Programmatic management of latent TB infection: Global perspective and updates

Haileyesus Getahun, MD, MPH, PhD.
What is latent TB infection?

A state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of clinically manifested active TB

No gold standard test to diagnose LTBI

“Seedbeds of tuberculosis in the community”

William Osler
LTBI is part of Spectrum of TB disease

<table>
<thead>
<tr>
<th>TST</th>
<th>Negative</th>
<th>Positive</th>
<th>Positive</th>
<th>Positive</th>
<th>Usually positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGRA</td>
<td>Negative</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Usually positive</td>
</tr>
<tr>
<td>Culture</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Intermittently positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Smear</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Usually negative</td>
<td>Positive or negative</td>
</tr>
<tr>
<td>Infectious</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Sporadically</td>
<td>Yes</td>
</tr>
<tr>
<td>Symptoms</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Mild or none</td>
<td>Mild to severe</td>
</tr>
<tr>
<td>Preferred treatment</td>
<td>None</td>
<td>None</td>
<td>Preventive therapy</td>
<td>Multidrug therapy</td>
<td>Multidrug therapy</td>
</tr>
</tbody>
</table>

LTBI test concept: persistent infection and incipient TB

Figure 1. The postulated spectrum of TB infection and the progression to active TB disease (adapted from Esmail et al. 2014)

- Persistent infection
- Incipient TB
- Clinical TB

Predicts that disease cannot happen because there is no persistent infection

“Persistent infection test”

Predicts that disease occurs because it has already started...

“Incipient TB test”

Esmail et al 2014
Cobelens et al 2016
WHO End TB Strategy

TARGETS: 90% reduction of deaths and 80% reduction in incidence by 2030

1. Early diagnosis of TB including universal drug-susceptibility testing and systematic screening of contacts and high-risk groups

2. Treatment of all people with TB including drug-resistant TB, and patient support

3. Collaborative TB/HIV activities, and management of co-morbidities

4. Preventive treatment of persons at high risk and vaccination of children

Integrated, patient-centered TB care and prevention

Bold policies and supportive systems

Intensified research and innovation
Two of 10 indicators to monitor the implementation of the End TB Strategy

- TB contact investigation coverage
- LTBI treatment coverage (PLHIV & child contacts)

Target: ≥90%
LTBI management - priority action for TB elimination

1. Ensure political commitment, funding and stewardship for planning and essential services of high quality
2. Address most vulnerable and hard-to-reach groups
3. Address special needs of migrants; cross-border issues
4. Undertake screening for active TB and latent TB infection in high-risk groups and provide appropriate treatment
5. Optimize prevention and care of drug-resistant TB
6. Ensure continued surveillance and programme monitoring & evaluation
7. Invest in research and new tools
8. Support global TB prevention, care and control

Towards TB Elimination
An Action Framework for Low-Incidence Countries

World Health Organization
LTBI management contributes to the End TB Strategy targets (Incidence of TB)

Baseline

End TB Strategy: -90% by 2035

LTBI management contributes to the End TB Strategy targets (Deaths)

Baseline

Mitigate risk factors

Prevent infection

Treat latent TB

Treat active TB

Treat active and latent TB

End TB Strategy: -95% by 2035

Two-prong policy based on TB burden and income:
Recommended risk groups

**Low-TB burden**
- TB incidence <100 per 100,000
- UMICs and HICs

**High-TB burden**
- TB incidence >100 per 100,000
- LICs and LMICs

**Conditional**
- Prisoners
- HCW
- Immigrants from HBC
- Homeless persons
- Illicit drug users

**Strong**
- Child and adult contacts
- PLHIV
- Transplant patients
- Silicosis patients
- Dialysis patients
- Anti-TNF patients

- PLHIV
- Household child contacts (<5y)
LTBI testing recommendation based on burden and income

**Low-TB burden**
- TB incidence <100 per 100,000
- UMICs and HICs
  - LTBI testing (TST and/or IGRA) and a positive test is required
  - Exclude active TB according to national guidelines

