TB PREVENTIVE TREATMENT

Sorting Myth from Fact

[insert presenter]
[insert date]
Using this Slide Deck

**Intended End-User(s):** CDC or other USG agency headquarters-based staff providing technical assistance, CDC or other USG agency country team programmatic staff, National TB Program staff, National HIV Program staff, clinical staff or health care workers, and other donor agencies and implementing partners

**Goals of Tool:** To provide evidence-based answers to common questions or misperceptions about TPT to inform HQ and in-country staff about this evidence-base to facilitate in-country discussions when similar questions arise.

In-country staff may adjust and use this presentation as needed for meetings with key stakeholders and partners. Disclaimer: New data and publications are constantly evolving so this presentation may not include all of the newest publications/literature.

**Description:** This presentation begins with an explanation of the rationale for TPT. It then proceeds to address eight common questions about TPT, providing the evidence-base for each one.

**Instruction to end-users:** Use these slides as a reference and/or training tool. If you have any questions, contact the TPT unit ([tptunit@cdc.gov](mailto:tptunit@cdc.gov))

[don’t forget to remove this slide before presentation!]
Introduction
Why IPT for PLHIV?

- PLHIV remain at substantially higher risk of active TB disease even if on ART and clinically stable (and even if CD4 counts >700)\(^1\)

- Isoniazid preventative therapy (IPT) works synergistically with ART to lower risk of active TB disease

- Multiple studies have demonstrated that IPT reduces TB incidence among PLHIV and is cost-effective\(^2\)-\(^9\)

- TEMPRANO study: six months IPT independently reduced mortality 39% at 78 months (graph)

Global IPT uptake

- IPT has been WHO priority for PLHIV for years, but global uptake is slow

- In 2016, only 940,269 PLHIV (42% of newly enrolled) started IPT (compared with 19.5M people on ART)

- In 2016, only 161,740 pediatric household contacts <5 years (13% of those eligible) started IPT

**Graph: WHO Global TB Report, 2017; UNAIDS Database 2017**
TB Preventive Treatment (TPT): Beyond isoniazid

- New terminology: **TB Preventive Treatment (TPT)**

- WHO recommended TPT options in low incidence settings:
  - Isoniazid x 6-9 months (6-9IPT)
  - Weekly Isoniazid + Rifapentine x 3 months (3HP)
  - Daily Isoniazid + Rifampicin x 3-4 months (3-4HR)
  - Rifampicin alone x 3-4 months (3-4R)

- WHO recommended TPT options in high incidence settings:
  - Isoniazid x 6 months (6IPT)
  - Isoniazid x 36 months (36IPT)*
  - Daily Isoniazid + Rifampicin x 3 months (3HR, for children and adolescents <15 years)
  - Weekly Isoniazid + Rifapentine x 3 months (3HP)

*Source: WHO LTBI Guidelines, 2018*
Myth-busters: Objective and Format

- **Objective:** Explore 8 common perceived barriers to IPT implementation and determine if they are myth or fact

- “**Myth-busters**” format:
  - Review current evidence
  - Conclude on whether perceived barriers are myths or facts
  - Review of WHO guidelines, PEPFAR priorities and resources for TPT implementation
Myth or Fact?

IPT should only be given to people with a positive tuberculin skin test (TST) or interferon-gamma release assay (IGRA)
Evidence for differential TPT effect by TST result status

- 12 trial meta-analysis (n=8,578 randomized participants)

- **TB incidence:**
  - Generally TPT resulted in lower TB incidence (RR 0.68, 95% CI 0.54-0.85)
    - Larger effect in TST+ positive: RR 0.38, 95% CI 0.25-0.57

- **Mortality:**
  - INH vs placebo had lower mortality in TST+ positive
    - RR 0.74, 95% CI 0.55-1.00
  - INH + rifampin had lower mortality regardless of TST status
    - RR 0.69, 95% CI 0.50-0.95

Source: Akolo et al Cochrane 2010
TPT and TST in children living with HIV

- Prospective double blind placebo controlled trial in children ≥8 weeks with HIV in 2 tertiary centers in South Africa (n=263)
  - Most children with negative TST due to immunosuppression (anergy*)

- Both mortality and incidence lower in the INH group vs placebo

Table 2 Mortality and hazard ratios (HR) in children allocated to isoniazid prophylaxis or placebo

<table>
<thead>
<tr>
<th>Tuberculin skin test result (n=257)</th>
<th>Isoniazid (%)</th>
<th>Placebo (%)</th>
<th>Total (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>0/15 (0)</td>
<td>0/7 (0)</td>
<td>0/22 (0)</td>
<td>No estimate</td>
</tr>
<tr>
<td>Negative</td>
<td>11/113 (10)</td>
<td>20/122 (16)</td>
<td>31/235 (13)</td>
<td>0.51 (0.24 to 1.07)</td>
</tr>
</tbody>
</table>

Table 3 Incidence of tuberculosis in children allocated to isoniazid prophylaxis or placebo

<table>
<thead>
<tr>
<th>Tuberculin skin test result (n=257)</th>
<th>Isoniazid n=132 (%)</th>
<th>Placebo n=131 (%)</th>
<th>Total n=263 (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>0/15 (0)</td>
<td>1/7 (14)</td>
<td>1/22 (5)</td>
<td>No estimate</td>
</tr>
<tr>
<td>Negative</td>
<td>5/113 (4)</td>
<td>12/122 (10)</td>
<td>17/235 (7)</td>
<td>0.32 (0.11 to 0.90)</td>
</tr>
</tbody>
</table>

Source: Zar et al. BMJ 2007

*Anergy= absence of the normal immune response
Countries recommending TST before IPT initiation

- **Brazil**
  - Annual TST screening in PLHIV without history of previous positive TST
  - Start TST positive patients on IPT
  - TST negative persons with close TB contact get give IPT

- **Cameroon**
  - Start TST positive patients on IPT
  - TST negative persons with close TB contact and CD4 ≤ 200 cells/mm³ should get give IPT

- **Thailand**
  - IPT is given to TST positive PLHIV

*South Africa previously recommended TST but in May 2018, removed this requirement as it was felt to be a major barrier to TPT scale-up*
Interferon-gamma release assay (IGRA)

