Challenges of MDR-TB in HIV-infected children

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Challenges with the numbers

Global burden of drug-resistant tuberculosis in children: a mathematical modelling study

Peter J Dodd, Charalambos Sismanidis, James A Seddon

Lancet Infect Dis 2016

Estimates for 2014: MDR-TB numbers based on model and numbers reported to Global Project on Antituberculosis Drug Resistance Surveillance at WHO and from surveys and surveillance reported between 1988 and 2014

- 850 000 children with TB
- 58 000 children INH mono-resistant TB
- 25 000 children MDR-TB
- 1 200 children XDR-TB

Infected with MDR-TB - 2 million children
DR-TB more common in HIV-infected children?

- No definite data in children
- From our 2-year surveillance periods since 2003 we could not show a difference per 2-year period
- However, with 14 yrs of data available in 2112 children (<13 years) with culture-confirmed TB: and both HIV status & DST known in 1738 (82.3%):
- Significantly more MDR/RIF resistance in HIV-infected children compared to HIV-uninfected but no difference in INH mono-resistance
<table>
<thead>
<tr>
<th>DST known</th>
<th>HIV-infected</th>
<th>HIV-uninfected</th>
<th>OR (95% CI) &amp; corrected P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All with DST/HIV (n=1738)</td>
<td>357 (20.5%)</td>
<td>1381 (79.5%)</td>
<td></td>
</tr>
<tr>
<td>Susceptible</td>
<td>290 (81.2%)</td>
<td>1179 (85.4%)</td>
<td></td>
</tr>
<tr>
<td>All resistance</td>
<td>67 (18.8%)</td>
<td>202 (14.6%)</td>
<td>1.35 (0.99-1.83); p=0.065</td>
</tr>
<tr>
<td>INH mono-resistant</td>
<td>18 (5.0%)</td>
<td>82 (5.9%)</td>
<td>0.84 (0.49-1.43); p=0.603</td>
</tr>
<tr>
<td>RIF mono-resistant</td>
<td>11 (3.1%)</td>
<td>20 (1.4%)</td>
<td>2.16 (1.03-4.56); p=0.064</td>
</tr>
<tr>
<td>MDR</td>
<td>38 (10.6%)</td>
<td>100 (7.2%)</td>
<td>1.52 (1.03-2.26); p=0.044</td>
</tr>
<tr>
<td>All RIF resistance</td>
<td>49 (13.7%)</td>
<td>120 (8.7%)</td>
<td>1.67 (1.17-2.38); p=0.006</td>
</tr>
</tbody>
</table>
Challenges with MDR-TB diagnosis

• Does the child have TB disease?
  - exclude infection only (may even be Xpert or culture-positive)
  - exclude other conditions – more common in HIV-infected children / may co-exist with TB

• Need to bacteriologically confirm TB and DR-TB whenever possible
  - obtain specimen for TB bacteriology BEFORE starting treatment (excl. in TBM/miliary TB)
  - do DST on ALL (HIV-infected) children with a positive culture for *M. tuberculosis*
Diagnosis: MDR-TB in children

DR TB is a **microbiological diagnosis**

In children often difficult (paucibacillary TB):

- **Confirmed** if DR *M. tuberculosis* strain is isolated from a child

- **Probable** DR-TB if there is known contact with an infectious adult DR-TB case (>78-90% concordance in several studies)

- **Suspect** DR-TB if:
  - a child gets worse on Rx, failing adherent Rx
  - an adult source case who has no DST-result is a treatment failure, a retreatment case or died of TB during adherent Rx
## Culture vs. Xpert MTB/RIF

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Culture and DST</th>
<th>Xpert MTB/RIF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Speed</strong></td>
<td>Slow (2-6 weeks)</td>
<td>Rapid (2 hours – capacity limit)</td>
</tr>
<tr>
<td><strong>Positive yield</strong></td>
<td>30-70%</td>
<td>60-70% of culture-POS cases</td>
</tr>
<tr>
<td><strong>Detection threshold</strong></td>
<td>10-100 cfu/ml</td>
<td>130-150 cfu/ml (Xpert-ULTRA 10-100??)</td>
</tr>
<tr>
<td><strong>DST</strong></td>
<td>Any drug DST/LPA</td>
<td>Only RIF DST</td>
</tr>
<tr>
<td><strong>Specimens</strong></td>
<td>Any type</td>
<td>Resp specimens, increasing number of other specimens</td>
</tr>
</tbody>
</table>
Challenges with DR-TB treatment

