Is IPT a priority?

Prof Harry Hausler
TB/HIV Care Association
Isoniazid preventive therapy (IPT) is a priority because:

- IPT works
- IPT is safe
- IPT does not increase risk of resistance
- IPT is feasible and cost effective
- IPT will help eliminate TB
- IPT is policy
WHO 2010 policy on collaborative TB/HIV activities

A. Establish and strengthen mechanisms for delivering integrated TB and HIV services
   ♦ Set up and strengthen coordinating body for collaborative TB/HIV activities at all levels
   ♦ Determine HIV prevalence among TB patients and TB prevalence among PLHIV
   ♦ Carry out joint TB/HIV planning to integrate the delivery of TB and HIV services
   ♦ Monitor and evaluate collaborative TB/HIV activities

B. Decrease burden of TB among PLHIV and initiate early ART (the Three I’s for HIV/TB)
   ♦ Intensify TB case finding and ensure high quality anti-TB treatment
   ♦ Initiate TB prevention with isoniazid preventive therapy and early antiretroviral treatment
   ♦ Ensure control of TB infection in health care facilities and congregate settings

C. Decrease burden of HIV among TB patients
   ♦ Provide HIV testing and counselling to patients with presumptive and diagnosed TB
   ♦ Provide HIV prevention interventions for patients with presumptive and diagnosed TB
   ♦ Introduce co-trimoxazole preventive therapy for TB patients living with HIV
   ♦ Ensure HIV prevention interventions, treatment and care for TB patients living with HIV
   ♦ Provide ART for TB patients living with HIV
IPT as part of a package

- IPT should be implemented as part of a package of combination TB prevention including:
  - TB infection control in health care and other congregate settings
  - Intensified case finding and effective treatment of TB (in PLHIV AND HIV negative people)
  - Initiation of antiretroviral treatment (ART)
Principles of Medical Ethics

• **Beneficence**: the health care professional should act in a way that benefits the patient

• **Non maleficence**: the healthcare professional should not harm the patient

• **Respect for autonomy**: enabling individuals to make reasoned informed choices

• **Justice**: distributing benefits, risks and costs fairly
Ethical Issue 1: Use what works
(Beneficence: evidence-based practice)

• IPT decreases TB incidence in PLHIV by 33% to 64%
• Long term IPT provides prolonged benefit
• IPT provides additional benefit to ART
Effect of IPT on TB in PLHIV: Meta-analysis of 7 randomised clinical trials (N=4136)

Relative risk, 95% CI

- Placebo Overall: 0.36
- TST+: 0.67
- TST-: 0.86

Akolo, Cochrane Collaboration 2010
6 vs 36 months IPT in Botswana: a randomised, double-blind, placebo-controlled trial

TST+ HR 0.08 (0.01–0.61)
TST- HR 0.86 (0.38–1.89)
Severe AEs >6 months
1% placebo, 1.3% INH

Samandari, Lancet 2011
IPT randomized trial and ART for PLWH
~6 year observation

3 year randomized controlled trial
Follow-up observation average 2.7 years/pt

6 months IPT (6H)
36 months IPT (36H)
Antiretroviral therapy
Increasing ART initiation

Number observed
1995
1678

Not dead, not lost to follow-up, not withdrawn or no TB

Agizew, BOTUSA, SA consultation on IPT guidelines 2012
Cumulative TB incidence in the in-trial & post-trial period by study arm for all participants

In trial n=1995

Cumulative TB incidence

P=0.04

Post-trial (no IPT) n=1678

Cumulative TB incidence

P=0.52

Agizew, BOTUSA, SA consultation on IPT guidelines 2012
Effectiveness of life-long IPT in TST+ HIV+ patients
Intent-to-treat vs “as-treated”

Martinson et al., NEJM 2011;365:11-20
## Reduction in TB incidence with 36 vs 6 months IPT

<table>
<thead>
<tr>
<th>Author</th>
<th>Location</th>
<th>Intention to treat</th>
<th>Starting masked tx</th>
<th>Per Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Martinson</strong></td>
<td>Soweto</td>
<td>26% (p=0.48)</td>
<td></td>
<td><strong>58% lower TB or death (p=0.02)</strong></td>
</tr>
<tr>
<td><strong>Samandari</strong></td>
<td>Botswana</td>
<td>43% (p=0.47)</td>
<td>53% (p&lt;0.05)</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TST+</td>
<td></td>
<td>74% (p=0.02)</td>
<td>92% (p&lt;0.05)</td>
<td><strong>100% (p=0.023) (n=173)</strong></td>
</tr>
<tr>
<td>TST-</td>
<td></td>
<td>25% (p=0.4)</td>
<td>14% (NS)</td>
<td></td>
</tr>
</tbody>
</table>

