PREVENTING TB IN PEOPLE WITH HIV: NO MORE EXCUSES

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Estimated prevalence of latent tuberculosis infection by country
(estimated global prevalence 23%)

Global TB Report WHO 2017

FIG. 5.3
Gaps in TB preventive treatment for people who were newly enrolled in HIV care in 2016, selected countries

- Started on preventive treatment
- Detected and notified with active TB disease
- Gap in TB detection and TB prevention

The selected countries are high TB or TB/HIV burden countries that reported on all three of the following: the number of people newly enrolled in HIV care; the number of TB cases detected among people newly enrolled on HIV care; and the number of people newly enrolled on HIV care who were started on TB preventive treatment. In high TB burden countries, testing for LTBI is not a requirement for initiation of TB preventive treatment, such that all those without active TB disease are eligible for TB preventive treatment.

The gap represents people living with HIV who should have undergone complete evaluation for TB disease or TB preventive treatment.
Poor Global Uptake of IPT for PLHIV

Provision of TB preventive treatment to people living with HIV, 2005–2015

Modeled approaches to reaching TB elimination

IPT is a necessary component if we are to eliminate TB

Dye, et al., Ann Rev Publ Health 2013
Cascade of Care for Latent LTBI Treatment

Intended for screening 100%
Initially tested 71.9% (71.8-72.0)
Received a test result 66.7% (65.6-66.9)
Referred if test positive 56.0% (55.2-56.8)
Completed medical evaluation 43.7% (42.5-44.9)
Recommended for treatment 35.0% (33.8-36.4)
Accepted and started treatment 30.7% (26.8-32.1)
Completed treatment 18.8% (16.3-19.7)

31% start PT
18.8% complete PT

Alsdurf et al., Lancet ID 2016
IPT in PLHIV: NO MORE EXCUSES

Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings

WHO 2011
IPT in PLHIV: NO MORE EXCUSES

1. Adults and adolescents living with HIV should be screened for TB with a clinical algorithm and those who do not report any one of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered IPT.

*Strong recommendation, moderate quality of evidence¹*

WHO 2011

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*Image of a stop sign with 'STOP TB' written on it.*
### IPT in PLHIV: NO MORE EXCUSES

<table>
<thead>
<tr>
<th></th>
<th>5% TB Prevalence</th>
<th></th>
<th>10% TB Prevalence</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NPV</td>
<td>(95% CI)</td>
<td>NNS</td>
<td>NPV</td>
</tr>
<tr>
<td>All study participants</td>
<td>97.7</td>
<td>(97.4-98.0)</td>
<td>12</td>
<td>95.3</td>
</tr>
<tr>
<td>Clinical setting</td>
<td>98.3</td>
<td>(97.5-98.8)</td>
<td>15</td>
<td>96.4</td>
</tr>
<tr>
<td>Community setting</td>
<td>97.3</td>
<td>(96.9-97.7)</td>
<td>11</td>
<td>94.5</td>
</tr>
<tr>
<td>SE Asia</td>
<td>98</td>
<td>(95.9-99.0)</td>
<td>16</td>
<td>95.9</td>
</tr>
<tr>
<td>s-S Africa</td>
<td>97.4</td>
<td>(97.1-97.8)</td>
<td>10</td>
<td>94.8</td>
</tr>
<tr>
<td>CD4+ count ≥200</td>
<td>96.9</td>
<td>(95.1-98.0)</td>
<td>16</td>
<td>93.6</td>
</tr>
<tr>
<td>CD4+ count &lt;200</td>
<td>98.9</td>
<td>(97.5-95.5)</td>
<td>16</td>
<td>97.8</td>
</tr>
</tbody>
</table>

NPV and NNS using rule ‘CFSW’ in a hypothetical population of PLHIV

IPT in PLHIV: NO MORE EXCUSES

TB screening algorithm

Person living with HIV

Screen for TB with any one of the following:
- Current cough
- Fever
- Night sweats
- Weight loss

None present  At least 1 present

TB excluded; potentially eligible for IPT

Investigate for TB and other diseases

Give appropriate treatment; potentially eligible for IPT
Follow up; potentially eligible for IPT
Treat for TB

Screen regularly for TB
IPT in PLHIV: NO MORE EXCUSES

3

Adults and adolescents living with HIV who have an unknown or positive TST status and are unlikely to have active TB should receive at least six months of IPT as part of a comprehensive package of HIV care. IPT should be given to such individuals irrespective of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB and pregnant women.

*Strong recommendation, high quality of evidence*
Effect of IPT on TB in PLHIV:

Meta-analysis of 7 randomised clinical trials (n=4136)
IPT in PLHIV: NO MORE EXCUSES

4

Adults and adolescents living with HIV who have an unknown or positive TST status and who are unlikely to have active TB should receive at least 36 months of IPT. IPT should be given to such individuals irrespective of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB and pregnant women.

