

- PWID: 23.1%
- MSM: 6.6%
- FSW: 6.3%
- New TB patient: 8.5%
- Male STI patients: 4.0%
- New military recruits: 1.4%
- Pregnant women: 0.8%
- Blood donors: 0.1%
High HIV prevalence in injection drug users – setting for TB
HIV patients more at risk of TB: South African Miners Cohort

Proportion with TB

Years since first negative test or since seroconversion

HIV +

HIV -

Sonnenberg JID 2005
TB in the course of HIV-infection

Seroconversion:
- Acute retroviral syndrome

Overall:
- > new infection
- > miliary, atypical pulmonary and extrapulmonary TB
- < smear +ve rate
- > high tissue load with no granulomata
- > mycobacteraemia

CD4^+ (cells/µL)

Years after infection

- Oral Candida-infection
- Kaposi sarcoma
- Lymphoma
- Dementia
- Oral haircell-leukoplacia
- Cachexia
- Toxoplasmosis
- PCP
- HSV
- Candida esophagitis
- Cryptococcosis
- MAC
- CMV
Initiating ARV therapy and reported cases of MDR/XDR TB 2005-13
Pitfall 7
Delaying HIV treatment
TB cases starting ART is a common access into treatment

<table>
<thead>
<tr>
<th>YEAR</th>
<th>Start ART</th>
<th>CD4 &lt;200</th>
<th>Past ART</th>
<th>TB</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>CD4 average</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>2011</td>
<td>1165</td>
<td>136</td>
<td>852</td>
<td>73</td>
</tr>
<tr>
<td>2012</td>
<td>783</td>
<td>165</td>
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<td>65</td>
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<tr>
<td>2013</td>
<td>1210</td>
<td>182</td>
<td>726</td>
<td>60</td>
</tr>
<tr>
<td>2014</td>
<td>1918</td>
<td>194</td>
<td>1107</td>
<td>58</td>
</tr>
<tr>
<td>2015</td>
<td>2191</td>
<td>208</td>
<td>1223</td>
<td>56</td>
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</table>
Delaying ART – competing risks

Immediate (< 2 wks)

Benefits:
• ↓ risk of other OI’s
• ↓ risk of death <50

Risks:
• ↑ adverse effects
• ↑ incidence of IRIS

Early (2 months)

Benefits:
• ↓ risk of IRIS

Risks:
• ↑ incidence of OIs
• ↑ risk of other death CD4 <50

Mortality
General schema for CAMELIA, STRIDE, and integrated arms of SAPIT

“Immediate ART” (within 2 weeks)

“Early ART” (2-3 months)

Primary endpoint

TB treatment

ART

TB treatment

ART

Study week

0 8 24
Effect of ART timing on death (CAMELIA) or death/AIDS (STRIDE, SAPIT)

- **CAMELIA**
  - Immediate: 34% ↓, p=0.004
  - Early: 19% ↓, p=0.45

- **STRIDE**
  - Immediate: 11% ↓, p=0.73
  - Early: 19% ↓, p=0.45

- **SAPIT**
  - Immediate: 11% ↓, p=0.73
  - Early: 11% ↓, p=0.73
Effect of ART timing on death (CAMELIA) or death/AIDS (STRIDE, SAPIT): CD4 <50

- CAMELIA: 34% ↓, p=0.004
- STRIDE: 42% ↓, p=0.02
- SAPIT: 68% ↓, p=0.06
Pitfall 8
Potential drug interactions and overlapping toxicities
## Rifamycins & ART

<table>
<thead>
<tr>
<th></th>
<th>Rifampicin</th>
<th>Rifabutin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NRTIs</strong></td>
<td>No problem</td>
<td>No problem</td>
</tr>
<tr>
<td><strong>Efavirenz (EFV)</strong></td>
<td>EFV AUC ↓ 26%</td>
<td>RFB AUC ↓ 38%</td>
</tr>
<tr>
<td><strong>Nevirapine (NVP)</strong></td>
<td>NVP AUC ↓ 40-60%</td>
<td>No problem</td>
</tr>
<tr>
<td><strong>Etravirine/Rilpivirine</strong></td>
<td>ETR/RPV ↓ 40-60%</td>
<td>NNRTI AUC ↓ 37%</td>
</tr>
<tr>
<td><strong>PIs unboosted</strong></td>
<td>PI AUC ↓ 80-90%</td>
<td>RFB AUC ↑ 200%</td>
</tr>
<tr>
<td><strong>PIs boosted</strong></td>
<td>PI AUC ↓ 60-75%</td>
<td>RFB AUC ↑ 300%</td>
</tr>
<tr>
<td><strong>Raltegravir</strong></td>
<td>Integrase AUC ↓ 40%</td>
<td>No problem</td>
</tr>
<tr>
<td><strong>Dolutegravir</strong></td>
<td>Integrase AUC ↓ 40%</td>
<td>No problem</td>
</tr>
<tr>
<td><strong>Maraviroc</strong></td>
<td>CCR5 AUC ↓ 60-70%</td>
<td>? No problem</td>
</tr>
</tbody>
</table>