- **Newer test for latent TB infection**
  - Whole-blood test
  - Limited studies done evaluating use of IGRA and TPT outcomes
  - Extrapolation of other study results and expert opinion serves as the basis for updated inclusion in WHO LTBI guidelines

- **Advantages:**
  - Requires only a single patient visit
  - Results can be available within 24 hours
  - Does not boost responses measured by subsequent visits
  - Prior BCG vaccination does not cause a false-positive IGRA test result

- **Disadvantages:**
  - Blood samples must be processed within 8-30 hours after collection
  - High error rate in sample collection and transport (especially with prolonged sample transport/processing time)
  - Likely expensive
Recommendations

2018 WHO recommendations:

- NEW: Either a TST or IGRA can be used to test for LTBI (*strong recommendation, very low-quality evidence*)

- TST/IGRA not a requirement for initiating TPT in PLHIV or child household contact <5 years (*strong recommendation, moderate quality of evidence*)

- People living with HIV who have a positive test for LTBI benefit more from IPT; LTBI testing can be used where feasible to identify such individuals (*strong recommendation, high quality of evidence*)
  - PLHIV with unknown TST/IGRA should start TPT after symptom-based screening

*Source: WHO guidelines for Latent Tuberculosis Infection 2018*
IPT should only be given to people with a positive tuberculin skin test (TST) or interferon-gamma release assay (IGRA)

Myth!
Myth or Fact?

If you cannot make a definitive diagnosis to rule out TB, you cannot start someone on TPT
TB medication decision tree

PLHIV

No TB Symptoms
- TPT

Symptoms
- Further Evaluation
  - TB Disease
    - TB Treatment
  - No TB Disease
    - TPT

Clinician Unsure about Diagnosis ± Programmatic Issues = Patient Gets Nothing
WHO 4 symptom screen for PLHIV

- WHO symptom screen: >1 of current cough, fever, night sweats, weight loss

- Meta-analysis of 12 studies in adults and adolescent PLHIV
  - At 5% TB prevalence: 97.7% negative predictive value (NPV)
  - At 20% TB prevalence: 90% negative predictive value (NPV)

**Negative Predictive Value (NPV)**

“Likelihood that PLHIV who have a negative TB screen truly don’t have TB disease”

\[
\text{Negative Predictive Value} = \frac{\text{True Negatives}}{\text{True Negatives} + \text{False Negatives}}
\]

*Negative predictive value is influenced by the prevalence of disease in a population!*

WHO 4 symptom screen for PLHIV

- WHO symptom screen: >1 of current cough, fever, night sweats, weight loss

- Meta-analysis of 12 studies in adults and adolescent PLHIV
  - At 5% TB prevalence: **97.7% negative predictive value (NPV)**
  - At 20% TB prevalence: **90% negative predictive value (NPV)**

Negative predictive value should be used when assessing the quality of various screening techniques for TPT purposes. It is preferred over the use of sensitivity because NPV depends on the background prevalence of TB (this is important).

Updated analysis: WHO 4 symptom Screen for PLHIV

- Recent systematic review and meta-analysis (Lancet HIV 2018) re-assessed the sensitivity and specificity of the 4 symptom screen, including stratification by ART status (18 studies, 7 with data on patients on ART)

<table>
<thead>
<tr>
<th>Symptom screening alone*</th>
<th>Number of studies</th>
<th>Sample size</th>
<th>Pooled sensitivity</th>
<th>Pooled specificity</th>
<th>NPV, hypothetical tuberculosis prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>On ART</td>
<td>7</td>
<td>4640</td>
<td>51.0% (28.4-73.2)</td>
<td>70.7% (47.8-86.4)</td>
<td>99.3% 96.5% 92.8% 85.2%</td>
</tr>
<tr>
<td>Not on ART</td>
<td>16</td>
<td>8664</td>
<td>89.4% (83.0-93.5)</td>
<td>28.1% (18.6-40.1)</td>
<td>99.6% 98.0% 96.0% 91.4%</td>
</tr>
<tr>
<td>Estimates by Getahun et al, 2011†</td>
<td>12</td>
<td>8148</td>
<td>78.9% (58.3-90.9)</td>
<td>49.6% (29.2-70.1)</td>
<td>99.6% 97.8% 95.5% 90.4%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptom screening plus chest radiography</th>
<th>Number of studies</th>
<th>Sample size</th>
<th>Pooled sensitivity</th>
<th>Pooled specificity</th>
<th>NPV, hypothetical tuberculosis prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>On ART</td>
<td>2</td>
<td>646</td>
<td>84.6% (69.7-92.9)</td>
<td>29.8% (26.3-33.6)</td>
<td>99.5% 97.4% 94.6% 88.6%</td>
</tr>
<tr>
<td>Not on ART</td>
<td>5</td>
<td>1801</td>
<td>94.3% (76.2-98.8)</td>
<td>20.1% (7.6-43.8)</td>
<td>99.7% 98.5% 97.0% 93.4%</td>
</tr>
<tr>
<td>Regardless of ART status</td>
<td>5</td>
<td>2447</td>
<td>91.2% (76.8-97.0)</td>
<td>25.0% (8.2-55.4)</td>
<td>99.6% 98.2% 96.3% 91.9%</td>
</tr>
<tr>
<td>Estimates by Getahun et al, 2011†</td>
<td>4</td>
<td>2805</td>
<td>90.6% (66.7-97.9)</td>
<td>38.9% (12.8-73.3)</td>
<td>99.4% 98.7% 97.4% 94.3%</td>
</tr>
</tbody>
</table>

Data are n or percentage (95% CI). ART=antiretroviral therapy. NPV=negative predictive value. *Because of substantial heterogeneity between studies, we did not do a meta-analysis using all populations regardless of ART status. †Most participants were not receiving ART.
What about chest radiography (CXR)?