*Conditional recommendation, moderate quality of evidence*
IPT randomised trial and ART for PLHIV
~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

Samandari T et al. Lancet 2011
6 vs 36 months IPT in Botswana: a randomised, double-blind, placebo-controlled trial

TST+ HR: 0.26 (0.09–0.80)
TST- HR: 0.75 (0.38–1.46)

Severe AEs >6 months
1% placebo, 1.3% INH

IPT benefit lost 6 months after completing IPT

Samandari T et al. Lancet 2011
6 vs 36 months IPT in Botswana: a randomised, double-blind, placebo-controlled trial

Samandari T et al. Lancet 2011
Cumulative TB incidence in the in-trial & post-trial period by study arm for all participants

In trial n=1995

Post-trial (no IPT) n=1678

Samandari T et al., Lancet 2011
Figure 1: Study design of the Temprano trial and post-trial phase
ART=antiretroviral therapy. IPT=isoniazid preventive therapy.

TEMPRANO

Eligibility criteria
- CD4 count < 800 cells per μL
- No WHO criteria for starting ART
- Informed consent

Randomisation

Immediate ART
- IPT, 6 months
- Deferred ART

Immediate ART
- IPT, 6 months

Temprano trial primary outcome
Severe morbidity at 30 months

Deferred ART

Post-trial phase primary outcome
Death as of Jan 5, 2015

No IPT

IPT

Temprano trial
Each participant was followed up for 30 months

Post-trial phase
Each participant was followed up until the last Temprano participant reached 30 months of follow-up

NEJM 2015; Lancet GH 2017
TEMPRANO
IPT reduced risk of death by 37% independent of ART

Badje et al, Lancet GH 2017
IPT in PLHIV: NO MORE EXCUSES

TST is not a requirement for initiating IPT in people living with HIV.

*Strong recommendation, moderate quality of evidence*
IPT plus ART to prevent TB in South Africa

A double-blind, placebo controlled RCT

Stratified by antiretroviral therapy status at baseline (i.e. ART at initiation versus maintenance of ART)

PLHIV without active TB (n = 1329)

1:1

IPT (n = 680)

IPT placebo (n = 689)

Primary endpoint: time to TB (definite, probably, possible)

Rangaka M et al. Lancet 2014
IPT plus ART to prevent TB in South Africa

Time to TB

Hazard ratio 0.63 (95% CI 0.41-0.94)

Rangaka M et al. Lancet 2014
Effect modification by TST status at baseline

**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 M et al. Lancet 2014
IPT ART risk:benefit

Number needed to treat to prevent 1 case TB = 25
Number needed to harm (stop study drug due to toxicity) = 100

Rangaka M et al. Lancet 2014
Providing IPT to people living with HIV does not increase the risk of developing isoniazid (INH)-resistant TB. Therefore, concerns regarding the development of INH resistance should not be a barrier to providing IPT.

*Strong recommendation, moderate quality of evidence*
Evidence suggests that IPT does not promote isoniazid resistance

Summary RR = 1.45 (95% CI 0.85, 2.47)

IPT does not increase TB resistance

• Most resistance arises from suboptimal treatment of active disease; preventing active disease should reduce resistance

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

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

• There is still a need for surveillance of resistance
IPT: hepatotoxicity is rare

South Africa, cohort, routine, pre-ART

- 1/777 stopped INH with asymptomatic raised AST Grant JAMA 2005;293:2719-2725

South Africa, placebo RCT, all on ART

- IHN discontinued for Grade 3-4 ALT rise in 19/662 (2.9%) INH recipients
- INH discontinued for Grade 3-4 ALT rise in 10/667 (1.5%) receiving INH placebo Rangaka M et al Lancet 2014
  - Risk ratio 1.9, 95% CI 0.9-4.09
IPT 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 than the cost of treating TB ($823-$1362) Hausler, Bulletin WHO 2006;84(7):528-36
Isoniazid preventive therapy (IPT) in PLHIV is a priority

- IPT works
- IPT is safe
- IPT does not increase risk of TB resistance
- IPT is feasible and cost effective
- IPT will help eliminate TB
- IPT is policy
Acknowledgments

Richard Chaisson
Anton Pozniak
TB Control and Elimination

FIND TB
Undiagnosed TB is common
3-4 million missed cases per year

TREAT TB
Early treatment saves lives
Treatment reduces transmission

Prevent TB
Isoniazid preventive therapy (IPT) works
IPT can reduce TB rates in patients on ART
## IPT in PLHIV: NO MORE EXCUSES

