Differentiated Service Delivery for TB Preventive Treatment

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(Acknowledgement: Gavin Churchyard)

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Overview

Background on TPT
New guidelines
Latest Regimens
Issues to consider in implementation
DSD and TPT
WHO End TB Strategy

Patient centred care & prevention

- Early diagnosis of TB
- Collaborative TB/HIV activities
- Preventive treatment for those at high risk of TB
- Treatment of all people with TB
UN HIGH-LEVEL MEETING ON TB KEY TARGETS & COMMITMENTS FOR 2022

1. COMMIT TO PROVIDE DIAGNOSIS AND TREATMENT with the aim of successfully treating 40 million people with tuberculosis by 2022.

2. COMMIT TO PROVIDE DIAGNOSIS AND TREATMENT with the aim of successfully treating 3.5 million children with tuberculosis by 2022.

3. COMMIT TO PROVIDE DIAGNOSIS AND TREATMENT with the aim of successfully treating 6 million people living with HIV, receiving preventive treatment.

4. COMMIT TO PREVENT TUBERCULOSIS for those most at risk of falling ill so that at least 30 million people, including 4 million children under five years of age, 20 million other household contacts of people affected by tuberculosis, and 6 million people living with HIV, receive preventive treatment.

5. ENFORCE AND SUPPORT LAWS AND POLICIES TO REDUCE STIGMA AND DISCRIMINATION, including by removing discriminatory laws, policies, and practices against people with tuberculosis, ensuring the protection and promotion of human rights and dignity.

6. REMOVE ALL BARRIERS TO TB PREVENTION, DIAGNOSIS, AND TREATMENT, especially for those who are vulnerable, including those in fragile circumstances.

7. COMMIT TO DELIVERING, AS SOON AS POSSIBLE, NEW, SAFE, EFFECTIVE, EQUITABLE, AFFORDABLE, AVAILABLE VACCINES, point-of-care and child-friendly diagnostics, drug susceptibility tests and safer and more effective drugs and shorter treatment regimens for adults, adolescents and children for all forms of tuberculosis and infection, as well as innovative strengthened health services such as information and communication tools and delivery systems for new and existing technologies, to enable integrated, cooled and reconditioned delivery of treatments.

8. REQUEST THE DIRECTOR-GENERAL OF THE WORLD HEALTH ORGANIZATION TO CONTINUE TO DEVELOP THE MULTISECTORAL ACCOUNTABILITY FRAMEWORK and ensure its timely implementation no later than 2019.

9. FURTHER REQUEST THE SECRETARY GENERAL WITH THE SUPPORT OF THE WORLD HEALTH ORGANIZATION TO PROVIDE A PROGRESS REPORT IN 2020 on global and national progress, across sectors, promoting efforts to achieve agreed tuberculosis goals, which will serve to inform preparations for a comprehensive review by Heads of State and Government at a high-level meeting in 2023.
Building a tuberculosis-free world: The *Lancet* Commission on tuberculosis

5 Priority Investments:

1. High quality person- & family-centred rapid diagnostics and treatment are provided to all individuals receiving care for tuberculosis, wherever they seek care
2. Reach those at High risk for TB
3. Develop new diagnostics, therapies and vaccines
4. Invest funds necessary to end TB
5. Hold countries accountable
Prospects for ending TB in S. Africa

General population: slow scale-up

- No intervention
- ART
- Doing the basics better
- Improved diagnostics
- LTBI treatment in HIV+
- LTBI treatment in HIV-

60% protected by 2030

A Reid, Int J. Tuberc Lung Dis. 2015.
Prospects for ending TB in S. Africa

General population - Rapid scale up

(TB incidence, 2013: 860/100,000)

- No intervention
- ART
- Doing the basics better
- Improved diagnostics
- Treat. latent MTB in HIV+
- Treat. latent MTB in HIV-

60% protected by 2018

A Reid, Int J. Tuberc Lung Dis. 2015.
Released in 2018

Recommendations cover:

- Daily INH for 6 months
- Daily INH for 36 months
- 3HP: Rifapentine plus isoniazid weekly for 3 months - New
- 3HR: Rifampicin plus isoniazid daily for 3 months for children and adolescents < 15y- New

Caution: Potential drug–drug interactions in rifampicin- and rifapentine-containing TPT for PLHIV on some ART regimens
Daily IPT (6m or 12m)