(Martinson, NEJM 2011)  
(Samandari, Lancet 2011)
Thibela TB: durability of IPT effect at individual level

<table>
<thead>
<tr>
<th>Interval</th>
<th>Arm</th>
<th>Adjusted IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9mth</td>
<td>IPT</td>
<td>0.37 (0.19-0.72)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>1</td>
</tr>
<tr>
<td>9-18mths</td>
<td>IPT</td>
<td>0.94 (0.57-1.54)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>1</td>
</tr>
<tr>
<td>&gt;18mths</td>
<td>IPT</td>
<td>0.79 (0.54-1.17)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>1</td>
</tr>
</tbody>
</table>
ART reduces TB incidence, but still high

Meta-analysis: ART any CD4 HR 0.35 (0.28-0.44)
ART CD4>350 HR 0.43 (0.3-0.63)
Suthar Plos Med 2012
# IPT & ART: Retrospective cohorts

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Brazil TB/100 PY (95% CI)</th>
<th>South Africa TB/100 PY (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ART or IPT</td>
<td>4.01 (3.4-4.69)</td>
<td>7.1 (6.2–8.2)</td>
</tr>
<tr>
<td>ART</td>
<td>1.90 (1.66–2.17)</td>
<td>4.6 (3.4–6.2)</td>
</tr>
<tr>
<td>IPT</td>
<td>1.27 (0.41–2.95)</td>
<td>5.2 (3.4–7.8)</td>
</tr>
<tr>
<td>IPT + ART</td>
<td>0.80 (0.38–1.47) RR=0.42 (0.2-0.8)</td>
<td>1.1 (0.02–7.6) RR=0.2 (0.01-1.14)</td>
</tr>
</tbody>
</table>

Golub AIDS 2007;21:1441
Golub AIDS 2009;23:631
IPT ART Study design

- Pragmatic randomized double-blind placebo-controlled trial
- INH/matching placebo, self-administered for 12 months in patients on ART
- Primary Endpoint: TB
- Secondary Endpoints: Grade 3/4 drug adverse events; death
- TAC provided treatment literacy & trial advocacy

Rangaka, Lancet 2014
Time to TB

Hazard ratio 0.63 (95% CI 0.41-0.94)

Rangaka, Lancet 2014
Effect modification by TST status at baseline

Cumulative TB incidence rate

TST pos/Placebo: 2.8/100PY
TST pos/INH: 2.6/100PY
HRu=0.92 (0.43-1.97)
Logrank P=0.83

TST neg/Placebo: 4.1/100PY
TST neg/INH: 1.7/100PY
HRu=0.41 (0.20-0.83)*
Logrank P=0.06

Rangaka, Lancet 2014
IPT ART risk:benefit

Number needed to treat to prevent 1 case TB = 25
(cost of 12H = R165)

Number needed to harm (stop study drug due to toxicity) = 100

Rangaka, Lancet 2014
IPT for secondary prevention for PLHIV

**Incidence Rate Ratios & 95% CI**

Reference

- Haller (1999): 0.3
- Fitzgerald (2000): 0.18
- Churchyard (2003): 0.45

1.0
Prophylactic effect of INH on primary TB in children

RCT: INH vs. Placebo (4-6mg/kg/day)

**2 Groups:**
- <3y of age – TST 5TU ≥5mm
- >3y of age - TST 5TU ≥5mm + CXR evidence Primary TB

<table>
<thead>
<tr>
<th></th>
<th>INH</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extra-pulmonary complications</td>
<td>5 (0.33%)</td>
<td>26 (1.91%)</td>
</tr>
</tbody>
</table>

80% cases prevented
P = 0.0002 Fishers Exact 2-tail test

INH reasonably effective for post-exposure prophylaxis

US Public Service TB prophylaxis trial – Am Rev TB 1957; 76: 942-63
IPT for HIV+ infants & children without active TB?

