Isoniazid resistant TB: treatment regimens, outcomes and update on new WHO guidelines

Professor Dr. Graham Bothamley
EACCTB, Rotterdam 2019
### Disclosure of speaker’s interests

<table>
<thead>
<tr>
<th>(Potential) conflict of interest</th>
<th>None</th>
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<tr>
<td>Potentially relevant company relationships in connection with event (^1)</td>
<td>NA</td>
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<tr>
<td>▪ Sponsorship or research funding (^2)</td>
<td>None</td>
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<td>▪ Fee or other (financial) payment (^3)</td>
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<td>▪ Shareholder (^4)</td>
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<td>▪ Other relationship, i.e. ... (^5)</td>
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Plan of talk

• Epidemiology
• Basic science
• Treatment regimens and outcomes
• WHO guidelines
• Phenotypic resistance
• Future regimens
Isoniazid resistance in Europe

katG: 30-95%
inhA: 5-30%
other: 5%
(300 mutations)

Vilcheze & Jacobs. Micro Spect 2014: 2(4)

Upward trend:
Austria
Czech Republic
Finland
France
Germany
Russia (oblast)
Serbia
Sweden
UK

Jenkins et al. PLoS ONE 2011; 6: e22927
Epidemiology of isoniazid (non-MDR) resistance

• Globally, 9.5% of all TB
  • Former Soviet Union states: 16.1%
  • Non FSU 7.5%
• 44% of world’s population without data

What causes isoniazid resistance?

The consequences of isoniazid resistance - MDRTB
Isoniazid

• Bactericidal
• Target: cell wall (mycolic acid) – no longer acid-fast
• 1950s, Navajo (no streptomycin)
• Activated by *katG* – NO formed in process
• Binds to *inhA* (enoyl acyl carrier protein reductase)
• Binds to beta-ketoacyl ACP synthase (KasA)
• Blocks fatty acid synthase
• Peak not AUC significant in treatment

![Isoniazid Structure](image)
Early bactericidal activity – dose of isoniazid

Sirgel et al. 2005
AJRCCM 172: 128
Spontaneous mutations or isoniazid-induced?

- Initially susceptible strains
- Grow in macrophages (THP-1) at 1 bacillus per 10 cells
- Mutation rate
  - No isoniazid until day 3: $4.4 \times 10^{-6}$
  - With isoniazid: $7.6 \times 10^{-6}$
  - + hydrogen peroxide: $3.6 \times 10^{-6}$
  - All partial deletions of katG (never S315T or inhA C-15T)
  - No oxyR-ahpC mutations
- katG mutation rate 43 X greater than rpoB mutations in same model
  [Rifampicin mono-resistance 329/146,321 (0.3%) cf. isoniazid 4.1% (14X) in USA (1998-2014)]

Bergval IL et al. JAC 2009; 64:515-23
Sharling L et al. CID 2019; pii:ciz499
WT population

inhA promoter mutation
LPA detected

inhA coding mutants and katG (non 315)
not LPA detected

katG 315
LPA detected

inhA promoter and katG 315

Pre-MDRTB

• Sequenced 8,316 strains of *Mycobacterium tuberculosis*
• Isoniazid mono-resistance in RH combination era (SNP dating)
• Hypotheses
  • *katG* non-essential gene (other enzymes can reduce ROS)
  • Hypermutators – no evidence (cf. PE-PPE genes and DR (CRISPR-Cas) repeats)
  • LTBI treatment (not in this series)
  • Drug availability – **low rifampicin**
• *katG* S315T mutation first to occur
  • Preserves catalase activity but affects isoniazid activation
• Pre-dated rifampicin resistance mutations in 155/162 MDRTB strains (96%)

Manson AL et al. Nat Genet 2017; 49: 395-402
Treatment

RCTs and cohort studies
RCT isoniazid-resistant TB: Swai OB et al 1988

306 patients
Failed 2STH/10-16TH (30%)
>15 yr; S+PTB; 1st 2m in hospital; DOT

Exclusions (27):
Isoniazid sensitive (1)
Culture-negative (4)
No DST (5)
RH-resistant (1)
HE-resistant (1)
RHE-resistant (1)
Death before treated (6)
Not started (4)
Other (4)

Exclusions (29):
Isoniazid sensitive (1)
Culture-negative (6)
No DST (6)
RH-resistant (1)
HE-resistant (1)
RHE-resistant (1)
Death before treated (7)
Not started (5)
Other (1)

Randomisation

152 2SRZE\textsubscript{25}/4RE\textsubscript{15}
125 started
6m treatment
113 completed
6m treatment

154 2SRZE\textsubscript{25}/7RE\textsubscript{15}
125 started
9m treatment
113 completed
9m treatment

Missed many doses (1)
Died (5)
No final bacteriology (6)

