What more is required to use rifamycin regimens to prevent TB in people living with HIV in resource constrained settings?

Gary Maartens
Which rifamycin regimens?

Excluded from my talk:

Rifampicin monotherapy - may select for rifamycin mono-resistance

2-3RZ and HRZ – too toxic

Included:

3HR

3H rifapentine (RPT)
Are rifamycin regimens more effective than IPT?
### H versus HR: TB incidence in HIV+

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatm 1 (INH)</th>
<th>Treatm 2 (SC-INH+RIF)</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 PPD+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martinez 2000</td>
<td>3/21</td>
<td>1/26</td>
<td>4.7 %</td>
<td>2.71</td>
<td>[0.42, 32.15]</td>
</tr>
<tr>
<td>Rivero 2007</td>
<td>4/108</td>
<td>5/103</td>
<td>27.1 %</td>
<td>0.76</td>
<td>[0.21, 2.76]</td>
</tr>
<tr>
<td>Whalen 1997</td>
<td>7/536</td>
<td>9/536</td>
<td>46.8 %</td>
<td>0.81</td>
<td>[0.30, 2.15]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>665</strong></td>
<td><strong>685</strong></td>
<td><strong>78.7 %</strong></td>
<td><strong>0.97</strong></td>
<td><strong>[0.47, 1.97]</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 PPD-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martinez 2000</td>
<td>1/143</td>
<td>1/143</td>
<td>5.3 %</td>
<td>1.00</td>
<td>[0.06, 15.48]</td>
</tr>
<tr>
<td>Rivero 2003</td>
<td>3/83</td>
<td>2/82</td>
<td>16.0 %</td>
<td>0.99</td>
<td>[0.21, 4.75]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>126</strong></td>
<td><strong>125</strong></td>
<td><strong>21.3 %</strong></td>
<td><strong>0.99</strong></td>
<td><strong>[0.25, 3.87]</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 PPD unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>0</strong></td>
<td><strong>0</strong></td>
<td><strong>0.0 %</strong></td>
<td><strong>0.0</strong></td>
<td><strong>[0.0, 0.0]</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>791</strong></td>
<td><strong>810</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.97</strong></td>
<td><strong>[0.52, 1.83]</strong></td>
</tr>
</tbody>
</table>

Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD000171
6H vs 3HR vs 3HRPT vs H continuous in HIV+

Crude TB incidence-rate ratios (6H as reference):

- 3HR (N=329) 1.02 (0.55–1.91)
- 3HRPT (N=328) 1.05 (0.56–1.97)
- H cont (N=164) 0.74 (0.29–1.73)
Network meta-analysis of LTBI treatments in HIV+ & HIV-
Tolerability H vs HR/HRPT

Adverse events stopping therapy

H vs HR (HIV+ only) RR 0.79 (95%CI 0.50, 1.23)

H vs HRPT vs HR (HIV+ only) 1.9% vs 1.8% vs 3.8%

H vs HRPT (most HIV-) 3.7% vs 4.9% (P=0.009)
Adherence H vs HR/HRPT

Better adherence did not result in lower TB incidence

>90% doses taken in allotted time:
- 6H: 83.8%
- 3HR: 94.8%
- 3HRPT: 95.7%
3HR vs 3HRPT

Availability of fixed dose combination HR is an advantage

Unclear if weekly dosing of HRPT will result in better adherence or better outcomes

DOT of HRPT not practical as services already stretched in most RLS and DOT has been shown to be costly for both patients & health systems

PloS ONE 2010; 5(11): e14014
Preventive therapy and ART

Most HIV+ people will be on ART:
- WHO 2013 start ART with CD4 <500
- UNAIDS 2014 “90 90 90”

Most evidence for preventive therapy is in people not on ART
- One RCT on ART: 12H better than placebo, well tolerated
- TST status not important
- Easy to implement

Duration of preventive therapy with ART not such an important issue

Long term IPT safety with ART unclear, recommended by WHO
- Increased risk of death in TST- participants on 36H in BOTUSA

Rangaka Lancet 2014
Samandari Lancet 2011
Rifampicin/RPT-ARV drug-drug interactions

NNRTIs
Efavirenz concentrations not significantly affected by RPT/rifampicin
Nevirapine modest reduction, higher risk of virologic failure
Rilpivirine & etravirine cannot be used

INSTIs
Raltegravir probably no need for dose adjustment
Dolutegravir dose 12 hourly
Elvitegravir cannot be used

PIs
Cannot be co-administered (double dose LPV-r too toxic for preventive therapy)
Could test 3H rifabutin three times a week
Effect of ART on WHO symptom screen to rule out TB

<table>
<thead>
<tr>
<th></th>
<th>Khayelitsha</th>
<th></th>
<th>Eastern Cape</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-ART</td>
<td>On ART</td>
<td>Pre-ART</td>
<td>On ART</td>
</tr>
<tr>
<td>n</td>
<td>654</td>
<td>775</td>
<td>215</td>
<td>522</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>47.6%</td>
<td>23.8%</td>
<td>91.2%</td>
<td>51.6%</td>
</tr>
<tr>
<td>Specificity</td>
<td>79.8%</td>
<td>94.4%</td>
<td>32.6%</td>
<td>55.8%</td>
</tr>
<tr>
<td>NPV</td>
<td>91.2%</td>
<td>95.6%</td>
<td>95.2%</td>
<td>94.8%</td>
</tr>
</tbody>
</table>

Rangaka CID 2012;55:1698
Ahmad Khan AIDS 2014;28:1463
Resistance and H-rifamycin regimens

• The poor sensitivity of TB symptom screen on ART is a strong argument in favour of H-rifamycin regimens, as they are less likely to select for resistance

• TB programs very concerned about widespread rifamycin use for prevention as this may result in rifamycin resistance

• Fixed dose combinations should reduce the risk of resistance
Pharmacodynamics of INH

• Most effective drug for rapidly dividing bacilli, but no “sterilising” activity (unable to kill “persisters”)

• Classical understanding of LTBI is infection with non-replicating bacilli, so why did we choose INH for prevention?

• INH increases “persisters” in chronically infected mice

• “Persister” *M smegmatis* bacilli phenotypically express less catalase-peroxidase, which is required to activate INH
IPT benefit is short-lived: BOTUSA

Benefit lost after 6 months

Samandari Lancet 2011
Duration of benefit of PT Uganda, post hoc

Johnson AIDS 2001
Ability of preventive therapy to cure latent *Mycobacterium tuberculosis* infection in HIV-infected individuals in high-burden settings

Rein M. G. J. Houben\textsuperscript{a,b,1,2}, Tom Sumner\textsuperscript{a,b,2}, Alison D. Grant\textsuperscript{b,c}, and Richard G. White\textsuperscript{a,b}

Mathematical model – only ART-naive
Proportion cured of LTBI by IPT very low (median 0%)
INH + rifampicin/rifapentine cures 19-100%
Suggest lifelong IPT in high TB incidence areas & more curative regimens in low incidence areas
Conclusions

Current evidence is that H-rifamycin regimens are no more effective & not better tolerated than IPT

Shorter duration of HR & HRPT not such an important issue in people on ART

Rifamycin-ARV interactions are a barrier, but not with efavirenz

H-rifamycin regimens MAY provide longer duration of benefit

Need for adequately powered RCT for enough time in people on ART of e.g. 12H vs 3HR