**Yes** – Zar et al BMJ 2007; 334: 36-43
5/131 vs 13/132 cases

**No** – Madhi et al N Engl J Med 2011; 365: 21 - 31

- TB cases per 100 HIV+ children per year
- Survival
- TB Disease-free Survival Percentage

*Fig 2 Survival in children on isoniazid (INH) or placebo*
Ethical Issue 2: Do no harm (Non-maleficence)

- TB – stigmatising life threatening disease that requires at least 6 months of treatment with drugs that can be toxic (liver, hearing, vision) – worth preventing!
- IPT has limited toxicity
- IPT does not increase isoniazid (INH) resistance
  - TB symptom screening is effective in detecting TB – negative predictive value is 98% (WHO meta-analysis)
  - If TB is latent, few organisms, thus low risk of selection of DR-TB
  - Most resistance arises from suboptimal treatment of active disease so preventing active disease will reduce resistance
IPT: hepatotoxicity rare

**Uganda RCT**
- 7/931 AST>135u/L (N 7-27 u/L); total 3 stopped with any adverse event Whalen NEJM 1997;337:801

**South Africa, routine, pre-ART**
- 1/777 stopped INH with asymptomatic raised AST Grant JAMA 2005;293:2719-2725

**South Africa, ART cohort**
- IPT not associated with higher risk of hepatotoxicity Hoffmann AIDS 2007;21:1301-8
Thibela TB - IPT is safe

- 24221 participants started IPT
  - 95% male, median age 40 years
- 130 individuals experienced 132 possible study defined AEs (0.54%)
  - Suspected hypersensitivity rash 61
  - Peripheral neuropathy 50
  - Convulsions 4
  - Hepatotoxicity 17
    - INH related 2
- One AE resulted in death: overall risk of death of 4 per 100,000 (0.004%)
Evidence suggests that IPT does not promote isoniazid resistance

Balcells Emerg Infect Dis 2006;12:744-51
Thibela TB - IPT does not generate resistance

Any INH resistance: Mean (95% CI)
IPT does not increase resistance

• If TB is latent, few organisms, dividing slowly, thus low risk of selection of DR-TB

• Risk of increased resistance, if any, is small:
  – Summary RR = 1.45 (95% CI 0.85, 2.47)

• Most resistance arises from suboptimal treatment of active disease, so preventing active disease will reduce resistance

• Early studies of isoniazid monotherapy showed 70% cure
  MRC Br Med J 1952;2(4787):735-46

• First line TB treatment is effective for INH-resistant TB

• There is still a need for surveillance of resistance
Ethical Issue 3: What would I want?
(Autonomy: allowing choice)

• Imperative to inform patients of benefits/risks of IPT and allow them to choose
• If I were living with HIV in South Africa I would not want to get sick with TB so I would want:
  – Good infection control in health facilities and communities to protect me
  – Regular TB screening to access treatment if I was sick with TB
  – IPT to treat my latent TB infection and prevent reinfection if I was asymptomatic
  – The option of 3 years IPT or longer
  – Early ART
Ethical Issue 4: Access (Justice)

- IPT is cost effective and easy to implement so it should be made available in all PHC facilities.
- TST difficult to perform and interpret and has been a barrier to IPT implementation.
- IPT is currently not provided in many facilities and this is unjust.
Systems Issues

• IPT is feasible
  – 270,500 started on IPT in South Africa in one year (April 2013 – March 2014)

• IPT is cost effective
  – Cost to prevent TB case in mines ($353) less than treating a TB case ($1,736) Kumaranayake, IAS 2004
  – Cost to prevent TB case in PHC clinics ($486-$962) less then the cost of treating TB ($823-$1362) Hausler, Bulletin WHO 2006;84(7):528-36
Requiring tuberculin skin tests before initiating IPT leads to avoidable and substantial number of TB cases

TST unknowns (who were never tested), IPT achieved a 50% reduction in TB incidence, going from an incidence rate of 2.5/100PY (95% CI 2.3 to 2.7) for those not on IPT down to 1.2/100PY (95% CI 0.7 to 20)

Golub JE et al. 18th Int AIDS conference, abstract MOAB0305, Vienna, 2010
Prevalence of TST-positivity among healthy HIV-positive Africans

- **27% of patients in Botswana**

- **52% in Cape Town**
  - 25% CD4<200, 57% CD4≥200

- **55% among South Africa gold miners**
TST reading by patients?

