Priorities and key challenges for HIV stakeholders

Reuben Granich
HIV/AIDS Department
World Health Organization
Immunosuppression, CD4 Level and TB Incidence

Havlir, Getahun et al. 2008 JAMA 300(4):423-430

“TB death zone”

Courtesy Abhishek Sharma_adapted from Havlir et al
WHO 2004 Interim Policy on Collaborative TB/HIV Activities

A. Establish NTP-NACP collaborative mechanisms
   - Set up coordinating bodies for effective TB/HIV activities at all levels
   - Conduct surveillance of HIV prevalence among TB cases
   - Carry out joint TB/HIV planning
   - Monitor and evaluate collaborative TB/HIV activities

B. Decrease burden of TB among PLHIV (the "Three I's")
   - Establish intensified TB case finding
   - Introduce INH preventive therapy
   - Ensure TB infection control in health care and congregate settings

C. Decrease burden of HIV among TB patients
   - Provide HIV testing and counselling
   - Introduce HIV prevention methods
   - Introduce co-trimoxazole preventive therapy
   - Ensure HIV/AIDS care and support
   - Introduce ARVs
PT is recommended for PPD+ HIV-infected individuals who do not have active tuberculosis. In some settings it may not be feasible to perform PPD testing. Under these circumstances the following individuals may still be considered for preventive therapy if they are infected with HIV:

- Those living in populations with a high prevalence of tuberculous infection (estimated to be >30%)
- Health care workers
- Household contacts of TB patients
- Prisoners
- Miners
- Other selected groups at high risk of acquisition or transmission of TB

Isoniazid is the recommended drug. 5mg/kg (max. 300mg) may be given as daily, self-administered therapy for six months. Individuals should be seen monthly and given only one month supply of medication at each visit.
Role of stavudine pre-therapy treatment in HIV-positive individuals

The theoretical benefits of PT are attractive. This table shows the potential disadvantages and necessary precautions.

<table>
<thead>
<tr>
<th>Potential disadvantage</th>
<th>Necessary precaution</th>
</tr>
</thead>
<tbody>
<tr>
<td>risk of drug toxicity (especially liver damage)</td>
<td>do not give to people with chronic disease or who regularly drink excessive amounts of alcohol</td>
</tr>
<tr>
<td>emergence of drug resistance (if the patient has undiagnosed TB disease and not just M tuberculosis infection)</td>
<td>in all cases exclude TB disease by CXR, in patients with cough of 3 weeks' duration or more, do spum microscopy</td>
</tr>
<tr>
<td>diminution of resources from HTF activities</td>
<td>funding must be from sources other than HTF (e.g. AIDS control programme, voluntary sector) or extra funding sources for the HTF must be found</td>
</tr>
</tbody>
</table>

145.3 WHO/UNAIDS recommendations on preventive therapy against TB in HIV-positive persons

Services needed before setting up a preventive therapy service

Before a preventive therapy service is considered, the following prerequisites should be in place:

- adequate capacity for HIV counseling which should include IEC about TB;
- sufficient trained health care staff;
- linkage between HIV care and TB control services;
- good TB control programme with high cure rates and combined default rates at the end of treatment of less than 1%.

Recommendations for a preventive therapy service

- Preventive therapy against TB should be a part of a package of care for people living with HIV/AIDS.
- Preventive therapy should be used only in settings where it is possible.
WHO Guidelines for National TB Programmes on the Management of Children

Figure 1: Approach to contact management when chest X-ray and tuberculin skin test are not readily available.

- Child in close contact with source case of smear-positive pulmonary TB
  - Under 5 years of age
    - Well
    - Symptomatic
  - Aged 5 years or over
    - Symptomatic
    - Well

- If becomes symptomatic
  - Evaluate for TB
  - No treatment

6H6

3 If TB is suspected, refer to Section 1.
6 Isoniazid 5 mg/kg daily for 6 months.
8 Unless the child is HIV-infected (in which case isoniazid 5 mg/kg daily for 6 months is indicated).
IPT is recommended for PLHIV

Intensified TB case finding in people living with HIV is essential, since TB is a curable disease. Intensified HIV case finding in people with TB is also essential, since co-trimoxazole prophylaxis can prevent complications.

WHO strongly recommends TB screening for all infants, children and adults with HIV. In addition, the information provided to all patients with HIV and caregivers of infants and children with HIV should address the risk of acquiring TB. Ways of reducing exposure, the clinical manifestations of TB, the risks of transmitting TB to others and, where appropriate, TB preventive therapy. Screening for TB is also essential to stop TB from worsening and to determine whether patients are eligible for IPT.