Missed many doses (9)
Died (1)
No final bacteriology (2)
Outcomes

113 completed 6 m treatment

91 H-mono-resistant

22 SH-resistant

3/72

3/14

Relapsed by 30-months

1 unfavourable outcome

End treatment (226)

113 completed 9 m treatment

25 SH-resistant

88 H-mono-resistant

2/72

1 unfavourable outcome

0/20
Interpretation of RCT evidence

- USA: 6 months treatment (6RZE)
  - BMRC trials: RHZ + S/E OK even in isoniazid resistance
  - Pyrazinamide for 6 months seemed better (23 patients; no 2m comparison)

- UK: 9 months treatment (2RZE/7RE)
  - Ormerod interpretation of same papers
    - 9m if resistance known from start and supplemented with streptomycin
    - Otherwise, 12 m regimen

HKCS. Am Rev Respir Dis 1987; 136: 1339-42 (5 year follow-up)
RCTs of management of isoniazid-resistance: network analysis

• 118 RCTs (59 studies)
• 43 studies of isoniazid mono-resistance
• Categorize by
  • </> 3 effective drugs for > 4m
  • 6m rifampicin protected by another drug(s)
  • </> 6m
• Have rifampicin > 6 m and at least 3 drugs for 4 m

Stagg HR et al. Thorax 2016; 71: 940-9
## Treatment regimens for isoniazid-resistant TB

<table>
<thead>
<tr>
<th>Source of guidance</th>
<th>Regimen</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>ATS</td>
<td>6RZE (FQ for extensive disease)</td>
<td>Blumberg HM et al. AJRCCM 2003; 167: 603-62.</td>
</tr>
<tr>
<td>WHO</td>
<td>High incidence, no DST: 2RHZE/4RHE DST: 6-9RZE +/- FQ (also SH-resistant)</td>
<td>WHO. Treatment of tuberculosis. 4th ed. 2009 WHO. Programmatic management ..., 2014</td>
</tr>
<tr>
<td>NICE</td>
<td>2REZ/10RE (unless S from beginning)</td>
<td>NICE, Tuberculosis, 2016.</td>
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Treating with first-line drugs

<table>
<thead>
<tr>
<th>Drug resistance</th>
<th>No.</th>
<th>Failure (%)</th>
<th>Relapse (%)</th>
<th>Acquired drug resistance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>12,690</td>
<td>4 (3 – 5)</td>
<td>0.6 (0.3 – 0.9)</td>
<td></td>
</tr>
<tr>
<td>Isoniazid alone</td>
<td>2,024</td>
<td>15 (12 – 18)</td>
<td>3.6 (2 – 5)</td>
<td></td>
</tr>
<tr>
<td>Isoniazid and WHO regimens:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2RHZE/4RH</td>
<td>701 vs. 5,415</td>
<td>11 (6 – 17)</td>
<td>10 (5 – 15)</td>
<td>8 (3 – 13)</td>
</tr>
<tr>
<td>2SRHZE/1RHZE/5RHE</td>
<td>284 vs. 2,091</td>
<td>6 (2 – 10)</td>
<td>5 (2 – 8)</td>
<td>3 (0 – 6)</td>
</tr>
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- 102 different regimens
- 3,744 patients cf. 19,012 FSTB

Gegia M et al.
Lancet Inf Dis 2017; 17: 223-34.
Individual patient data meta-analysis*

<table>
<thead>
<tr>
<th>Indices</th>
<th>≥6(H)REZ vs. &gt;6(H)REZ</th>
<th>≥6(H)REZFq vs. ≥6(H)REZ</th>
<th>≥6(H)REZ₁₃ₛ₂ vs. ≥6(H)REZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success</td>
<td>254/262 vs. 989/1088</td>
<td>245/251 vs. 1253/1350</td>
<td>271/325 vs. 1253/1350</td>
</tr>
<tr>
<td>Adjusted odds ratio</td>
<td>2.4 (1.0 – 5.5)</td>
<td>2.8 (1.1 – 7.3)</td>
<td>0.4 (0.2 – 0.7)</td>
</tr>
<tr>
<td>Risk difference per 100</td>
<td>4 (0 – 8)</td>
<td>5 (0 – 9)</td>
<td>-120 (-190 to -60)</td>
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*Only statistically significant results shown

- FQ better success (cure and treatment completion)
- Streptomycin unhelpful
Problems of individual patient data meta-analysis with propensity scoring

• Regimen defined at 2 weeks
• Doses of ethambutol and moxifloxacin
• Success includes treatment completion
• Confounding by indication (which patients had a FQ)
• Variation in applying WHO outcome failure
• Managing data from treatment interruptions and deaths
## London isoniazid-resistance

