Is IPT a Priority for South Africa?

Robin Wood
Desmond Tutu HIV Centre
University of Cape Town
Is IPT a Priority for South Africa?

Four questions that need to be addressed

1. Is the research good enough to support a decision on whether or not to implement IPT as a public health intervention?
2. Is the research transferable to the potential recipients of the intervention?
3. Is this the best use of scarce resources?
4. Are there potential harms of the intervention?

L Rychetnic et al. Criteria for evaluating evidence on public health interventions  *J. Epidemiol Community Health* 2002
INH preventive therapy

H. Esmail, C. E. Barry, 3rd, D. B. Young and R. J. Wilkinson. The ongoing challenge of latent tuberculosis Phil. Trans. R. Soc. 12 May 2014
Indications and recommendations for the use of prophylactic treatment

Prophylactic treatment is, for all practical purposes, rarely indicated. Even if the evidence is scant, however, it makes sense to provide it to a new-born child with a potentially infectious parent, especially the mother. This is recommended in industrialized countries, but should most likely be a universal indication.

Figure 53. Protection from prophylactic treatment in the prevention of acquisition of tuberculous infection in four clinical trials conducted by the US Public Health Service.\textsuperscript{641}
The South African Antiretroviral Treatment Guidelines 2013

7.2 INH Prophylaxis

- All people living with HIV should be screened for active TB and eligibility for ART.
- Those who are eligible should be started on ART.
- TB preventive therapy is an effective intervention for HIV infected individuals.
- All people living with HIV, in whom active TB has been reasonably excluded, should be started on IPT (as soon as practically possible after initiation of ART in those who are eligible for ART).
- In patients with no TB signs or symptoms, TB prophylaxis with Isoniazid Preventive Therapy (IPT) should be started, unless alcohol abuse, adherence or side-effects are a concern, 5mg/kg to a maximum dose of 300mg daily, with pyridoxine 25mg/day. **A TST (Mantoux) test is required.**
- Pregnancy is not a contraindication to INH prophylaxis.
- If no TST is done IPT should be continued for 6 months as per existing guidelines but all effort should be made to perform TST as soon as possible after starting IPT.

<table>
<thead>
<tr>
<th>Summary Recommendations</th>
<th>Pre-ART(CD4&gt;350)</th>
<th>On ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST not done*</td>
<td>IPT for 6 months</td>
<td>IPT for 6 months</td>
</tr>
<tr>
<td>TST negative</td>
<td>IPT for 6 months</td>
<td>IPT for 12 months</td>
</tr>
<tr>
<td>TST positive</td>
<td>IPT for at least 36 months</td>
<td>IPT for at least 36 months</td>
</tr>
</tbody>
</table>
Unclear of what INH does?

- Prophylaxis before and after known TB exposure
- Sterilization of LTBI recently or distantly acquired
- Treatment of childhood active TB
- Treatment of pauci/multi bacillary adult disease

Unclear who will benefit?

- Anergic patients are not a group without prior TB exposure
- INH before and after ART seems to act differently – Pre-ART studies are less relevant now in today’s ART “universal access”.
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## South African IPT Randomised Controlled Studies

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Mean age</th>
<th>Baseline ART</th>
<th>Baseline TB prev %</th>
<th>TB incidence per 100 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zar et. al.</td>
<td>263, HIV+ hospital symptomatic</td>
<td>25 m</td>
<td>9%</td>
<td>N/A</td>
</tr>
<tr>
<td>Madhi et. al.</td>
<td>548, HIV+ hospital outpatients</td>
<td>4 m</td>
<td>32%</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>804, HIV- exposed outpatients</td>
<td>4 m</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Gray et. al.</td>
<td>167, HIV+ hospital &amp; outpatients</td>
<td>35 m</td>
<td>100%</td>
<td>7%</td>
</tr>
<tr>
<td>Mohammed et. al.</td>
<td>118, HIV+ symptomatic, TST-ve</td>
<td>38 y</td>
<td>0</td>
<td>9.3</td>
</tr>
<tr>
<td></td>
<td>20 HIV+ symptomatic, TST+ve</td>
<td>36 y</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Rangaka et. al.</td>
<td>1,580, HIV+ ART clinic attenders</td>
<td>34 y</td>
<td>72%</td>
<td>16.2</td>
</tr>
<tr>
<td>Churchyard et. al.</td>
<td>78,744, mining workforce</td>
<td>41 y</td>
<td>2.7%</td>
<td>6.9††</td>
</tr>
</tbody>
</table>
Study variability & trial design differences?