- In original meta-analysis (Getahun) of 12 studies, CXR increased sensitivity of the 4-symptom screen, but decreased negative likelihood ratio (NLR)\(^1\)
  - Without CXR: sensitivity 78.9% (95% CI 58.3-90.9), specificity 49.6% (29.2-70.1), NLR 0.426 (0.3-0.5)
  - With CXR: sensitivity 90.6% (95% CI 66.7%-97.9%), specificity 38.9% (95% CI 12.8%-73.3%), NLR 0.242 (95% CI 0.1-0.6)

- Recent meta-analysis (Hamada) suggested CXR could increase sensitivity among PLHIV on ART (with decrease in specificity), but without much difference in negative predictive value (at varying levels of TB prevalence)\(^2\)

- Modeled use of CXR + symptoms vs. symptoms only resulted in excess cases of TB and of death with CXR added\(^3\)
  - Attributed to delays in initiation of IPT while waiting for CXR results

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Summary: Chest radiography

- **Potential benefits of adding chest radiography to the four-symptom screening rule:**
  - Marginal improvement in performance
  - Increase TB case-finding

- **Potential harms of adding chest radiography to the four-symptom screening rule:**
  - Increase false-positive results (or reduce negative likelihood ratio), which would require more investigations for TB and other illnesses
  - Potential delays in treatment initiation (or loss of patients due to additional step)
WHO Guidelines 2018

- Adults and adolescents living with HIV should be screened for TB according to a clinical algorithm. Those with a negative symptom screen are unlikely to have active TB and should be offered preventive treatment, regardless of their ART status (Strong recommendation, moderate-quality evidence).

- Chest radiography may be offered to people living with HIV and on ART, and preventive treatment be given to those with no abnormal radiographic findings (Conditional recommendation, low-quality evidence).

WHO Remark: Chest radiography should not be a requirement for initiating preventive treatment.

Source: WHO guidelines for Latent Tuberculosis Infection 2018
What about children?

- Little data published on use of TB symptom screening in children (CLHIV or children without HIV exposed to TB)

- Recommended symptom screen: poor weight gain or weight loss, fever, current cough, or TB contact
  - Could also consider reduced playfulness
  - Children <12 months should include investigations for TB, not the symptom screen alone
  - Note: Children living in close contact with a sputum smear+ TB patient have a 5x risk for TB compared with adults in the same household!

Recommended Algorithm for TB screening, Diagnosis, Treatment, and Prevention in Children

Sources: CDC TPT Toolkit
If you cannot make a definitive diagnosis to rule out TB, you cannot start someone on TPT

Myth!
Myth or Fact?

TPT increases TB drug resistance
TPT and drug resistance: Concerns

- TPT will promote drug resistance when used to treat latent TB infection (and contribute to global MDR and XDR TB)
- TB symptom screening is not sufficient to rule out TB, and TPT may inadvertently be initiated among patients with active TB disease
- Although TPT is efficacious, does the potential threat of resistance outweigh the benefits?
IPT drug resistance: Isoniazid resistance after IPT in Thibela TB Study (South Africa)

- Cluster randomized trial of community-wide IPT among >24,000 S. African miners
- Sub-study of miners who developed active TB after IPT
- 71 with drug susceptibility results (58 first episode, 13 retreatment episodes)
- No statistically significant difference in isoniazid resistance among those who had received IPT (vs. control clusters)

Source: Van Halsema et al. AIDS 2010; 24: 1051
**IPT and drug resistance: Meta-analysis incidence of isoniazid resistance, IPT vs. no IPT**

- 13 studies, N=13,080 (similar results for HIV-infected and non-infected)

**Source:** Ballcells et al. Emerg Infect Dis 2006; 12: 744
IPT and drug resistance: The verdict

- Multiple studies have shown no statistically significant increase in drug resistance, but unclear whether widespread programmatic scale-up will differ, and limited data exists on rifamycins

- The benefits of IPT outweigh potential concerns about resistance

**WHO recommendation:**

**Drug resistance and surveillance**

There is no evidence of a significant association between bacterial resistance to TB drugs and use of isoniazid or rifamycins for the treatment of LTBI. Nonetheless, active TB disease must be excluded before TB preventive treatment is initiated, and regular follow-up is required to ensure early identification of people who develop active TB while receiving TB preventive treatment. National surveillance systems for resistance to TB drugs should be established in countries implementing programmatic management of LTBI.

*Source: WHO guidelines for Latent Tuberculosis Infection 2018*
IPT and Drug Resistance: Safeguards

- Safeguards programs can take against development of drug resistance (DR):
  - Educate health workers on how to rule out active TB before starting TPT
  - If TB symptoms while on TPT: stop TPT and rule-out or confirm active TB. If confirmed, do drug susceptibility testing and treat accordingly
  - Develop and implement national/international DR surveillance
  - Educate patients on the importance of self-monitoring and reporting symptoms of TB, especially if on TPT
TPT increases TB drug resistance

Myth, but it’s complicated
Myth or Fact?

TPT causes hepatotoxicity and other adverse reactions that prevent its programmatic use
The Issue...

- Clinicians and programs express concern about potential toxicity of TPT medications, especially isoniazid used in combination with ART
  - Hepatotoxicity
  - Neuropathy
Adverse events with isoniazid preventive therapy: experience from a large trial

Alison D. Grant\textsuperscript{a}, Kathryn T. Mngadi\textsuperscript{b}, Clare L. van Halsema\textsuperscript{a}, Mariëtha M. Luttig\textsuperscript{b}, Katherine L. Fielding\textsuperscript{a} and Gavin J. Churchyard\textsuperscript{a,b}

- Target group: Community-wide IPT use among gold miners in South Africa (HIV prevalence 30%)
- Exclusion criteria
  - Active TB disease
  - Hypersensitivity to isoniazid
  - Chronic liver disease or active hepatitis
  - Heavy alcohol use
  - History of convulsions/psychosis/neuropathy
  - Pregnancy/postpartum/refused contraceptive use
  - Concomitant use of other hepatotoxic drugs
  - Weight <40 Kg
- Received 9 months of IPT (with pyridoxine)
- Adverse events were closely monitored
Concluded that risk of AEs low and clinical criteria can be used to screen patients prior to/during IPT

Source: Grant, AIDS 2010
Target group: Non-pregnant PLHIV aged 18-70 years without evidence of active TB

Exclusion criteria (baseline labs checked prior to IPT initiation)
- AST >85 IU/L or ALT >103 IU/L (both ≥ 2.5X upper limit of normal)
- Bilirubin >39 µmol/L (≥ 1.5X upper limit of normal)

Adverse events were monitored
- AST/ALT/Bilirubin were rechecked 2 weeks after starting IPT
- Clinical screening (fatigue, jaundice, icterus, nausea/vomiting/abdominal pain, itching, and neuropathy) was then done every 3 months
### Summary:
- Rates of clinically significant hepatitis in an HIV-positive cohort remained relatively low
- However, there is still need for awareness of hepatotoxicity and the need for patient and provider monitoring for adverse events