Relative Risk (Fixed) & 95% CI

- Reference
- PPD+
- PPD-
- PPD-unknown
- Overall

Akolo. 2010, Cochrane review
**IPT with ART**

HR: 0.63 (95% CI 0.41-0.94)

Rangaka et al, AIDS2012
IPT is cheap and effective, yet IPT uptake in high burden settings remains low

IPT uptake\(^1\) among PLHIV\(^2\)

Barriers to IPT uptake

- Long (6-36 months) and complex treatment options
- Poor adherence
- Re-infection in high burden settings
- Challenging to scale up
- Deprioritized vs. other interventions
PREVENT TB: 3HP

TBTC Study 26: TST converters in US, Canada, Brazil & Spain

- Treatment completion: 82% vs. 69%
- Treatment limiting AEs: 4.9% vs. 3.7%
- Hepatotoxicity: 0.4% vs. 2.7%

Sterling NEJM 2011;365:2155
Other Regimens

**4R: Rifampicin x 4 months**: 3443 (7732 years follow up) 4R group vs 3416 (7652 years follow up) in 9H group in 9 countries
- Similar efficacy
- Treatment completion: 78.8% vs 63.2%
- Treatment stopped due to adverse events: 2.2% vs 4.8%

**3HR**: evidence from low incidence settings
- Similar efficacy and safety to 3HP
- Recommended for children and adolescents – can be given to children < 2 years

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Daily Rifapentine INH x 1 month (1HP): BRIEF TB

Multicentre, RCT, 3000 individuals ± 1100 from SA and Botswana

TB incidence: 33/4897 (0.67%) vs. 32/4926 (0.65%)

Adverse events and treatment completion

- Serious adverse events: 6% (1HP) vs 7% (9H) group (P = 0.07)
- Incidence of adverse events: 0.029 (1HP) vs 0.047 (9H) per 100 per years, IRR 1.587
- Treatment completion: 97% (1HP) vs 90% (9H), P < 0.001

3HP Post marketing surveillance
Centers for Disease Control and Prevention

After CDC guidelines on 3HP published in 2011
16 sites across the U.S.—operational settings
- Rifapentine currently available only in the U.S.

2011 - 2016
3,288 persons started 3HP and were eligible to complete treatment during study period
- 2,861 (87%) completed treatment
  - Children age 2-17 years: 155/164 (94.5%)
  - Homeless: 81% completion
- Adverse event rates similar to the PREVENT TB study

Sandul, CID, 2017
3HP vs other regimens: *systematic review*

15 studies published b/w Jan 2006–Jun 2017

Similar effectiveness: OR: 0.89 (0.46, 1.70)

Higher Treatment completion rates: (87.5% (83.2%-91.3%) vs 65.9% (53.5%- 77.3%)
  - Similar for DOT vs SAT : 86.6% (81.3%-91.1%) vs 81.9% (73.8%-88.9%)

Similar risk of
  - adverse events (RR 0.59 (0.23-1.52))
  - Discontinuing treatment because of adverse events (RR.48 (0.17-1.34)
  - Death (RR 0.79, (0.56-1.11))
Safety of 3HP: a systematic review

23 RCTs & 55 non-randomised studies

Rate of any AE: 3HP (11.5%), 3-4R (20.%), 6H (36.1%), 9H (17.6%)
Withdrawals due to AEs: 3HP (1.7%) vs 9H (6.4%), 6H (3.8%)
Flu like reactions: 3HP (2.2%) vs INH (0.05%)
Hepatotoxicity: 3HP (1%), 3-4R (0.01%), 6H(6.3%), 9H (3.1%)
DOLPHIN: DTG and 3HP in patients with HIV

SAFETY

<table>
<thead>
<tr>
<th>AE Severity</th>
<th>Total ( n )</th>
<th>Prior to 1(^{st} ) HP dose ( n )</th>
<th>After 1(^{st} ) HP dose ( n )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2</td>
<td>2</td>
<td>1(^{a})</td>
<td>1(^{b})</td>
</tr>
<tr>
<td>Grade 3</td>
<td>3</td>
<td>1(^{c})</td>
<td>2(^{d})</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^{a}\)Gastrointestinal disturbance (D4); \(^{b}\)Flu-like reaction (D72)
\(^{c}\)Elevated creatinine (D11); \(^{d}\)Elevated creatinine (D85), hypertension (D71)

VIROLOGICAL OUTCOMES

Viral load < 40 copies/mL at Baseline, Week 9 in all participants

One participant with VL = 2,300 copies/mL at Wk 24 (4 weeks post-HP); following adherence counseling, on recheck VL < 40 copies/mL