**High-TB burden**
- TB incidence >100 per 100,000
- LICs and LMICs
  - LTBI testing (TST and/or IGRA) not a requirement
  - TST is encouraged in PLHIV
  - IGRA should not replace TST
  - Exclude active TB with investigations according to national guidelines
Isoniazid preventive therapy has been recommended for PLHIV and child contacts for ages
Progress of implementation of IPT in PLHIV

Only 57 countries report implementation in 2015

Nearly 1M PLHIV received IPT in 2015
Availability of data on preventive treatment among child household contacts <5yrs, 2015

87,000 (7% of estimated eligible) in 88 countries received PT
Challenges

Implementation of isoniazid preventive therapy for people living with HIV worldwide: barriers and solutions

Haileyesus Getahun\textsuperscript{a}, Reuben Granich\textsuperscript{b}, Delphine Sculier\textsuperscript{a}, Christian Gunneberg\textsuperscript{a}, Leopold Blanc\textsuperscript{a}, Paul Nunn\textsuperscript{a} and Mario Raviglione\textsuperscript{a}

\textit{AIDS} 2010, \textbf{24} (suppl 5):S57–S65

Policies and practices on the programmatic management of latent tuberculous infection: global survey

Y. Hamada,\textsuperscript{*} A. Sidibe,\textsuperscript{*} A. Matteelli,\textsuperscript{*} A. Dadu,\textsuperscript{†} M. A. Aziz,\textsuperscript{‡} M. del Granado,\textsuperscript{§} N. Nishikiori,\textsuperscript{‖} K. Floyd,\textsuperscript{*} H. Getahun\textsuperscript{*}

\textsuperscript{*}Global TB Programme, World Health Organization (WHO), Geneva, Switzerland; \textsuperscript{†}WHO Regional Office for Europe, Copenhagen, Denmark; \textsuperscript{‡}WHO Regional Office for the Eastern Mediterranean, Cairo, Egypt; \textsuperscript{§}WHO Regional Office for the Americas, Washington DC, USA; \textsuperscript{‖}WHO Regional Office for the Western Pacific, Manila, The Philippines
Key barriers for TB prevention scale up

- Does it really work?
  - Reluctance of programme managers and health workers
  - Are we not doing harm?

- Difficulty to exclude active TB and drug resistance fear
  - Inadvertent mono-treatment

- Operational barriers
  - Poor adherence of clients
  - Access to INH and who owns it
Risk of drug resistance following LTBI treatment

• No significant association of risk of drug resistance.
  - INH – RR (95%CI) = 1.45 (0.85, 2.47)
  - Rifamycin – RR (95%CI) = 1.12 (0.41, 3.08)
Challenge: multiple service provider units with no harmonisation of data and practice
LTBI digital tool key characteristics

- Free – downloadable from WHO website
- Adaptable - to country specific context and needs
- Functional - on mobile devices
- Flexible - record data offline and synchronise later and use local server

https://www.youtube.com/watch?v=QxJknYG53jM
Support the harmonization of policy recommendations across countries, regardless of the burden of TB.
Consolidated and updated LTBI guidelines

Consolidated WHO LTBI guidelines - 2017
Seven PICO questions examined for high burden countries

- Preventive treatment for HIV negative household contacts
- Screening to exclude TB in HIV negative household contacts
- Accuracy of WHO 4 symptomatic to exclude TB in PLHIV on ART
- IGRA as alternative to tuberculin skin tests
- 3 month daily rifampicin plus INH for children and adolescents
- 3-month weekly rifapentine and INH as an alternative to IPT
- Preventive treatment recommendation for MDR-TB contacts
Conclusions

• Programmatic management of LTBI is essential component of End TB Strategy and TB elimination

• Research for best test and treatment should be integral to the programmatic implementation

• WHO guidelines are being updated and large scale changes anticipated

Acknowledgment: Yohhei Hamada