### Table 1. Increases in Isoniazid-Associated Transaminases During 6 Months of Isoniazid Preventive Therapy in HIV-Infected Adults by Grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>Transaminase (IU/L)</th>
<th>Transaminase Relative to ULN</th>
<th>Number of Participants</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34 &lt; AST ≤ 86, 41 &lt; ALT ≤ 103</td>
<td>&gt;ULN – 2.5 × ULN</td>
<td>354*</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>86 &lt; AST ≤ 171, 103 &lt; ALT ≤ 206</td>
<td>&gt;2.5–5.0 × ULN</td>
<td>34†</td>
<td>8.4</td>
</tr>
<tr>
<td>3‡</td>
<td>171 &lt; AST ≤ 681, 206 &lt; ALT ≤ 821</td>
<td>&gt;5.0–20.0 × ULN</td>
<td>15</td>
<td>3.7</td>
</tr>
<tr>
<td>4‡</td>
<td>AST &gt; 681, ALT &gt; 821</td>
<td>&gt;20.0 × ULN</td>
<td>3†</td>
<td>0.74</td>
</tr>
<tr>
<td>5‡</td>
<td>Death</td>
<td></td>
<td>1†</td>
<td>0.25</td>
</tr>
<tr>
<td>Total:</td>
<td></td>
<td></td>
<td>407</td>
<td>100.0</td>
</tr>
</tbody>
</table>

The observed 1.1% rate of severe isoniazid-associated hepatitis was similar to rates in HIV-uninfected populations.

*Source: Tedla, Am J respire Crit care Med, 2010*
Outcomes of isoniazid-associated hepatitis in adults infected with HIV initiating 36 months of IPT

1006 participants randomized to 36 months IPT

- No hepatitis \( (\leq \text{G1 EST}) \)
  - \( n=956 \) (95%)

- Moderate hepatitis \( (34 \text{ G2 EST}) \)
  - \( n=34 \) (3.4%)

- Severe hepatitis \( (12 \text{ G3}, 2 \text{ G4}, 2 \text{ G5 EST}) \)
  - \( n=16 \) (1.6%)

Moderate hepatitis \( (31 \text{ G2 EST}), n=31 \) (3.1%)
- 24 resolved on IPT (15 on ART, 9 not on ART)
- 3 no more blood tests but asymptomatic on IPT
- 2 persisted G2 on IPT (1 on ART, 1 not on ART)
- 1 persisted off IPT and no ART
- 1 died of uncertain cause without jaundice

Severe hepatitis \( (15 \text{ G3}, 2 \text{ G4}, 2 \text{ G5 EST}) \)
- \( n=19 \) (1.9%)

IPT stopped

WHO recommendations

- Most reactions are minor and rare, but attention should be paid to preventing drug-induced hepatotoxicity
  - Health care providers should explain the disease process and rationale of treatment, and advise patients to contact them if they experience any related symptoms

- There is insufficient evidence to support testing of baseline liver function, though it is recommended *where feasible* for people with a history of liver disease, regular alcohol use, HIV, age >35, pregnancy/postpartum
  - Should not be a barrier to TPT use if not routinely feasible
  - Also should be available for people with symptoms of hepatotoxicity while on treatment

*Source: WHO guidelines for Latent Tuberculosis Infection 2018*
Other possible strategies...

- This risk of hepatotoxicity is not zero, but it can be mitigated by proper screening of high-risk patients and appropriate adverse event monitoring
  - Risk increases with age, alcohol or nevirapine use, active hepatitis or severe immunosuppression

- Neuropathy risks can be mitigated by prescribing isoniazid with concurrent pyridoxine (vitamin B6, 10 mg/day)

- And don’t forget: educating patients on potential side effects and empowering patients to notify providers when they have concerns is incredibly important!
Again, every programmatic and clinical decision is about weighing risks and benefits...

(TPT scale-up should be **widely**, but **wisely**)

- **Risks**: Low but existing potential for a serious adverse event
- **Benefits**: High potential to reduce morbidity and mortality
TPT causes hepatotoxicity and other adverse reactions that prevent its programmatic use

Myth!
It is unsafe to give TPT to children and adolescents, and pregnant women
Evidence for IPT in CLHIV

- Among 277 HIV-infected children (median age 2.1y) not on ART, IPT decreased active TB by 72% and mortality by 54%

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Safety of isoniazid for CLHIV

- IPT has been successfully given to CLHIV with documented completion rates and has been shown to be effective in reducing TB incidence\(^1,^2\)
  - Additionally, adverse events are no more than with placebo\(^3\)

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Adherence, intercurrent hospital admissions and adverse events in children by dosing schedules</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>INH (n = 85)</td>
</tr>
<tr>
<td>Adherence %, mean ± SD</td>
<td></td>
</tr>
<tr>
<td>Hospital admission</td>
<td>96 ± 7</td>
</tr>
<tr>
<td>Adverse events</td>
<td>4 (67)</td>
</tr>
</tbody>
</table>

\(P = 0.06\)  \(P = 0.04\)  \(P = 1.0^*\)  \(P = 1.0^*\)

\(^*\) Fisher's exact test.
INH = isoniazid; SD = standard deviation; RR = relative risk; CI = confidence interval.