- 4 out of 6 SA RCTs showed no significant IPT benefit
- Much fewer TB clinical events with ART use
- Much lower TB incidence in those studies with MTB culture at screen
- Thibela, 7% more TB found in IPT arm at screening than standard of care screening in control arm
- Rangaka study 250 TB cases diagnosed at baseline (39 post randomisation) far exceeded the 21 cases (58 versus 37) “prevented by IPT”
Incidences of Confirmed TB in Cochrane Review 2011

### 1.2.1 PPD+

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Treatment Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight %</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mwinga 1998</td>
<td>2</td>
<td>101</td>
<td>4</td>
<td>60</td>
<td>9.3%</td>
<td>0.30 [0.06, 1.57]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>101</strong></td>
<td></td>
<td><strong>60</strong></td>
<td></td>
<td><strong>9.3%</strong></td>
<td><strong>0.30 [0.06, 1.57]</strong></td>
</tr>
<tr>
<td>Total events</td>
<td>2</td>
<td></td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 1.43 (P = 0.15)

### 1.2.2 PPD-

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Treatment Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight %</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gordin 1997</td>
<td>3</td>
<td>260</td>
<td>6</td>
<td>257</td>
<td>11.2%</td>
<td>0.49 [0.12, 1.95]</td>
</tr>
<tr>
<td>Mwinga 1998</td>
<td>12</td>
<td>351</td>
<td>5</td>
<td>166</td>
<td>12.6%</td>
<td>1.14 [0.41, 3.17]</td>
</tr>
<tr>
<td>Rivero 2003</td>
<td>7</td>
<td>242</td>
<td>4</td>
<td>77</td>
<td>11.3%</td>
<td>0.56 [0.17, 1.85]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>853</strong></td>
<td></td>
<td><strong>500</strong></td>
<td></td>
<td><strong>35.0%</strong></td>
<td><strong>0.74 [0.38, 1.45]</strong></td>
</tr>
<tr>
<td>Total events</td>
<td>22</td>
<td></td>
<td>15</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 1.21, df = 2 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.86 (P = 0.39)

### 1.2.3 PPD unknown

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Treatment Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight %</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hawken 1997</td>
<td>19</td>
<td>342</td>
<td>22</td>
<td>342</td>
<td>40.8%</td>
<td>0.86 [0.48, 1.57]</td>
</tr>
<tr>
<td>Mwinga 1998</td>
<td>7</td>
<td>251</td>
<td>6</td>
<td>124</td>
<td>14.9%</td>
<td>0.58 [0.20, 1.68]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>593</strong></td>
<td></td>
<td><strong>466</strong></td>
<td></td>
<td><strong>55.7%</strong></td>
<td><strong>0.79 [0.47, 1.32]</strong></td>
</tr>
<tr>
<td>Total events</td>
<td>26</td>
<td></td>
<td>28</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.42, df = 1 (P = 0.52); I² = 0%
Test for overall effect: Z = 0.91 (P = 0.36)

### Total (95% CI)

| Treatment Events | Control Events | Total Events | Heterogeneity: Chi² = 2.83, df = 5 (P = 0.73); I² = 0%
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1547</strong></td>
<td><strong>1026</strong></td>
<td><strong>50</strong></td>
<td>Test for overall effect: Z = 1.58 (P = 0.11)</td>
</tr>
</tbody>
</table>

Favours treatment vs. control
Cumulative rates of tuberculosis among HIV-infected participants commencing masked medication after 180 days of open-label isoniazid, Botswana 2004-2009

Samandari et al. Lancet 2011
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Antiretroviral Therapy for Control of the HIV-associated Tuberculosis Epidemic in Resource-Limited Settings

Stephen D. Lawn, MD<sup>a,b,*</sup>, Katharina Kranzer, MD<sup>a,b</sup>, Robin Wood, FCP MMed<sup>a</sup>

Fig. 3. TB incidence rates during ART. The graph shows data from studies included in (see Table 2) in which changing TB incidence rates were calculated according to increasing duration of ART. The two lowest curves present data from studies conducted in high-income countries.15,18 The remaining four studies are from South Africa (diamonds13 and inverted triangles14), a range of resource-limited countries (circles15), and Uganda (squares16).

