Treatment of Drug-resistant TB

Gerry Davies
Professor of Infection Pharmacology
Institutes of Infection and Global Health & Translational Medicine
Overview

- Burden and outcomes of drug-resistant TB
- Standardised and individualised regimens
- Shorter regimens using existing drugs
- Bedaquiline and linezolid in longer regimens
- Delamanid and pretomanid
- 2018 WHO Guidelines
First-line TB therapy

THE LANCET, NOVEMBER 9, 1974
CONTROLLED CLINICAL TRIAL OF FOUR SHORT-COURSE (6-MONTH) REGIMENS OF CHEMOTHERAPY FOR TREATMENT OF PULMONARY TUBERCULOSIS
SECOND EAST AFRICAN / BRITISH MEDICAL RESEARCH COUNCIL STUDY

THE LANCET, AUGUST 12, 1978
CONTROLLED CLINICAL TRIAL OF FIVE SHORT-COURSE (4-MONTH) CHEMOTHERAPY REGIMENS IN PULMONARY TUBERCULOSIS
First Report of 4th Study
EAST AFRICAN AND BRITISH MEDICAL RESEARCH COUNCILS

N=953
~240 per arm

N=696
~130 per arm
Rifampicin resistance
## Impact of resistance

Relative Risk in New Cases treated with first-line therapy

N=5526

<table>
<thead>
<tr>
<th>Resistance</th>
<th>Treatment Failure</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any INH resistance</td>
<td>3.06 (1.81-5.05)</td>
<td>1.08 (0.54-2.14)</td>
</tr>
<tr>
<td>Any RIF resistance</td>
<td>5.48 (3.04-9.87)</td>
<td>0.68 (0.16-2.39)</td>
</tr>
<tr>
<td>INH and RIF resistance</td>
<td>15.4 (10.6-22.4)</td>
<td>3.73 (2.13-6.53)</td>
</tr>
</tbody>
</table>

MDR-TB = RIF + INH resistance

Espinal M JAMA 2000 283 : 2537-2545
Multi-drug resistant TB

Percentage of new TB cases with MDR/RR-TB

* Figures are based on the most recent year for which data have been reported, which varies among countries. Data cover the period 2002–2018.
Second line drugs

- PAS
- Ethionamide
- PZA
- Levo/Ofloxacin
- Terizidone
- Ethambutol
- Cycloserine
- Kanamycin
- Moxifloxacin
- Thiacetazone
- Capreomycin
Composing MDR-TB regimens

Standardised

Individualised

<table>
<thead>
<tr>
<th>Drug</th>
<th>P(Susceptible)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PZA</td>
<td>0.2</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>0.4</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>0.6</td>
</tr>
<tr>
<td>Kapamycin</td>
<td>0.8</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>1.0</td>
</tr>
</tbody>
</table>

For the individualised approach, the graph shows the probability of susceptibility for each drug, with the following percentages:

- PAS + CS: 0.964
- PAS + CS + CPM: 0.977
- PAS + CS + CPM + Q: 0.999
- PAS + CS + CPM + Q + Z: 0.999
- PAS + CS + CPM + Q + Z + Eth: 0.999

These values indicate the probability of susceptibility for different combinations of drugs.
Complexity of TB Treatment

Drug-sensitive TB

- Rifampicin
- Isoniazid
- Pyrazinamide
- Ethambutol

6 months

Multidrug-resistant TB

- Amikacin
- Pyrazinamide
- Moxifloxacin
- Prothionamide
- Cycloserine
- Linezolid

24 months
Outcomes of MDR-TB Treatment

Collaborative meta-analysis of 6724 patients on individualised regimens from 26 centres

- MDR-TB: 64%
- MDR-TB+I: 56%
- MDR-TB+Q: 48%
- XDR-TB: 40%

Falzon D Eur Resp J 2013 42 : 156-168
Acquired resistance on treatment

A

Acquired extensive drug resistance

<table>
<thead>
<tr>
<th>Number of selected drugs to which the pre-treatment isolate was resistant</th>
<th>%</th>
<th>GLC</th>
<th>non-GLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1-2</td>
<td>3-4</td>
<td>5-9</td>
</tr>
<tr>
<td>-</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>5-9</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10+</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

B

Acquired fluoroquinolone resistance

<table>
<thead>
<tr>
<th>Number of selected drugs to which the pre-treatment isolate was resistant</th>
<th>%</th>
<th>GLC</th>
<th>non-GLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1-2</td>
<td>3-4</td>
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<td>5-9</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10+</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