### Diagnostic performance of 23 candidate 1-of-n rules

<table>
<thead>
<tr>
<th>Rule</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>LRN (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFSW</td>
<td>78.9 (58.3–90.9)</td>
<td>49.6 (29.2–70.1)</td>
<td>0.426 (0.349–0.520)</td>
</tr>
<tr>
<td>HFSW</td>
<td>75.7 (53.9–89.2)</td>
<td>52.7 (31.8–72.7)</td>
<td>0.461 (0.391–0.544)</td>
</tr>
<tr>
<td>CFW</td>
<td>74.0 (51.7–88.3)</td>
<td>53.8 (32.8–73.6)</td>
<td>0.483 (0.416–0.561)</td>
</tr>
<tr>
<td>CSW</td>
<td>73.4 (51.0–88.0)</td>
<td>53.8 (32.8–73.5)</td>
<td>0.494 (0.428–0.570)</td>
</tr>
<tr>
<td>CFS</td>
<td>73.1 (50.6–87.9)</td>
<td>61.1 (39.7–79.0)</td>
<td>0.440 (0.382–0.506)</td>
</tr>
<tr>
<td>HFW</td>
<td>70.6 (47.5–86.4)</td>
<td>57.5 (36.2–76.4)</td>
<td>0.511 (0.454–0.576)</td>
</tr>
<tr>
<td>FSW</td>
<td>69.2 (45.9–85.6)</td>
<td>55.7 (34.5–75.0)</td>
<td>0.554 (0.497–0.617)</td>
</tr>
<tr>
<td>HSW</td>
<td>68.1 (44.6–85.0)</td>
<td>58.7 (37.3–77.2)</td>
<td>0.544 (0.492–0.602)</td>
</tr>
<tr>
<td>CW</td>
<td>65.3 (41.6–83.3)</td>
<td>60.3 (38.8–78.4)</td>
<td>0.576 (0.530–0.625)</td>
</tr>
<tr>
<td>CF</td>
<td>65.0 (41.3–83.1)</td>
<td>68.6 (47.7–83.9)</td>
<td>0.510 (0.470–0.553)</td>
</tr>
<tr>
<td>HFS</td>
<td>63.7 (39.9–82.3)</td>
<td>66.3 (45.2–82.4)</td>
<td>0.548 (0.509–0.589)</td>
</tr>
<tr>
<td>FW</td>
<td>63.1 (39.3–81.9)</td>
<td>61.4 (40.0–79.1)</td>
<td>0.601 (0.560–0.644)</td>
</tr>
<tr>
<td>SW</td>
<td>61.0 (37.2–80.5)</td>
<td>61.9 (40.5–79.5)</td>
<td>0.630 (0.594–0.669)</td>
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<tr>
<td>CS</td>
<td>59.7 (35.9–79.6)</td>
<td>69.4 (48.7–84.4)</td>
<td>0.581 (0.551–0.613)</td>
</tr>
<tr>
<td>HW</td>
<td>56.8 (33.3–77.6)</td>
<td>66.8 (45.7–82.8)</td>
<td>0.647 (0.620–0.675)</td>
</tr>
<tr>
<td>FS</td>
<td>56.3 (32.8–77.3)</td>
<td>70.1 (49.6–84.9)</td>
<td>0.623 (0.598–0.649)</td>
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<td>HF</td>
<td>52.0 (29.2–74.1)</td>
<td>75.0 (55.6–87.7)</td>
<td>0.640 (0.620–0.660)</td>
</tr>
<tr>
<td>W</td>
<td>49.3 (27.0–71.9)</td>
<td>71.1 (50.8–85.5)</td>
<td>0.712 (0.693–0.733)</td>
</tr>
<tr>
<td>F</td>
<td>42.8 (22.2–66.3)</td>
<td>79.8 (62.4–90.4)</td>
<td>0.716 (0.695–0.738)</td>
</tr>
<tr>
<td>HS</td>
<td>38.9 (19.5–62.6)</td>
<td>78.1 (59.9–89.5)</td>
<td>0.782 (0.753–0.813)</td>
</tr>
<tr>
<td>C</td>
<td>38.5 (19.2–62.2)</td>
<td>81.8 (65.3–91.5)</td>
<td>0.753 (0.724–0.783)</td>
</tr>
<tr>
<td>S</td>
<td>31.4 (14.8–54.6)</td>
<td>82.2 (65.9–91.7)</td>
<td>0.835 (0.780–0.893)</td>
</tr>
<tr>
<td>H</td>
<td>5.9 (2.3–14.5)</td>
<td>94.4 (87.6–97.6)</td>
<td>0.996 (0.735–1.351)</td>
</tr>
</tbody>
</table>