- WHO strongly recommends 6 months of INH for all CLHIV aged ≥12 months who live in a high TB prevalence setting, and those <12 months with known TB exposure for whom TB disease has been excluded\(^4\)
  - Conditionally, also CLHIV who have completed a TB treatment course

\(^1\) Masini PHA 2013; \(^2\) Ayieko BMC ID 2014; \(^3\) Gray et al. IJTLID 2014; \(^4\) WHO guidelines for Latent Tuberculosis Infection 2018
TB screening and prevention in pregnant women living with HIV (PWLHIV)

- Higher TB incidence in postpartum period compared to non-peri-partum period
- South Africa study found substantial TB burden among PWLHIV during pregnancy and postpartum
- TB screening algorithms have poorer performance in PWLHIV compared to other PLHIV

Sources: Gupta, JID 2011; Tiam, JAIDS 2014; Hoffman, PLOS One 2013; LaCourse, JAIDS 2014; Gounder, JAIDS 2011; Modi, CROI 2015; Kancheya, IJTLD 2014; Odayar, IJTLD 2018; Graphic courtesy of Lisa Cranmer, Emory University
Safety of isoniazid for PWLHIV

- FDA Category C

- Hepatotoxicity
  - Concern for hepatotoxicity arose from 20 deaths in California reported in 1989 related to isoniazid (INH); 4 were among postpartum women who started INH in pregnancy.\(^1\)
  - Retrospective analysis of 3,681 pregnant women also in California treated with INH found 5 cases of INH hepatitis, 2 resulting in death. Comparison with a previously-collected INH hepatitis surveillance study from 1971-72 did not show a statistically-significant increase in hepatotoxicity.\(^2\)
  - P1078 study conducted in 8 countries among 956 pregnant women found no statistically significant increase in hepatotoxicity between IPT during pregnancy vs. postpartum period.\(^3\)

- Experience in Botswana
  - A 36-month daily INH TB-prevention trial in Botswana found no association with adverse pregnancy outcomes even in the context with ART exposure.\(^4\)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adverse outcome no. (%)</th>
<th>No adverse outcome no. (%)</th>
<th>uOR</th>
<th>95% CI</th>
<th>aOR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid exposure in pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>32 (31.1)</td>
<td>71 (68.9)</td>
<td>0.6</td>
<td>0.3–1.1</td>
<td>0.6</td>
<td>0.3–1.1</td>
</tr>
<tr>
<td>No</td>
<td>40 (43.1)</td>
<td>53 (57.0)</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

Sources: \(^1\)Moulding, AJCRRM, 1989; \(^2\)Franks; Public Health reports, 1989; \(^3\)Gupta, 2018, CROI abstract; \(^4\)Taylor, Infectious Diseases in Obstetrics and Gynecology, 2013
Example: Outcomes for pregnant women and children on IPT (in Western Kenya)

- **Of 10,000 pregnant women enrolled in PMTCT on IPT**
  - Completed IPT = 95%
  - Dead = 0.2%
  - Toxicity = 0.2%
  - Developed TB = 0.02%

- **Of 13,000 children on IPT**
  - Completed IPT = 91%
  - Dead = 0.07%
  - Toxicity = 0.09%
  - Developed TB = 0.009%

Source: CDC Kenya presentation at 2017 CDC DGHT Annual Meeting
Emerging data on safety of IPT in pregnancy: P1078 Study

- Women were randomized to receive IPT during pregnancy or deferred until 12 weeks postpartum.
- All women were on ART, with majority receiving EFV-based treatment.

Source: Gupta A, 2018, CROI abstract
P1078 Study found possible increased adverse pregnancy outcomes with IPT

- Statistically significant increase in composite adverse pregnancy outcome measures* among women who initiated IPT during pregnancy compared to those who deferred until postpartum

- No statistically significant difference in drug-related maternal safety and toxicity, including hepatotoxicity

- No difference in TB disease incidence

- Ongoing analyses will assess risk according to gestational age and interactions between IPT and Efavirenz
  - If EFV increases risk of adverse pregnancy outcomes, then TLD transition may decrease this risk

*Composite outcomes included any fetal demise, low birth weight <2500g, preterm delivery <37 weeks, and congenital anomaly. Individually, there was no statistically-significant difference between arms

Source: Gupta A, 2018, CROI abstract
Safety and optimal timing of IPT in PWLHIV remain unclear

WHO currently still recommends initiation of IPT for PWLHIV who do not have TB disease. WHO Guideline Review Committee requires a systematic review process and extensive consultation.

Country programs should consider the benefits and risks of deferring IPT initiation in their epidemiologic context and provide evidence to support an informed individual choice for PWLHIV.

Given negative consequences of TB disease during pregnancy, PMTCT programs should continue to screen women for active TB disease and ensure linkage to treatment for those with TB along with household contact screening.
It is unsafe to give TPT to children and adolescents

Myth!
But it’s complicated for pregnant women (awaiting more data on safety to fetus)
Myth or Fact?

6 months of IPT is the only recommended regimen and duration of therapy for TPT.

- In settings with high TB incidence and transmission, PLHIV, who have an unknown or positive TST status, and among whom active TB disease has been safely ruled out, should receive ≥36 months of IPT

*(conditional recommendation, low quality of evidence)*
What is the best length of therapy with isoniazid?

- Trials have shown that 6 months of IPT reduces incidence of TB
- TB preventive benefit may be lost 6–18 months after completion of IPT
- Two hypotheses for short-lived effect of IPT in PLHIV:
  1. **Relapse**
     - Inadequate eradication of LTBI
  2. **Reinfection**
     - Repeat infection with a new strain of TB
- Limited durability of 6 months of IPT in PLHIV prompted investigation of extended durations of IPT
The BOTUSA Trial

- **Design**
  - Randomized, double-blind, placebo-controlled trial among PLHIV

- **Control group**
  - 6 months INH (6IPT)

- **Intervention group**
  - 36 months INH (36IPT) as a proxy for continuous (lifelong) INH

- **Inclusion criteria**
  - Adults with HIV aged ≥18 years at government clinics in Botswana

- **Exclusion criteria**
  - Active TB or previously treated for TB (or LTBI)

Cumulative TB incidence in participants receiving 6 months and 36 months of IPT

TB incidence in 6IPT group: 1.26% per year
TB incidence in 36IPT group: 0.72% per year
Hazard ratio (HR): 0.57, 95% CI 0.33–0.99, \( P = 0.047 \)
Cumulative TB incidence in participants receiving 6 months and 36 months of IPT by TST status

--- **TST+, 6IPT**: 13/216 (6.0%) developed TB

--- **TST+, 36IPT**: 4/252 (1.6%) developed TB

HR: 0.26, 95% CI 0.09–0.80, \( P = 0.02 \)
Why is continuous IPT superior to 6IPT for PLHIV in high TB incidence settings?