• “Rapidly” changing scene!? 
• Dose-finding and safety studies for existing 2\textsuperscript{nd}-line drugs, new and repurposed drugs – correct doses & safety important for HIV co-infected children on ART 
• New shorter 9-12 month regimen recently approved by WHO for RIF-mono and strictly MDR-TB cases (4-6hdH/Eto/Mxf/Cfz/Km/Z/E+5-6Mfx/Cfz/Z/E) – limited application in SA context (\textit{need rapid 2\textsuperscript{nd}-line DST} – GenoType MTBDRs/ LPA now approved) 
• Many shortened/new regimens currently studied in adults: if it has efficacy in adults, then only need dose & safety evaluation in children
<table>
<thead>
<tr>
<th>Trial</th>
<th>Components of intervention arm</th>
<th>Trial</th>
<th>Components of intervention arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC005</td>
<td>PZA, BDQ, PTA</td>
<td>VQUIN</td>
<td>LFX</td>
</tr>
<tr>
<td>Opti-Q</td>
<td>LFX + standard of care</td>
<td>TB-CHAMP</td>
<td>LFX</td>
</tr>
<tr>
<td>STREAM II</td>
<td>BDQ, CFZ, EMB, PZA, LFX, INH, PTO</td>
<td>PHOENIx</td>
<td>DLM</td>
</tr>
<tr>
<td>NIX-TB</td>
<td>Lzd, BDQ, PTA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STAND</td>
<td>PZA, MFX, PTA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEXT-TB</td>
<td>PZA, LFX, ETO/hdINH, Lzd, BDQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C208</td>
<td>BDQ + standard of care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial 213</td>
<td>DLM + standard of care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>endTB</td>
<td>Combinations including Lzd, BDQ, CFZ</td>
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</tbody>
</table>

PZA—pyrazinamide; BDQ—bedaquiline; PTA—pretomanid; LFX—levofloxacin; EMB—ethambutol; MFX—moxifloxacin; PTO—prothionamide; CFZ—clofazimine; hdINH—high dose isoniazid; Lzd—linezolid; ETO—ethionamide; DLM—delamanid
Challenges in DR-TB treatment/ART

• WHO 2016 guidelines: ART is recommended for all patients with HIV and DR-TB requiring second-line anti-TB drugs irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of anti-TB treatment (strong recommendation, very low-quality evidence).

• However: Early initiation of ART in TBM has a risk of intracranial IRIS – may be fatal. Usually treat TB a few weeks before starting ART. If ART started early – be aware of signs of raised intracranial pressure
Drug-drug interactions

• WHO guidelines 2016: The complexity of ARV regimens and second-line TB treatment, each with its own toxicity profiles and some of which may be potentiated by concomitant therapy, demands rigorous clinical monitoring.

• Drug-drug interactions:
  - Few known with 2\textsuperscript{nd}-line drugs – pharmacovigilance NB
  - Delamanid – no known DDIs of importance
  - Bedaquiline – LPV/r increases Bdq and M2 (metabolite) exposure; EFV may reduce Bdq exposure by 50%: Needs further evaluation regarding relevance

• New ARVs such as integrase inhibitors – seem safe with second-line anti-TB drugs
<table>
<thead>
<tr>
<th>WHO MDR-TB drug grs</th>
<th>Recommended doses</th>
<th>CSF penetrat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gr. A Fluoroquinolones</td>
<td></td>
<td></td>
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<tr>
<td>Levofloxacin</td>
<td>15-20 mg/kg (higher?)</td>
<td>Moderate to good (60-80%)</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>10 mg/kg (PK studies)</td>
<td></td>
</tr>
<tr>
<td>Gr. B 2\textsuperscript{nd}-line Inject</td>
<td>15-20 mg/g</td>
<td>Poor (&lt;20%)</td>
</tr>
<tr>
<td>Km/Am/Cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gr. C: Other core 2\textsuperscript{nd}-line drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethionamide /Pto</td>
<td>15-20 mg/kg</td>
<td>Good</td>
</tr>
<tr>
<td>Cycloserine / Tzd</td>
<td>15-20 mg/kg</td>
<td>Good</td>
</tr>
<tr>
<td>Linezolid</td>
<td>&lt;10 yrs: 10mg/kg bd</td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td>&gt;10 yrs: 300-600mg/day</td>
<td>Good</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>2-5 mg/kg; max 100mg (alternate day dosing?)</td>
<td>Poor</td>
</tr>
<tr>
<td>MDR-TB drug groups</td>
<td>Recommended dose</td>
<td>CSF penetration</td>
</tr>
<tr>
<td>-------------------</td>
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</tr>
<tr>
<td><strong>Group D: Add-ons</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D1: Pyrazinamide</td>
<td>30-40 mg/kg</td>
<td>Good</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>20-25 mg/kg</td>
<td>Poor (&lt;20%)</td>
</tr>
<tr>
<td>High-dose INH</td>
<td>15-20 mg/kg (400mg)</td>
<td>Good</td>
</tr>
<tr>
<td><strong>D2: Bedaquiline</strong></td>
<td>&gt;12 yrs &gt;33kg as in adults</td>
<td>Likely Poor</td>
</tr>
<tr>
<td>Delamanid</td>
<td>&gt;6yrs/&gt;20kg - 50mg bd</td>
<td>Likely Poor</td>
</tr>
<tr>
<td><strong>D3: PAS</strong></td>
<td>&gt;12yrs/&gt;35kg - 100mg bd</td>
<td>Poor – single dose for $C_{\text{max}}$</td>
</tr>
<tr>
<td>Amox/Clav used with imipenem/meropenem</td>
<td>25-30mg/kg tds</td>
<td>Poor</td>
</tr>
</tbody>
</table>
Challenges with drug administration

• ARVs and MDR-TB treatment together – often also supplements, treatment of other conditions
• Child-friendly formulations of second-line anti-TB drugs rarely available – being addressed slowly
• Currently all children co-infected with MDR-TB/HIV receive a daily second-line injectable agent – clinic staff often refuse to administer – often hospitalised
Challenges with Adverse Effects

• Similar toxicities, e.g. mitochondrial toxicity to be considered with Lzd, Bdq and NRTI’s/NNRTI’s

• Adverse effects of DR-TB Rx reported to be more common in HIV-infected children

• Need to develop injectable-sparing regimen for MDR-TB treatment
Alphabetical Toxicity list – which drug causes what?