Adapted from [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org) with approximated AUC percentages displayed; Refer to individual SPCs for further details on drug interactions.

NRTIs=nucleoside reverse transcriptase inhibitors; NNRTIs=non-nucleoside reverse transcriptase inhibitors; PIs=protease inhibitors; AUC=Area under curve; ABC=Abacavir; AZT=Zidovudine.
### AE problems - overlapping

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile, generally unwell</td>
<td><em>IRIS, paradoxical reactions, MDR TB</em></td>
</tr>
<tr>
<td>Abnormal LFTs</td>
<td><em>TB drugs (RIF/INH/PZA), HIV drugs, paradoxical reactions, IRIS, hepatitis virus ‘flares’</em></td>
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<tr>
<td>Neuropathy</td>
<td><em>d4T, ddI, 3TC, HIV, isoniazid, ethionamide, linezolid, cycloserine</em></td>
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<tr>
<td>Eye problems</td>
<td><em>Ethambutol, rifabutin, linezolid, ethionamide</em></td>
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<tr>
<td>CNS</td>
<td><em>Efavirenz, cycloserine, quinolones</em></td>
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<tr>
<td>Cardiac</td>
<td><em>PIs, quinolones</em></td>
</tr>
<tr>
<td>Arthropathies</td>
<td><em>HIV, pyrazinamide, quinolones, PAS</em></td>
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Pitfall 9
Not identifying IRIS
Not identifying IRIS

- Patients on TB treatment
  - ART
  - Patients not on TB treatment
  - ART
  - Paradoxical TB-IRIS
  - Unmasking TB-IRIS
Paradoxical TB-IRIS

- Incidence 8-54% (15.7% in meta-analysis)
- Median 14d onset after starting ART
- Focal and often systemic features
- Hospitalisation in up to half
- Median duration 2-3 months but can be years
- Mortality infrequent
- Differential diagnosis wide
Lymph-node, lung, brain, and liver most common
Effect of ART timing on IRIS (STRIDE, SAPIT): CD4 >50
Challenges in differential diagnosis of IRIS

**ALTERNATIVE DIAGNOSIS**
- Bacterial/fungal infections
- NTM and PCP
- Lymphoma
- KS

**DRUG RESISTANCE**
- 14/141 suspected TB-ISIS had MDR or rifampicin resistance

**DRUG REACTION**
- Especially if HEPATIC involvement
IRS management

- IRS treatment
  - Continue TB and ARV treatment
  - NSAID’s then
  - Prednisolone (remember RIF induction) tapering off
  - Montelukast no harm
  - Thalidomide
  - Others
Matched groups at BL apart from length of time from starting TB treatment to starting ART: longer in prednisolone arm.

35 patients initiated OL prednisolone; 20 in placebo arm and 15 in prednisolone arm.

P = 0.03

Meintjes G, et al
Oral Abstract 34
Challenges
Rich or poor, TDR-TB is a threat to everybody

Over 15.5 lakh people infected by TB in 2011, and 3 lakh have died so far

Soumena Majumdar
Mumbai

There has been an overall drop globally in the population of people infected by tuberculosis. These infections have decreased by 6 million worldwide to 8.9 million in 2011, as against 9 million in 2005. But in India, over 15.5 lakh people have been infected by TB in 2011, and it took 3 lakh lives. Multi-drug resistant TB strains, which make up more than 20% of all cases, have raised concern lately.

As Karnataka State Tuberculosis Eradication Association has come up with the Anti-TB Week from February 21-27, experts said children from well-to-do families from the city, too, are falling prey to it.