C

Acquired kanamycin resistance

<table>
<thead>
<tr>
<th>Number of selected drugs to which the pre-treatment isolate was resistant</th>
<th>%</th>
<th>GLC</th>
<th>non-GLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1-2</td>
<td>3-4</td>
<td>5-9</td>
</tr>
<tr>
<td>-</td>
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<tr>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10+</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</table>
Bangladesh Regimen

N=1006

The graph shows the successful outcome probability over time for HIV-negative and HIV-positive participants. The successful outcome probability is higher for HIV-negative participants (83.4%) compared to HIV-positive participants (71.7%). The number at risk and months since treatment start are detailed in the table below:

- **HIV-negative**:
  - Months: 0, 3, 6, 9, 12
  - Number at risk:
    - 0 months: 806
    - 3 months: 767
    - 6 months: 733
    - 9 months: 572
    - 12 months: 378

- **HIV-positive**:
  - Months: 0, 3, 6, 9, 12
  - Number at risk:
    - 0 months: 200
    - 3 months: 173
    - 6 months: 159
    - 9 months: 126
    - 12 months: 80

The graph includes events such as Death, LTFU, Transfer, and Failure, with counts provided for each event type.
STREAM Trial

Regimen A: Locally used WHO-approved MDR-TB regimen (treatment phases may vary)

Regimen B: KM + INH + PTO + MFX + CFZ + EMB + PZA
           MFX + CFZ + EMB + PZA

Regimen C: INH + PTO + BDQ + LFX + CFZ + EMB + PZA
           BDQ + LFX + CFZ + EMB + PZA

Regimen D: KM + INH + BDQ + LFX + CFZ + PZA
           BDQ + LFX + CFZ + PZA

First dose
0  8  16  28  40
Time weeks

Intensive phase  Continuation phase  Follow-up
STREAM Trial

- MITT RD -1% (-7.5 – 9.5%) p=0.02 for non-inferiority
- Bacteriological failure 10.6% versus 5.6%
- LTFU 2.4 versus 0.4%
WHO Guidelines: Shorter regimens

Is any of the following present?

• Preference by the clinician and patient for a longer MDR-TB regimen
• Confirmed resistance to or suspected ineffectiveness of a medicine in the shorter MDR-TB regimen (except isoniazid resistance)*
• Exposure to one or more second-line medicines in the shorter MDR-TB regimen for >1 month (unless susceptibility to these second-line medicines is confirmed)
• Intolerance to medicines in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions)
• Pregnancy
• Disseminated, meningeal or CNS TB
• Any extrapulmonary disease in PLHIV
• One or more medicines in the shorter MDR-TB regimen not available

Failing shorter regimen or non-response, drug intolerance, emergence of any other exclusion criterion

Individualized, longer MDR-TB regimens

Standardized, shorter MDR-TB regimen may be offered (conditional recommendation)

* Strains from MDR/RR-TB patients should ideally be tested for resistance to fluoroquinolones and other regimen components regardless of the type of MDR-TB treatment regimen offered.
New drugs

- Clofazimine
- Bedaquiline (TMC-207)
- Delamanid (OPC-67683)
- Linezolid
- Pretomanid (PA-824)
Bedaquiline: pharmacology

- PKa 8.1-13.6 (strong base)
- logP 7.3
- Protein-binding >99%
- Metabolised by CYP3A4, exposure reduced 50% with RIF
- Complex PK with t½ 6 months
- Concerns about QTc prolongation
- Targets atpE gene product, ATP synthase

Andries K 2005 Science 307: 223-7
Bedaquiline: efficacy

C208 Stage 2: Time to Culture Conversion (Wk 24 – mITT)

Primary endpoint (difference in TtC):
p = <0.0001

Proportion of Culture Positive

BDQ/BR vs Placebo/BR:
BDQ/BR (N=56) Placebo/BR (N=56)
58 61
37 53
25 40
12 30
7 22
3 5

Time to Culture Conversion (Weeks)

Median time to culture conversion was 12 weeks in the BDQ group and 18 weeks in the placebo group. p-value from Cox proportional model adjusting for strata.