- Continuous IPT likely prevents reinfection with TB, not relapse

1. Molecular epidemiology studies show that rates of reinfection are higher in HIV+ than HIV- persons

2. 6IPT has durable TB preventive effect in PLHIV living in low or medium TB incidence settings

3. TB preventive effect of 36IPT waned in post-trial period, too (HR 0.82, 95% CI 0.46–1.49, P =0.52)

Durability of IPT in PLHIV in high TB incidence settings
Example: Malawi

- Estimated TB incidence: 193 per 100,000
  - Local TB epidemiology varies
  - 10/28 (36%) districts in country account for 75% of TB burden

- Duration of IPT based on local TB epidemiology
  - Districts with high case notification get 36 months of isoniazid

Source: CDC Malawi presentation at 2017 CDC DGHT Annual Meeting

http://www.emapsworld.com/malawi-political-map.html
TB Preventive Treatment (TPT): Beyond isoniazid

Prior to 2018, isoniazid was the only WHO-recommended regimen for TPT, but now...

- **WHO recommended TPT options in low incidence settings:**
  - Isoniazid x 6-9 months (6-9IPT)
  - Weekly Isoniazid + Rifapentine x 3 months (3HP)
  - Daily Isoniazid + Rifampicin x 3-4 months (3-4HR)
  - Rifampicin alone x 3-4 months (3-4R)

- **WHO recommended TPT options in high incidence settings:**
  - Isoniazid x 6 months (6IPT)
  - Isoniazid x 36 months (36IPT)*
  - Daily Isoniazid + Rifampicin x 3 months (3HR, for children and adolescents <15 years)
  - Weekly Isoniazid + Rifapentine x 3 months (3HP)

*For PLHIV in settings with both high TB incidence and transmission
RCT (open-label) done in South Africa

PLHIV with positive TST and not on ART randomly assigned to:
- Weekly rifapentine (900 mg) and isoniazid (900 mg) x 12 weeks
- Twice weekly rifampin (600 mg) and isoniazid (900 mg) x 12 weeks
- Continuous daily isoniazid (300 mg)
- Daily isoniazid (300 mg) x 6 months (CONTROL GROUP)

Primary endpoint: TB-free survival

Study conclusions:

- Three new regimens had similar—but not superior—efficacy to 6IPT
- Higher rates of adherence in the shorter regimens
- No evidence that TB preventive treatment selected for drug resistance in the small number of TB cases isolated in the study

Study limits:

- Patients were not on ART
  - Drug interactions?
  - Different efficacy when combined with ART?

Three-month weekly rifapentine plus isoniazid for tuberculosis preventive treatment: a systematic review

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*Global TB Programme, and †Department of HIV, World Health Organization, Geneva, Switzerland

SUMMARY

BACKGROUND: Uptake of preventive treatment for tuberculosis (TB) remains poor. A 3-month regimen of rifapentine (RPT) plus isoniazid (INH) (3HP) could facilitate its scale-up. We conducted a systematic review to assess the effects of 3HP compared with daily 6- or 9-month INH monotherapy.

METHODS: We searched the following databases to identify randomised controlled trials: PubMed, Embase, the Web of Science, Cochrane Central Register of Controlled Trials, three ongoing trial registers and conference abstracts up to 24 January 2017. Where possible, we pooled data using a random-effects model.

RESULTS: Four studies were included. Of those, we included two studies that compared 3HP with daily 6- or 9-month INH (6/9H) among adults with human immunodeficiency virus (HIV) co-infection, one among HIV-negative adults and one among predominantly HIV-negative children and adolescents. Risk of active TB was not significantly different between 3HP and 6/9H (risk ratio [RR] 0.73, 95% CI 0.23–2.29, in adults with HIV; RR 0.44, 95% CI 0.18–1.07, in adults without HIV; RR 0.13, 95% CI 0.01–2.54, in children and adolescents). Risk of hepatotoxicity was significantly lower in the 3HP group among adults with HIV (RR 0.26, 95% CI 0.12–0.55) and those without HIV (RR 0.16, 95% CI 0.10–0.27). 3HP was also associated with a higher completion rate in all subgroups.

CONCLUSIONS: 3HP was shown to have a preventive effect similar to that of INH monotherapy, with fewer adverse events and higher completion rates. 3HP can contribute significantly to the scale-up of preventive treatment.

KEY WORDS: LTBI; latent tuberculous infection; isoniazid preventive therapy
<table>
<thead>
<tr>
<th>Study</th>
<th>Events/total</th>
<th>Risk ratio (95%CI)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>3HP</td>
<td>6/9H</td>
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<tr>
<td><strong>Active TB</strong></td>
<td></td>
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<tr>
<td>Sterling, 2016</td>
<td>2/206</td>
<td>6/193</td>
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<td>Martinson, 2011</td>
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<td>Random effects model (I^2 = 53.0%, P = 0.145)</td>
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<td><strong>All-cause mortality</strong></td>
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<td>6/207</td>
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<td>Random effects model (I^2 = 0.0%, P = 0.489)</td>
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<td><strong>Grade 3 or 4 adverse events</strong></td>
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<td>Random effects model (I^2 = 0.0%, P = 0.691)</td>
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<td><strong>Hepatotoxicity</strong></td>
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<td><strong>Drug-resistant TB</strong></td>
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<td><strong>Completion rate</strong></td>
<td></td>
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<td>Sterling, 2016</td>
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<td>Martinson, 2011</td>
<td>314/326</td>
<td>274/327</td>
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<tr>
<td>Random effects model (I^2 = 91.0%, P = 0.001)</td>
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</table>

**Figure 2**  3HP vs. 6/9H in adults with HIV. 3HP = 3-month regimen of weekly rifapentine plus isoniazid; 6/9H = 6 or 9 months of isoniazid monotherapy; CI = confidence interval; TB = tuberculosis.
Recent 3HP updates (2019)

- **3HP-Dolutegravir (DTG) pharmacokinetic and safety data from the DOLPHIN study (CROI 2019)**
  - Single arm, phase I/II study among ~60 adult PLHIV (already on DTG-based ART regimen 8 weeks)
  - Co-administration well-tolerated: no grade 3 or higher HP-related AEs or any AEs leading to withdrawal
  - Trough DTG concentrations reduced ~50% and AUC ~30% but virologic suppression maintained >4 weeks after 3HP completion
    - No DTG dose adjustment needed
    - Implications for 3HP start on new DTG initiates

- IMPAACT4TB planning to scale 3HP use in 12 countries

- Unitaid working on price negotiations

- Fixed dose combination (FDC) option now filed for WHO pre-qualification

Source: Dooley et al, CROI 2019, abstract 80
Pros/Cons of 3HP

▪ Pros
  – Lower rates of hepatotoxicity
  – Higher adherence/completion rates

▪ Cons
  – More expensive
  – Different M&E support and infrastructure compared to IPT due to different length of therapy
  – Limited data on the durability of protection with shorter regimen for PLHIV in high-TB transmission settings
1HP in our future?