A TDR-TB case needs to be dealt separately, said Dr. Sumant Mamtani, consultant pulmonology, Apollo Hospital.

“Antibiotics given by WHO and they should be followed strictly. The isolation period is usually two to three weeks and it takes the same time to convert the disease non-infectious,” he said.

While the doctor had treated a single case of TDR-TB, he has dealt with several cases of Multi Drug Resistant (MDR) TB of late. There is no standard drug regimen for the diagnosis has been confirmed.

“Only if the TB is localized in a certain part of the body, then surgical resection could be one of the options. The best way to tackle this problem is educating TB patients, who are undergoing the treatment. They should be told to complete the full course of treatment and not neglect or ignore the doctor's advice,” said Dr. Shantanu Rahman, founder and medical director, National Aloe Primary Healthcare Services Pvt. Ltd.

Medical TB registry should be maintained and all patients undergoing treatment should have regular proactive follow-up from the treating physician, he added.

However, what is more worrying is that there are several instances of children falling prey to tuberculosis, despite having adequate nutrition.

TB is not a ‘disease of poverty’ anymore. It is regularly found in the higher socio-economic population as well.

There are no specific reasons for this phenomenon. One of the major reasons could be the Vitamin D deficiency, though there is no scientific study to support this hypothesis,” said Dr. Mantri.

While textbook signs of long TB are persistent cough lasting for more than three weeks or cough with blood in the sputum, patients with weakness or fatigue, weight loss, loss of appetite, low-grade fever and night sweats should also be tested for TB, he said. Dr. Rahman. Younger patients with history of poor immune status are more at risk of contracting TB, he added.

How can parents ensure that children don’t get the disease? First, newborns should be administered with a BCG vaccine. Children should be given a diet that is scientific study to support the hypothesis said Dr. Rahman.

While textbook signs of long TB are persistent cough lasting for more than three weeks or cough with blood in the sputum, patients with weakness or fatigue, weight loss, loss of appetite, low-grade fever and night sweats should also be tested for TB.

TB scourge acquires a new dimension: Emergence of Totally Drug-Resistant (TDR) Tuberculosis in India

The CALIBRE
www.thecalibre.in

TB scourge acquires a new dimension: Emergence of Totally Drug-Resistant (TDR) Tuberculosis in India
• Resistant to all 2\textsuperscript{nd} line drugs
• Culture and smear remain +ve after 18m f 2\textsuperscript{nd} line therapy
• Described mainly in India but also elsewhere
TO THE EDITOR: Multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) are an increasing public health threat. Bedaquiline and delamanid are two drugs that were recently approved by the Food and Drug Administration for treatment of MDR-TB and XDR-TB. Here we describe the stepwise amplification of drug resistance in a patient who had emigrated from Tibet to Switzerland in December 2010 and who presented to a Swiss hospital with preextensively drug-resistant tuberculosis at that time.
Local management
Myanmar: TB cases and deaths 1990-2014

**MYANMAR 2014**
- Notified TB cases: 141,957
- Notified MDR/RR-TB: 3,495
- Patients started on MDRTB treatment: 1,537
- Estimated MDRTB cases: 9,000
SE Asia: MDR/RR-TB outcome

Treatment outcomes for MDR/RR-TB

- **Cure**
- **Failure**
- **Died**
- **LTFU**

<table>
<thead>
<tr>
<th>Year</th>
<th>Cure</th>
<th>Failure</th>
<th>Died</th>
<th>LTFU</th>
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<td>2007</td>
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<td>2012</td>
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% of cohort
Myanmar: MDR/R-RTB outcome

![Bar chart showing outcome distribution over years: Cure, Failure, Died, LTFU.]

- **2009**: Cure: 70%, Failure: 10%, Died: 10%, LTFU: 10%
- **2010**: Cure: 65%, Failure: 15%, Died: 10%, LTFU: 10%
- **2011**: Cure: 60%, Failure: 20%, Died: 10%, LTFU: 10%
- **2012**: Cure: 55%, Failure: 25%, Died: 10%, LTFU: 10%
Aims for today

• What is MDRTB?
• The pitfalls in management:
  • Not suspecting and failing to make and early diagnosis
  • Failing to prevent hospital acquired infection
  • Not using an effective ant-TB regimen and not considering XDR-TB
  • Not considering HIV