• Methods
  – Patients were trained to read their TST result
  – Given clinic card with 5 mm hole punch
  – Asked to return in 48-72 hours for nurse to read

• Results
  – 201/227 (93%) returned to clinic for TST reading
  – Sensitivity 79% (73-85%)
  – Specificity 72% (58-87%)
  – Positive predictive value 42% (30-54%)
  – Negative predictive value 93% (89-97%)

Cox, SA HIV Clinicians Society Conference, 2014
## THRio Study: TB screening and IPT in HIV clinics

Stepped wedge, cluster randomised trial in 29 clinics

Staff trained on TB screening, TST, IPT

12 836 patients

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cases</th>
<th>Crude HR (95% CI)</th>
<th>p-value</th>
<th>Adjusted HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intent To Treat</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB</td>
<td>475</td>
<td>0.87 (0.69-1.10)</td>
<td>0.24</td>
<td>0.73 (0.54-0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>TB or Death</td>
<td>1313</td>
<td>0.76 (0.66-0.87)</td>
<td>&lt;0.001</td>
<td>0.69 (0.57-0.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Per-protocol (Stayers)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB</td>
<td>399</td>
<td>0.43 (0.31-0.58)</td>
<td>&lt;0.001</td>
<td>0.42 (0.31-0.58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TB or Death</td>
<td>1055</td>
<td>0.50 (0.41-0.60)</td>
<td>&lt;0.001</td>
<td>0.50 (0.41-0.60)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Stayers – per-protocol - Among those remaining in clinic contact

Operational training on TBS, TST, IPT reduced incident TB and deaths

Durovni et al., Lancet Infect Dis. 2013;10:852-8
IPT in PEPFAR assisted sites: 2010-2011

SA 2013/4: 270 500 patients

Bristow, IJTLD 2012
## IPT implementation in SA
### April 2013-March 2014

<table>
<thead>
<tr>
<th>Province</th>
<th>Target</th>
<th>Achieved</th>
<th>% target achieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eastern Cape</td>
<td>79 151</td>
<td>43 533</td>
<td>55%</td>
</tr>
<tr>
<td>Free State</td>
<td>39 732</td>
<td>6 935</td>
<td>17%</td>
</tr>
<tr>
<td>Gauteng</td>
<td>208 430</td>
<td>75 035</td>
<td>36%</td>
</tr>
<tr>
<td>KwaZulu-Natal</td>
<td>169 293</td>
<td>69 410</td>
<td>41%</td>
</tr>
<tr>
<td>Limpopo</td>
<td>50 384</td>
<td>18 138</td>
<td>36%</td>
</tr>
<tr>
<td>Mpumalanga</td>
<td>72 360</td>
<td>28 220</td>
<td>39%</td>
</tr>
<tr>
<td>Northern Cape</td>
<td>9 780</td>
<td>4 694</td>
<td>48%</td>
</tr>
<tr>
<td>North West</td>
<td>46 362</td>
<td>18 545</td>
<td>40%</td>
</tr>
<tr>
<td>Western Cape</td>
<td>28 521</td>
<td>5 989</td>
<td>21%</td>
</tr>
<tr>
<td>South Africa</td>
<td>693 000</td>
<td>270 500</td>
<td>39%</td>
</tr>
</tbody>
</table>

2.5 million people on ART in SA should be screened for TB and IPT!

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South African Department of Health, 2014
Adherence interventions to consider

• Simplify the treatment to be taken – 300 mg tablet
• Link to adherence clubs
• Education and counseling is beneficial
• Monitor adherence on treatment – pill counts
• Notice if people miss visits
• Consider the use of reminders, food supplementation
• Watch for high-risk groups

Orrell, SA HIV Clinicians Society Conference, 2014
International Advocacy for IPT

- WHO 3 I’s meeting, April 2008
- Global Leaders Forum, 9 June 2008
- WHO HIV/AIDS Department Priority Interventions, IAS Mexico, August 2008
- Stop TB Partnership, March 2009

Stop TB Partnership Consensus Statement: “IPT works, IPT is safe, IPT works with ART or by itself. Ensure that all people living with HIV in countries where TB is common are offered IPT”
The burden of TB incidence:

- Global: 125/100k
- Target: 10/100k

Year:
- 2000
- 2010
- 2020
- 2030
- 2040
- 2050
- 2060
- 2070
- 2080
- 2090
- 2100
- 2110
- 2120
- 2130
- 2140
- 2150
- 2160
- 2170
- 2180
- 2190
Modeled approaches to reaching TB elimination

If IPT could be scaled up to 75% in 2035:
TB incidence would fall from 10 000 to 1 400 per million
TB deaths would fall from 2 180 to 200 per million

Dye, Ann Rev Publ Health 2013
National Strategic Plan (NSP) for HIV and TB 2012-2016

- Zero new infections from HIV and TB
- Zero preventable deaths associated with HIV and AIDS and TB
- Zero transmission of HIV from mother to child
- Zero discrimination towards people living with HIV or TB
NSP: 2012-2016

• Strategic Objective 2
  – Prevent new TB Infections:
    • Biomedical Interventions: IPT

• The implementation, monitoring and evaluation of IPT scaled-up
  – Adults and children living with HIV
  – Asymptomatic child contacts
  – Mine workers

• Preferably with positive TST
## NEW IPT Guidelines

<table>
<thead>
<tr>
<th></th>
<th>Pre-ART (CD4 &gt; 350)</th>
<th>On ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST not available</td>
<td>6 months</td>
<td>12 months</td>
</tr>
<tr>
<td>TST negative</td>
<td>No IPT</td>
<td>12 months</td>
</tr>
<tr>
<td>TST positive</td>
<td>36 months</td>
<td>36 months</td>
</tr>
</tbody>
</table>

NB: Provision is made for TST not available but recommend that it should be done within one month of initiating IPT. Do not delay IPT while waiting for TST.

SA Antiretroviral Treatment Guidelines, Department of Health 2013
Practical algorithm

• Pre-ART and ART
  – Screen for TB
    • Symptoms – investigate for TB (GXP)
    • No symptoms – start IPT

• Pre-ART
  – Do TST
    • Negative - stop IPT
    • Positive – continue for 36 months
    • Not done – continue for 6 months

• ART
  – Do TST
    • Negative or not done – continue IPT for 12 months
    • Positive – continue IPT for 36 months
IPT in child contacts

• Children who meet the following criteria, once active TB is excluded:
  ➢ All HIV-infected children who are close contacts of a person with confirmed infectious TB regardless of age
  ➢ All children < 5 who are close contacts of a person with confirmed infectious TB regardless of HIV status
How well is post-exposure prophylaxis given to TB-exposed children in public programs?

- Poor
  - 46 029 TB cases registered in W Cape in 2012
    - 2680 child contacts <5 years received IPT
    - Only 45% completed 6 months IPT in 2012 but completion increased to 79% in Q1 2013
  - Du Preez et al – Ann Trop Paediatr 2011; 31: 301-10
    - Missed opportunities for IPT in 71% of 221 children with culture+ TB in Cape Town
Provision of IPT

• For first 6 months, provide as a one-month supply
  – For long term IPT provide as 3 month supply
• In adults, TB preventive therapy is offered as a once off for now
• In children, TB preventive therapy is repeated if there is another direct contact with active infectious TB patient
IPT Monitoring

- On-going counselling and patient education
- Adherence monitoring (i.e. pill count)
- Early identification and management of adverse events
- TB symptom screening for early detection of active TB
- Social support and care
- As much as possible ensure visits coincide with other chronic visits to avoid multiple visits
- Record on HIV clinical stationery and TIER
TIER

- **Tier.Net**

  - Systems prompt for IPT information
  - IPT outcomes available
  - ‘Visits” are captured
  - Tool available in the facility
  - Monthly initiation report
IPT is a priority!

• IPT works
• IPT is safe
• IPT does not increase risk of resistance
• IPT is feasible and cost effective
• IPT will help eliminate TB
• IPT is policy
Call to action – join the I can campaign
I can implement IPT!

• IPT for PLHIV and child contacts is an important element of a combination TB prevention package
• Failure to offer IPT is unethical and will compromise TB control efforts
• Partnerships needed between DOH and civil society to:
  – Inform and mobilise patients
  – Create patient-centred systems to initiate IPT, do and read TST, provide adherence support
  – Use TIER.net to monitor
Acknowledgements

• Richard Chaisson, David Dowdy – Johns Hopkins
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