Isoniazid preventive therapy in the context of drug resistance: challenges and solutions

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Challenges

• Weighing up risks and benefits of isoniazid preventive therapy (IPT) in settings of drug resistance
  – will it work?
  – will it make resistance worse?
Challenges

• Weighing up risks and benefits of isoniazid preventive therapy (IPT) in settings of drug resistance
  – will it work?
IPT prevents TB among PWHIV: meta-analysis of RCTs

Relative risk, 95% CI

Placebo
Overall
TST+
TST-

0.36
0.67
0.86
1.0

Akolo 2010, Cochrane review
Does IPT work where there is resistance?

- IPT (probably) ineffective in individual with latent INH-resistant TB
  - though different mutations confer different degrees of resistance
  - *kat* G: high level resistance
  - *inh* A: lower level resistance, can be overcome with high dose INH
IPT prevents TB among PWHIV: meta-analysis of RCTs

Relative risk, 95% CI

Placebo
Overall
TST+
TST-

0.36
0.67
1.0
0.86

Akolo 2010, Cochrane review
IPT similar to RZ, Haiti, 1990-4

17% any H resistance in new TB cases

Figure 2: Kaplan-Meier plot of proportions of patients developing confirmed, probable, or possible tuberculosis by treatment regimen

Halsey, Lancet 1998;351:786; Chaisson ARRCCM 1996;154:1034
IPT routine for latent TB among US migrants
primary INH resistance in foreign-born 10-12%
Who has drug-resistant latent TB?

- best data from studies of contacts of drug-resistant TB cases
- contacts with latent TB infection may not have the same strain/resistance pattern as the index case
Household contacts may not have the same resistance pattern as index

- Retrospective cohort, Rio de Janeiro, Brazil, 1988-92
- 64 index cases with resistance to >1 drug
- 17/218 HIV neg household contacts developed TB
- 13/17 culture + with DST:
  - 6 (46%) identical DST to index case
  - 4 (31%) resistance, with different pattern
  - 3 (23%) fully susceptible

Kritski AJRCCM 1996;153:331
Household contacts may not have the same resistance pattern as index cases.

<table>
<thead>
<tr>
<th></th>
<th>MDR index case</th>
<th>XDR index case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contacts culture+ with DST</td>
<td>26</td>
<td>29</td>
</tr>
<tr>
<td>Fully sensitive</td>
<td>2 (8%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>MDR</td>
<td>14 (54%)</td>
<td>8 (28%)</td>
</tr>
<tr>
<td>XDR</td>
<td>10 (38%)</td>
<td>19 (66%)</td>
</tr>
</tbody>
</table>

Data from KwaZulu Natal, South Africa: Moll et al, Union conference, Cancun 2009
IPT may work even in contacts of drug-resistant index cases

- Among TST+ (>10mm) contacts of DR index cases (Brazil, 1988-92):
  - no IPT: active TB in 13/145 (9.0%)
  - IPT: TB in 2/45 (4.4%) (OR 0.46, 95% CI 0.07-2.32)
    - 2 cases post IPT both had MDR strains, as did index cases

Kritski AJRCCM 1996;153:331
Challenges

• Weighing up risks and benefits of isoniazid preventive therapy (IPT) in settings of drug resistance
  – it will work, for most people
  – will it make resistance worse?
IPT for latent infection does not promote INH resistance

• IPT does not promote isoniazid resistance when used to treat latent TB infection
  – in latent TB few organisms, dividing slowly, hence low risk of selecting drug-resistant mutant
Meta-analysis, incidence of isoniazid resistance, IPT vs. no IPT

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Balcells Emerg Infect Dis 2006;12:744
Isoniazid resistance after IPT: data from Thibela TB

Cluster-randomised trial of community-wide IPT: >24,000 gold miners started IPT, South Africa

• substudy of 126 gold miners developing active TB after receiving IPT (125 men, median 43y, 86% HIV+)

• 71 with drug susceptibility results (58 first episodes, 13 retreatment)

van Halsema AIDS 2010;24:1051
Prevalence of any isoniazid resistance in TB episodes after IPT (bars=95% CI)

van Halsema AIDS 2010;24:1051
Effect of IPT on isoniazid resistance

• IPT does not promote isoniazid resistance when used to treat latent TB infection
  – unless a person with active TB is given inadvertent isoniazid monotherapy
  – thus importance of screening to exclude active TB prior to IPT
Wider benefits of screening plus IPT

• screening (intensified case finding) is an integral part of IPT programme

• benefits all PLWHIV:
  – those with active TB: earlier treatment, better outcomes
  – all clinic attendees [and staff] benefit from less exposure to infectious TB
  – those without active TB may benefit from IPT, will not make resistance worse
Risks vs. benefits of IPT for PWHIV in settings of resistant TB

• no evidence about threshold prevalence of INH resistance at which IPT risks exceed benefits
Solutions: what can we do?

• Review data:
  – outcomes from IPT programmes among PWHIV in settings of high prevalence of isoniazid resistance
## IPT use where isoniazid resistance, new cases, >15%

<table>
<thead>
<tr>
<th>country</th>
<th>year of resistance survey</th>
<th>prevalence any isoniazid resistance, new TB cases</th>
<th>started IPT, 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dominican Republic</td>
<td>1995</td>
<td>19%</td>
<td>443</td>
</tr>
<tr>
<td>Georgia</td>
<td>2006</td>
<td>23%</td>
<td>301</td>
</tr>
<tr>
<td>Kazakhstan</td>
<td>2001</td>
<td>42.8%</td>
<td>656</td>
</tr>
<tr>
<td>Mozambique</td>
<td>1999</td>
<td>16.5%</td>
<td>724</td>
</tr>
<tr>
<td>Vietnam</td>
<td>2006</td>
<td>19%</td>
<td>500</td>
</tr>
</tbody>
</table>

WHO drug resistance survey 2008; IPT data courtesy WHO
Solutions: what can we do?

- Review IPT programmatic outcomes from settings of high resistance
- Decision analysis: modelling risks vs. benefits for range of prevalence of resistance

Sterling Ann Intern Med 1995;155:1622

Figure 4. Three-way sensitivity analysis of isoniazid-associated hepatitis and hepatitis fatality rates in the presence of varied isoniazid resistance rates in tuberculin reactors aged 20 to 34 years.
Solutions: what can we do?

- Review IPT programmatic outcomes from settings of high resistance
- Decision analysis: modelling risks vs. benefits for range of prevalence of resistance
- Weigh risks and benefits of IPT for PLWHIV:
  - most will benefit from IPT
  - will not promote resistance if active TB excluded
  - screening for active TB is an integral part of an IPT programme
  - clinic-based screening ± IPT benefits all PWHIV
Acknowledgements

• Haileyesus Getahun
• Sarita Shah
• Tim Sterling
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Effect of IPT on prevalence of resistance

<table>
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<th>Latent TB</th>
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<tbody>
<tr>
<td>Isoniazid</td>
<td>Control</td>
</tr>
<tr>
<td>Active TB</td>
<td>Active TB</td>
</tr>
</tbody>
</table>

Prevalence of resistance: 50%  
Prevalence of resistance: 25%

Incidence of resistance:  
10% individuals exposed to INH  
10% individuals exposed to control

INH-resistant  
INH-sensitive