- Randomized, open-label, phase 3 non-inferiority trial comparing safety and efficacy of 1HP vs 9H in PLHIV (n=3000, followed median 3.3 years)
  - 1HP: 4 weeks of daily, weight-based RPT + 300mg INH + B6
- No difference in primary endpoint (TB or death): 0.65 vs 0.67/100PY
- No difference in severe adverse events: 6% vs 7%
- Higher treatment completion rates in 1HP group: 97% vs 90%

Source: Swindells, et al. NEJM. 2019; 380: 1001-11
6 months of IPT is the only recommended regimen and duration of therapy for TPT

Myth!
Myth or Fact?

IPT completion is a challenge, so why bother
TPT Adherence: Concerns

- Adhering to preventive medical regimens can be difficult, especially if patients feel well.

- Reported adherence rates to TPT are highly variable (<45% to >98%, multiple studies)\(^1\)\(^{-2}\)

- The consequences of diminished adherence to preventive therapy are not the same as the consequences of diminished adherence to treatment.

- **Concerns about adherence should NOT impede implementation of TPT, however program personnel and clinicians should make every effort to promote adherence to maximize the protective potential of TPT.**

---

1. Guidelines for intensified tuberculosis case-finding and IPT for PLHIV. World Health Organization; 2011
TPT Adherence: Potential Solutions

- **Good IPT adherence has been linked to:**
  - Patient counselling before IPT initiation (including description of IPT as treatment for probable infection, rather than prevention of disease)\(^1\)
  - In-depth patient understanding of rationale and potential side effects before initiating therapy\(^1-3\)
  - Shorter regimen duration\(^1\)
  - Integration of and collaboration between TB/HIV services\(^1,4-5\)
  - Healthcare worker training specifically on IPT provision\(^6\)

- **Poorer IPT adherence has been linked to:**
  - Patient denial of or stigma associated with HIV infection\(^1\)
  - Male gender, young age, conflicting work commitments\(^1,7\)

---

2. Gibb DM, et al. Sulfamethoxazole/trimethoprim/isoniazid/pyridoxine scored tablets are bioequivalent to individual products and are acceptable to patients with advanced HIV infection in the REALITY trial. 46th Union World Conference on Lung Health; 2015; Cape Town, South Africa.
**TPT adherence: Potential solutions**

- **Reported patient preferences include**: 
  - Positive provider messaging, and motivational interviewing by providers to help patients address and overcome own barriers to TPT
  - SMS use for treatment support

*Graph: South African study of patient preferences for IPT provision (n=334)*

---

TPT adherence: Potential solutions

- Another patient preference reported by multiple studies is INH co-formulation with cotrimoxazole (CTX) and vitamin B6\textsuperscript{1-5}
  - A co-formulated fixed-dose combination (FDC) IPT/B6/CTX pill received WHO pre-qualification and inclusion on the Essential Medicines List
  - Several countries registered for procurement from Cipla, who plan to lower the price to $1.99/month

1. Gibb DM, et al. Sulfamethoxazole/trimethoprim/isoniazid/pyridoxine scored tablets are bioequivalent to individual products and are acceptable to patients with advanced HIV infection in the REALITY trial. 46th Union World Conference; 2015; Cape Town, South Africa.
TPT adherence: Potential solutions

- Potential implication for differentiated models of service delivery (DSD):
  - Prescribing and dispensing practices for TPT should align with those for ARVs even as ARV pick up intervals are spaced for differentiated HIV service delivery
  - WHO revising TPT guidelines to likely reduce frequency of follow-up for patients on TPT, with stronger emphasis on patient counselling
  - Considerations document drafted by CDC Atlanta (image) and IAS/CQUIN working on a framework

Differentiated service delivery models for delivery of TB preventive treatment: General programmatic considerations

Purpose
Tuberculosis preventive treatment (TPT) PEPFAR targets may not be met if TPT is only provided to newly-diagnosed people living with HIV (PLHIV). In considering TPT scale-up, it is important to consider how to deliver TPT both to newly-diagnosed PLHIV and to stable PLHIV on antiretroviral therapy (ART) in differentiated service delivery (DSD) models.

Background
In HIV care, DSD describes the adaptations that can be made to HIV services, including ART delivery, to meet the care needs and preferences of PLHIV, while also streamlining care in the context of limited human resources and infrastructure. DSD models vary across domains of HIV care delivery of what (ART, clinical monitoring, sampling for laboratory testing), when (frequency of contact), where (in a facility, in the community), and by whom (physician, other healthcare provider, community health worker, peer). DSD models are important in HIV care because they facilitate integration with care for co-morbidities, and because they empower health workers and recipients of care through task shifting. They also allow PLHIV stable on ART (that is, those PLHIV who have achieved documented viral load suppression and have no clinical evidence of opportunistic infections) to attend clinic less frequently, which may improve patient retention and satisfaction, as well as free up space and time in the clinic for health professionals to focus on newly-diagnosed or unstable PLHIV.

Patients with TB disease should be prioritized for models of differentiated care adapted specifically to patients with advanced disease. Example DSD models for stable HIV patient care and ART delivery are displayed in the graphic below. For more information on DSD models, visit [http://www.differentiatedcare.org/](http://www.differentiatedcare.org/).
TPT adherence: Potential solutions

- For new ART patients, programs like Kenya require TPT completion to be considered stable for a decanted ART delivery model
  - Other countries could consider similar completion of at least 5 months IPT or full short-course regimen as eligibility criteria for “stable” for new ART patients (requires TPT initiation within 1 month of ART)

- Reaching TB_PREV targets will require providing TPT to TX_CURR population
  - Need to balance “breaking” an existing model to provide oversight of TPT initiation, with desire to minimally disrupt working models
  - In Malawi, lifelong IPT is incorporated into routine 3 month fast-track ART dispensing (model “broken” at 1 month after IPT initiation for an extra clinical encounter, and then resumed as before)