Fig. 4. Decreasing TB incidence rates (cases/100 person-years, white squares) and rising median CD4 cell counts (cells/mL, black diamonds) during the first 3 years of ART. These data are from a community-based ART cohort in a township in Cape Town, South Africa. (Data from Refs.13,19,56).
Tuberculosis during the first year of antiretroviral therapy in a South African cohort using an intensive pretreatment screening strategy

Stephen D. Lawn\textsuperscript{a},\textsuperscript{b}, Katharina Kranzer\textsuperscript{a},\textsuperscript{b}, David J. Edwards\textsuperscript{a}, Matthew McNally\textsuperscript{c}, Linda-Gail Bekker\textsuperscript{a} and Robin Wood\textsuperscript{a}

\textbf{Conclusion:} Systematic culture-based screening detected a very high burden of prevalent TB present at baseline. This intensified screening strategy was associated with an approximately two-fold lower incidence rate in the first 4 months of ART than previously observed in this cohort. This suggests that many incident cases of symptomatic TB presenting during early ART can be detected as prevalent disease prior to ART initiation using sensitive diagnostic tests.
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Opportunities and Challenges for HIV Care in Overlapping HIV and TB Epidemics

Diane V. Havlir, MD; Haileyesus Getahun, MD, PhD, MPH; Ian Sanne, MBBCH, FCP(SA); Paul Nunn, MD, FRCP

Impact of ART on TB Case Fatality Stratified by CD4 Count for HIV-Positive TB Patients in Cape Town, South Africa (2009–2011)

Richard Kaplan, MD,* Judy Caldwell, RN, RM, BCur,† Keren Middelkoop, MBChB, PhD,*† Linda-Gail Bekker, MBChB, FCP, PhD,*† and Robin Wood, MMed, FCP, DSc*†

CD4 count distribution by ART uptake for HIV+ve patients with baseline CD4 counts over the 3 year period (n=37,162)
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Significance:
Using mathematical modeling, fitted to trial data, we show IPT does not cure Mycobacterium tuberculosis infection in the majority of HIV-infected individuals. These results contrast with long-held beliefs about the working mechanism of IPT, but explain the empirical results. These results are important for determining appropriate clinical guidelines for IPT use in varying epidemiological settings.
A return to the Pre-antibiotic era?
Isoniazid preventive therapy and risk for resistant tuberculosis (13 studies HIV+ & HIV-)

How will INH resistance develop if 6.5 million HIV+ individuals in South Africa receive IPT in the public sector?

These are relative risks
NB. SA RCTs reported 12%, 23% & 24% INH resistance

A Deeper Look at Drug Resistance

Although some things may seem obvious at first glance, looking in more depth may paint a different picture. In some complex situations, asking questions in different ways may lead to very different answers. One example is the use of isoniazid preventive therapy (IPT) for tuberculosis (TB) in HIV-prevalent communities. Because HIV-infected individuals are much more likely to develop TB than immunocompetent people, the World Health Organization has recommended the use of IPT in HIV-infected individuals that are symptom-free for TB co-infection. The use of IPT has raised the specter of drug resistance; however, to date, studies have not observed an increase in drug-resistant TB in individuals on IPT. Now, Mills et al. use mathematical modeling to show that even if IPT does not increase drug resistance in infected individuals, community-wide IPT can drive increases in drug resistance at the population level.

They found that community-wide IPT increases selective suppression of drug-sensitive infection, thus indirectly conferring an advantage to drug-resistant strains. These data should be considered when determining policy for preventive therapy.
**Conclusions:** INH preventive therapy—will it contribute to TB control in RSA?

- Total lack of any effect in a large community study
- Modest impact in 1 of adult studies
- Active intensive screening pre-IPT more productive!
- Rebound TB on stopping IPT (even after 36 months)
  - lack of cure
  - removal of protection
- Risk of resistance, especially when screening relaxes
- Spending resources on IPT with little or no benefit will divert us from meeting the ART gap
- And thinking about transmission interruption......
TB notification rates Cape Town, England & Wales and New York 1910-2012

The current (2009-2012) HIV-negative rate in Cape Town was 445 per 100,000 population, the HIV-positive rate was 6338 per 100,000 population.
Transforming the Fight Against Tuberculosis: Targeting Catalysts of Transmission

David W. Dowdy, Andrew S. Azman, Emily A. Kendall, and Barun Mathema

Step 1: Contact
A person with active TB and a susceptible person come into sufficiently close contact for airborne transmission of *M. tuberculosis* to occur.

Step 2: Generation of Infectious Particles
The person with active TB aerosolizes particles of appropriate quality (size, etc.) containing bacilli of sufficient number and virulence to transmit infection.

Step 3: Infection and Disease Progression
The susceptible host has an immune background that facilitates initial infection, non-sterilization of the corresponding granuloma, and eventual progression to infectious disease.

*Catalyst:* Increased contact rates
*Catalyst:* Increased infectiousness
*Catalyst:* Increased susceptibility

Figure 1. The cascade of tuberculosis (TB) transmission and disease.
Insanity is doing the same thing over and over again and expecting different results

Albert Einstein 1879-1955