<table>
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<th>9 months 2RZE/7RE</th>
<th>12 months 2RZE/10RE</th>
</tr>
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<tbody>
<tr>
<td>No FQ</td>
<td>116</td>
<td>70</td>
</tr>
<tr>
<td>With FQ</td>
<td>63</td>
<td>31</td>
</tr>
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- FQ duration: median 5.5 (IQR 3.9 – 8.7)
- FQ dose usually moxifloxacin 400 mg od
- 68% power
- 98 (26%) different regimens

- No significant difference in outcomes with or without FQ
  - 5 relapses (follow-up incomplete)
  - 4 rifampicin resistance
  - 1 ethambutol resistance
- No 6-month regimens
- > 1/3 DST > 2m

Stagg HR et al. ERJ 2019; 54: 1900982
Moxifloxacin 400 mg △ and rifampicin 600 mg ●

Moxifloxacin

M1 metabolite

M2 metabolite

Weiner N et al. AAC 2007; 51: 2861-6
Clinical considerations in H-resistant TB

• Prevent MDR-TB by measuring rifampicin levels (100-fold variation)
• Moxifloxacin-rifampicin interaction
  • 8-27% AUC reduction in moxifloxacin
  • 30% reduction if efavirenz
  • Moxifloxacin dose to reach 2-4 mg/L is 600 mg (so, 800 mg OK)
• Moxifloxacin-ethambutol interaction
  • 30-70% reduction by *in vitro* model of metabolizing enzymes
  • *In vivo* data: may be OK

Weiner N, et al. AAC 2007; 51:2861-6
Te Brake LH, et al. AAC 2016; 60: 7105-14
Naidoo A et al. JAC 2017; 72: 1441-9
### WHO consolidated guidelines 2019

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
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</table>
| Isoniazid resistance cases:  
  • with/without katG and normal/high isoniazid  
  • with/without inhA and normal/high isoniazid  
  • where E/Z/S resistance | 6REZ | >6REZ | • Completion/cure  
• Failure and/or relapse  
• Survival (or death)  
• Adverse reactions (severity, type, organ)  
• Acquired drug resistance |
| Previous TB Cavities  
HIV co-infection with/without ART  
Children (0-14 y)  
DM | 2REZ/4RE & FQ | 6+REZ | 6+REZ |
| | 6+REZ & FQ | 6+REZ | 6+REZ |
| | 6+REZ & S | 6+REZ | |

- All recommendations conditional and very low grade of evidence
- High dose isoniazid discredited (see MIC data)
- **No difference 6REZ vs. > 6REZ** (power, as limited numbers of FQ and S)
- Fregonese et al. – but 3276 potential patients, not 5418
- Z < 3m; aOR 0.4 (0.2 – 0.7)
- Drug resistance affected by non-drug factors
- FQ: aOR 2.8 (1.1 – 7.3) success; death and drugR non-significant (small numbers)
- Lfx re adverse events; Mfx better bactericidal drug
- Streptomycin: worse outcome (indication bias)
Conclusions

• High-dose isoniazid is unlikely to overcome resistance
• Check for rpoB, pncA, gyrA/B mutations at start
• 2REZFq/4RE(Z)Fq most likely effective regimen
  • give after confirmation of isoniazid resistance
• Measure rifampicin levels to avoid creating MDR-TB
• Measure fluoroquinolone levels if moxifloxacin or
  • give Mfx 800 mg od or
  • Lfx: 750 mg - 1g od (safety, drug interactions, OK with rifampicin)
• If HIV co-infection give ART
Phenotypic resistance

What can we learn? The future for treating isoniazid-resistant TB
Phenotypic resistance and isoniazid

Isoniazid most effective first 2-5 days, Grosset et al. AJRCCM 2013; 188:608

Jindani et al. AJRCCM 2003; 167: 1348

100 patients
Sputum cfus
Change in lung CFU counts in mice treated with increasing doses of isoniazid (H) given alone (A) or in combination with 10 mg/kg rifampin (R) and 150 mg/kg pyrazinamide (Z) (B).

Potential problems

• Fluoroquinolones encourage persisters
  • reduce protein production (slow growth)
  • DNA repair affected (mutations)
  • changes in metabolism (slow growth)

• Anaerobic respiration protects Mtb (sdh1 deletions)

• NO sources
Anti-persister molecules

**Inhibit persister response**
- relaxin (stringent response)
- NO (CD4 cells; pretomanid)
- quorum sensing (M64)
- persister specific genes (cadaverin)
- arrest cell cycle and promote DNA repair (lexA3)

**Direct killing of persister cells**
- membrane depolarization (boromycin; anti-microbial peptides; L-arginine; penetratin (12 aminoacids))
- DNA cross-linking (mitomycin C, cisplatin)
- inhibit essential enzymes (lassomycin – Clp protease)
- generate ROS

**Stimulate aerobic respiration**
- glucose, fructose, pyruvate, mannitol
- L-serine
- N-acetylcysteine
The future

• Treat non-katG S315T differently to other mutations
• Activate cell respiration
• Consider
  • clofazimine
  • boromycin
  • pretomanid