- Fewer clinical encounters requires capacitating clients and their supporters to self-monitor and seek care between visits
  - These patients have already demonstrated adherence to ART

- Consider needed adaptations existing TPT or DSD M&E tools to capture TPT uptake and outcomes within different models of ART delivery
Improving IPT delivery models among PLHIV in Swaziland

- **IPT roll-out in Swaziland began in 2011**
  - 2014 review at 4 facilities found <10% eligible PLHIV initiated on IPT, and only 32% of those who started completed 6 months of treatment

- **Prospective cohort of 3 delivery models in 5 facilities in 2015:**
  - Patients select own IPT delivery method: routine facility-based (FB), community-based (CB) or peer-supported with expert client (1 site)
  - INH refills aligned with ART (frequency varied by adherence)
  - HCWs trained on motivational interviewing techniques

- **908 enrolled and followed for 5590 person-months**

- **Choice of model: FB 88%, CB 12%, peer support (0%)**

Improving IPT delivery models among PLHIV in Swaziland

- 6-month completion high!
- IPT stopped in 6% for both models, n=57)
  - 29 “AEs” (1/7 hepatitis listed as severe [with full recovery], 8 “allergy, 8 nausea, 2 psychotic behavior, 1 cramping, 3 not specified)
  - 7 pill burden
  - 3 poor adherence
  - 3 erratic drug supply
  - 15 other reasons
  - Deaths: 1 unknown, 1 suicide

= 96% clients with no adverse event at 6 months

No confirmed TB cases

Community TPT and ART delivery in South Africa

- IPT integrated into community-based ART in study sites in Kwazulu Natal resulted in high levels of uptake, feasibility, safety and adherence
  - Community ART included quarterly refills, mobile monitoring and access to facility-based services as needed
  - Lay HWs screened for TB symptoms and IPT contra-indications at each visit

Shapiro et al. CROI 2019. Abstract 723
Community TPT and ART delivery in Uganda

- Cross-sectional study of adult ART patients starting IPT in 5 communities in Uganda (2016)

- Convenience sample of “stable” patients from the SEARCH T&S trial who were getting a DSD model, vs a sample of “stable” patients getting standard of care in the same facilities but not living in SEARCH communities
  - DSD model = welcoming environment, quarterly clinic visits and refills, and nurse-conducted visits

- IPT completion 72% in DSD models (n=114) and 53% in SOC (n=161) (p<0.01)
  - People in DSD models had 2.2x odds of completion (95% CI: 1.4-3.6), even when adjusting for age, gender and community

- Some results suggest the DSD model allowed for a stronger patient-provider relationship, education, counselling, communication, empowerment, etc
  - A strong belief in the efficacy of IPT was associated with completion in the DSD arm, but not the SOC arm
  - Side effects associated with lower completion in SOC arm, but not DSD arm

Tram et al, AIDS Care, June 10, 2019
TPT adherence: Recommendations

- Clear explanation of the purpose of TPT (treatment of probable infection) and possibility of adverse events; motivational interviewing if staff trained
- Use of patient-preferred models for TPT service delivery, where possible
- TPT provision from convenient, integrated clinics (patient-centered delivery)
- TPT delivery alignment with ARV and cotrimoxazole delivery (and coformulation with B6 when available)
- Country-specific programming to support adherence to TPT and other medications
- Operational research on regional predictors of adherence to inform policy

Take away: successful TPT completion can be achieved!
IPT completion is a challenge, so why bother

Myth!
Is TPT a priority for YOU??
Resources
External resources to help you succeed!

TB preventive therapy for people living with HIV: key considerations for scale-up in resource-limited settings

I. Pathmanathan,* S. Ahmedov,* E. Pevzner,* G. Anyalechi,* S. Modi,* H. Kirking,* J. S. Cavanaugh†

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SUMMARY

Tuberculosis (TB) is the leading cause of death for persons living with the human immunodeficiency virus (PLHIV). TB preventive therapy (TPT) works synergistically with, and independently of, antiretroviral therapy to reduce TB morbidity, mortality and incidence among PLHIV. However, although TPT is a crucial and cost-effective component of HIV care for adults and children and has been recommended as an international standard of care for over a decade, it remains highly underutilized. If we are to end the global TB epidemic, we must address the significant reservoir of tuberculous infection, especially in those, such as PLHIV, who are most likely to progress to TB disease. To do so, we must confront the pervasive perception that barriers to TPT scale-up are insurmountable in resource-limited settings. Here we review available evidence to address several commonly stated obstacles to TPT scale-up, including the need for the tuberculin skin test, limited diagnostic capacity to reliably exclude TB disease, concerns about creating drug resistance, suboptimal patient adherence to therapy, inability to monitor for and prevent adverse events, a ‘one size fits all’ option for TPT regimen and duration, and uncertainty about TPT use in children, adolescents, and pregnant women. We also discuss TPT delivery in the era of differentiated care for PLHIV, how best to tackle advanced planning for drug procurement and supply chain management, and how to create an enabling environment for TPT scale-up success.

KEY WORDS: TB prevention; isoniazid preventive therapy; TB-HIV
Resources from CDC HQ to help you succeed!

TB Preventive Treatment (TPT) Implementation Roadmap and Tools

Policy & Planning

Country Consultation
- 01 TPT Country Baseline Assessment
- 02 TPT Myth Busters
- 03 TPT FAQs for Programs
- 04 TPT Emerging Clinical Considerations (Pregnancy/Adherence/TLD)
- 05 TPT Technical Assistance Request SOW
- 06 TPT Implementation Checklist

Partner Management
- In-person meeting
- Budget Planning
- 07 TPT Costing Tool

Pre-Implementation

Set Targets
- 08 TPT TB_PREV Target Setting Considerations

M&E Preparations
- 09 TPT Indicators
- 10 Data Flow Assessment
- 11 TPT Register Example

Preparations for Implementation and Training

Job Aids
- 12 TPT Adult Clinical Algorithm
- 13 TPT Pediatric Clinical Algorithm
- 14 TPT FAQs for Patients
- 15 TPT Adverse Events
- 16 DSD Model Considerations
- 17 TPT Commodity Forecasting Tool
- 18 TPT Clinical Site Assessment Tool

Early Implementation

MER Monitoring
- POART Support

Routine Implementation

Monitoring & Evaluation
- Ongoing Training
- MER Monitoring
- POART Support