FDA NDA 204-384 Briefing package November 2012
Bedaquiline : mortality

SA Programme data 2014-16 N=19,617

Delamanid: pharmacology

- PKa 5.51
- LogP 6.14
- Protein-binding >99.5%
- Prodrug reduced by FGD1/F_{420} (Rv3547)
- Complex metabolism on albumin and CYP3A4
- t_{1/2} 38 hours
- Mechanism of action complex involving intra-mycobacterial NO release
- Spontaneous mutation rate $\sim 10^{-5}$
Delamanid: Trial 213

- 511 patients recruited worldwide
- 2:1 allocation ratio active:control
- 85% follow-up to 30 months
- Primary endpoint TTSCC at 6m median 51 vs 57 days (p=0.056)
- 77.9 vs 76.5% cure at 24m (NS)
- 4.1 vs 3.5% mortality (NS)
- QtcF prolongation less than previous trials, no new AEs
Pretomanid: pharmacology

- PKa 8.1 - 13.6 (strong base)
- LogP 3.39
- Protein-binding 95%
- Prodrug reduced by FGD1/F_{420} (Rv3547)
- \( t_{1/2} \) 18 hours
- Inhibition of tubular creatinine secretion
- Likely similar mechanism of action to delamanid
- Spontaneous mutation rate \( \sim 10^{-6} \)
Pretomanid: NIX-TB

- **Proportion of Patients**

- **Number at Risk**
  - TI/NR MDR-TB: 20
  - XDR-TB: 48

- **Time from Enrollment (weeks)**
  - TI/NR MDR-TB: 14, 4, 2, 0
  - XDR-TB: 36, 13, 7, 1

<table>
<thead>
<tr>
<th>mITT Population</th>
<th>Patients (n)</th>
<th>Favorable (95% CI)</th>
<th>Favorable (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>XDR-TB</td>
<td>55</td>
<td></td>
<td>89% (78, 96)</td>
</tr>
<tr>
<td>TI/NR MDR-TB</td>
<td>25</td>
<td></td>
<td>92% (74, 99)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>80</strong></td>
<td></td>
<td><strong>90% (81, 96)</strong></td>
</tr>
</tbody>
</table>
WHO Guidelines: IPD Meta-analysis

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**Adjusted risk difference (%)**

- **Favours Control**
  - Ethambutol (n=2598)
  - Pyrazinamide (n=1818)
  - Thioamides (n=3434)
  - Cycloserine (n=5682)
  - PAS (n=2605)
  - Kanamycin (n=2523)
  - Amikacin (n=1393)
  - Capreomycin (n=938)
  - Levofloxacin (n=1450)
  - Moxifloxacin (n=1031)
  - Linezolid (n=799)
  - Clofazimine (n=564)
  - Bedaquiline (n=490)
  - Carbapenems (n=138)

- **Favours Active**
  - Kanamycin (n=2523)
  - Amikacin (n=1393)
  - Capreomycin (n=938)
  - Levofloxacin (n=1450)
  - Moxifloxacin (n=1031)
  - Linezolid (n=799)
  - Clofazimine (n=564)
  - Bedaquiline (n=490)
  - Carbapenems (n=138)

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Lancet 2018 392:821-34
## WHO Guidelines: Longer regimen

<table>
<thead>
<tr>
<th>GROUPS &amp; STEPS</th>
<th>MEDICINE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group A:</strong> Include all three medicines</td>
<td>Levofloxacin OR Moxifloxacin, Bedaquiline, Linezolid</td>
</tr>
<tr>
<td><strong>Group B:</strong> Add one or both medicines</td>
<td>Clofazimine, Cycloserine OR Terizidone, Ethambutol</td>
</tr>
<tr>
<td><strong>Group C:</strong> Add to complete the regimen and when medicines from Groups A and B cannot be used</td>
<td>Delamanid, Pyrazinamide, Imipenem-cilastatin OR Meropenem</td>
</tr>
<tr>
<td></td>
<td>Amikacin (OR Streptomycin), Ethionamide OR Prothionamide, p-aminosalicylic acid</td>
</tr>
</tbody>
</table>

Summary

- MDR-TB burden is high worldwide and only a minority of patients are accessing treatment
- Treatment regimens in MDR-TB are evolving rapidly
- Shorter regimens are achievable using historical drugs
- Bedaquiline and linezolid are radically improving outcomes in longer regimens
- Nitroimidazooxazines still lack clear evidence of independent efficacy
- MDR-TB regimens shorter than 9 months are within reach