Concerns raised over patients starting ART – patients enrolled when already suppressed
Other Issues to Consider

- Cost and cost-effectiveness
- Drug Resistance
- Adherence
- Durability of protection
- Drug formulations and paediatric formulations
- Monitoring for adverse events
Cost effectiveness of 3HP vs IPT

Per 1000 individuals on ART, 3HP vs IPT estimated to avert 9 cases of TB and 1 death: Cost $9402 per DALY averted

Cost-effectiveness depended on price of rifapentine, completion of 3HP, prevalence of latent TB

At a willingness to pay of $1000 per DALY averted, 3HP is likely to be cost-effective relative to IPT only if

- Price of RPT can be greatly reduced (to ~$20 per course)
- High treatment completion (85%) can be achieved

1HP: 1.4x cost due to higher amount of rifapentine

Johnson. CID. 2018
Risk of rifampicin resistance with rifamycin based TPT

6 RCTs reported drug resistance:
- no increased risk of rifamycin resistance found.
  \[ \text{RR} = 3.45, \text{95\%CI 0.72-16.56}; P = 0.12 \]
In 3 studies of intermittent rifamycin based TPT:
- 3 cases of rifampicin resistance in 4673 individuals on rifamycin-containing regimens
- 0 cases with rifampicin resistance in 4427 in control regimens
- \[ \text{RR} = 3.3, \text{(95\%CI 0.44–34.56; P = 0.22).} \]
Adherence issues to consider

Directly observed Therapy vs Self-administered treatment

Use of Digital Adherence Tools
- 99 DOTs, Medication boxes, Video DOT

Integration with HIV service delivery

Fixed dose combinations

M Health Platforms for treatment support e.g. Keheala intervention

Indepth counselling

Self selection: adherence delivery or ?regimen
Adherence: self-adm vs DOT

An open-label, phase 4 randomized clinical trial designed as a noninferiority study with a 15% margin.

1002 adults (aged ≥18 years) recommended for treatment of LTBI United States, Spain, Hong Kong, and South Africa

Participants received DOT, self-administration with monthly monitoring, or self-administration messages.

Treatment completion: 87.2% DOT group vs 74.0% in the self-administration group, and 76.4% the self-administration-with-reminders group.

Better in the US group

Belknap, Ann Intern Med, 2017
Durability of TPT

Cumulative TB incidence

Days after enrolment

6H
36H

Samandari, AIDS. 2015 Jan 28;29(3):351-9
Durability of TPT

Cumulative TB incidence

Days after enrolment

Post-trial (no IPT) n=395

Days after trial end

Samandari, CROI2012
Issues with DSD of HIV

Screening for TB
Receiving TPT
Sputum transportation: community- or household-level case finding
Monitoring of adverse events
Limiting clinics to diagnosis of treatment with advanced disease: Infection control becomes more important
137 HIV-infected adults from 5 communities participating in the SEARCH HIV test and treat trial (NCT01864603) for IPT eligibility.

All participants were receiving differentiated HIV care consisting of nurse triage, quarterly ART visits, and patient-centered care at five government-sponsored clinics in rural Uganda.

Patients started on IPT (INH with B6) returned to clinic for a 2-week assessment for possible side effects and then monthly thereafter for 5 months.

Treatment completion (5m treatment pickup): 73% of patients completed IPT and that viral suppression remained high after initiating IPT.
Opportunities for Differentiated Service Delivery

Provision of TB PT in the context of less-intensive DSD models (e.g., community ART groups)

Distribution of drugs – use of Pele-boxes

Opt-out prescribing

Household contact tracing
  ◦ Provision of TB PT in households vs clinic facilities
  ◦ HIV-infected vs negative household contacts
  ◦ Paed contacts – paediatric formulations
Conclusions

IPT is cheap, accessible, safe; yet scale up remains low

New regimens may be an opportunity to improve coverage and completion
  ◦ 3HP is a short course regimen that
    ◦ has similar efficacy, less toxicity, better adherence and treatment completion rates, and lower risk of resistance
    ◦ Seems to be safe & lower DDI with DTG
    ◦ Is expensive, but interventions to reduce the cost of rifapentine are ongoing
  ◦ Other regimens on the horizon: 1HP and 4R

New DSD models may also provide an opportunity to improve coverage and completion, whether with IPT or newer regimens
Acknowledgements

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Thank you for joining

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