- Arthralgia/arthritis: FQNs/PZA/RFB
- Blood dyscrasias: INH/RIF/PZA/LZD/FQNs/PAS and more
- Central nervous system toxicity: headache, drowsiness, seizures, weakness, insomnia, hallucinations: FQNs
- Depression/Psychosis: INH/ETO/TZD
- Endocrine effects – hypothyroidism: PAS/ETO, gynaecomastia: ETO/INH
- Flu-like syndrome: RIF/RFB/PAS
- GIT disturbances – nausea, vomiting, abdominal pain, diarrhoea: Many! ETO/PAS/FQNs/CFZ/LZD/BDQ

Alphabetical Toxicity List – which drug does what?

- **H**earing impair/ototoxicity: AM/KM/CM
  
- **H**air loss (alopecia): INH/ETO

- **I**diopathic intracranial pressure: FQNs

- **Jaundice/hepatotoxicity**: PZA/INH/RIF/ETO/PAS/MFX

- **K**+ decrease: Electrolyte disturbance: CM/PAS

- **L**actic acidosis: LZD

- **M**yelosuppression: LZD

- **N**ephrotoxicity: AM/KM/CM/SM

- **O**ptic neuritis/vision disturbance/colour blindness: EMB/LZD/INH/ETO/PAS

*Expert Opinion Drug Safety – Schaaf et al – in press*
Alphabetical Toxicity list – which drug causes what?

• **P**eripheral neuropathy: INH/ETO/LZD/TZD

• **P**ancreatitis: LZD

• **Q**Tc interval prolongation: FQN/CFZ/CLA/BDQ/DLM

• **R**ashes: PZA/FQNs/TZD/PAS and many other

• **S**kin discolouration – red skin: CFZ

• **T**endinitis/tendonopathy: FQNs

• **U**veitis: RFB

• **V**estibular toxicity: AM/KM/CM/SM

*Expert Opinion Drug Safety – Schaaf et al – in press*
59/325 (18%) were HIV-infected children – no influence on mortality

Own experience is that HIV-infected children do have higher mortality
The Challenge of Prevention

- Appropriate TB infection control measures in all facilities caring for people with HIV and efforts to optimize adherence and completion of TB treatment are important to help reduce the incidence of MDR-TB. (WHO 2016)

- To effectively “bend the curve” (accelerate decline in TB incidence)—will require not only finding and treating those with TB, but will also require treating those with TB infection who may become sick in the future. (Dye C, et al. Prospects for tuberculosis elimination. Annu Rev Public Health 2013;34:271-286.)
  - this should include those with DR-TB infection
Desired decline in global TB incidence rates to reach the 2035 targets

- Optimize use of current & new tools emerging from pipeline, pursue universal health coverage and social protection
- Introduce new tools: a vaccine, new drugs & treatment regimens for treatment of active TB disease and latent TB infection, and a point-of-care test

Current global trend: -1.5%/year
-10%/year by 2025
-5%/year
-17%/year

New diagnostics and healthcare for all

Including: Vaccine, Treatment of TB disease and infection
THE END TB STRATEGY: PILLARS AND PRINCIPLES

PILLAR 1
Integrated, patient-centered TB care and prevention

PILLAR 2
Bold policies and supportive systems

PILLAR 3
Intensified research and innovation

Government stewardship and accountability, with monitoring and evaluation

Building a strong coalition with civil society and communities

Protecting and promoting human rights, ethics and equity

Adaptation of the strategy and targets at country level, with global collaboration
Preventing MDR/XDR-TB

• WHO does not support drug treatment for prevention of MDR-TB – according to “Grade” system, too little data

• No RCT to support MDR-TB preventive therapy, but many good observational studies (prospective and retrospective) have shown that MDR-TB is preventable and preventive treatment is safe
Challenge: To prevent MDR/XDR-TB

• This policy brief followed from a meeting of >50 TB practitioners from 19 countries on MDR-TB prevention
• The current evidence base is 10 observational studies (published and unpublished), including >600 contacts treated for presumed MDR-TB infection – all studies showed success in preventing MDR-TB in contacts
• The group felt strongly that the time for MDR-TB preventive treatment has come
• Fluoroquinolone-based preventive regimen preferred
• However – RCTs to confirm efficacy should go ahead
• Prevention of XDR-TB remains a problem – new drugs?
The challenges are ours to find solutions!

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