The TB status of HIV-infected patients should be monitored on all visits to healthcare providers and those with symptoms or signs suggestive of TB should undergo further clinical investigation. Most-at-risk populations, including injecting drug users, require specific targeting. Approaches to reducing the risk of latent TB infection progressing to TB-disease include treatment of the latent TB itself and, also, improvement in immune function as a result of antiretroviral therapy.

TB infection control measures are essential to prevent the spread of TB through populations. Appropriate infection control measures (for example, developing a TB infection control plan, “fast-tracking” coughing patients, assuring rapid TB diagnosis and improving ventilation) should be implemented and reviewed periodically to minimize the transmission risk.

Isoniazid is an effective, well tolerated and inexpensive antibiotic for TB preventive therapy, and should be provided to all people with HIV once active TB disease has been excluded. Criteria for starting isoniazid for HIV infected adults may be adapted for different country settings but, once it is started, WHO recommends isoniazid daily for six months. Specialist advice should be sought for preventive therapy for people with multidrug-resistant or extensively drug-resistant TB. Previous TB is not a contraindication to TB preventive therapy.

Key resources: 141 22 142 143 144 145 146

Interim policy on collaborative TB/HIV activities

Essential prevention and care interventions for adults and adolescents living with HIV in resource-limited settings

Intensified Case Finding (ICF), Isoniazid Preventive Therapy (IPT) and TB Infection Control (IC) for people living with HIV, April 2008,
LINK http://www.who.int/hiv/pub/meetingreports/WHO_3is_meeting_report.pdf

Isoniazid preventive therapy (IPT) for people living with HIV
WHO 2010 IPT/ICF Recommendations
Person living with HIV

---

**Screen for TB with any one of the following:**
Current cough; Fever; Weight loss; Night Sweats

---

**No**
- Assess IPT contraindications
  - **No**
    - Give IPT
  - **Yes**
    - Defer IPT

**Yes**
- Investigate for TB & other disease
  - **Other diagnosis**
    - Appropriate treatment & consider IPT
  - **Not TB**
    - Follow up & consider IPT
  - **TB**
    - Treat for TB

---

Screen for TB regularly
IPT and Drug Resistant TB (Balcell's 2006 meta-analysis)

- Review of 13 IPT trials
- ~35,000 participants
- Low risk of selecting resistance
  - (RR 1.45, 95% CI 0.85-2.47)

## GRADE profile table 10: Drug resistance and use of preventive therapy


<table>
<thead>
<tr>
<th></th>
<th>Quality assessment</th>
<th>Summary of findings</th>
<th></th>
<th></th>
<th></th>
<th>Effect</th>
<th></th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mono-resistance to IPT vs. Placebo (IPT vs. placebo)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of studies</td>
<td>Design</td>
<td>Limitations</td>
<td>Inconsistency</td>
<td>Indirectness</td>
<td>Imprecision</td>
<td>Other considerations</td>
<td>Anti-TB medications</td>
<td>No medications</td>
<td>Relative (95% CI)</td>
</tr>
<tr>
<td>7</td>
<td>randomised trials</td>
<td>Serious&lt;sup&gt;1&lt;/sup&gt;</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>Serious&lt;sup&gt;2&lt;/sup&gt;</td>
<td>none</td>
<td>11/1255 (0.9%)</td>
<td>5/1069 (0.5%)</td>
<td>RR 1.87 (0.65 to 5.38)</td>
</tr>
<tr>
<td><strong>Mono-resistance to IPT vs. Rifampin (IPT intervention vs. Rifampin as control)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>randomised trials</td>
<td>Serious&lt;sup&gt;1&lt;/sup&gt;</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>Very Serious&lt;sup&gt;3&lt;/sup&gt;</td>
<td>none</td>
<td>3/1469 (0.2%)</td>
<td>1/1469 (0.1%)</td>
<td>RR 2 (0.18 to 22.03)</td>
</tr>
</tbody>
</table>

<sup>1</sup> Incomplete accounting of patients and outcomes  
<sup>2</sup> Low number of cases and patients  
<sup>3</sup> Low number of patients
Key recommendations: INH Resistance

• Providing IPT to people living with HIV does not increase the risk of developing INH resistant TB. Therefore concerns regarding the development of INH resistance should not be a barrier to providing IPT (Strong recommendation)
WHO Rapid Advice December 2009
TB Incidence on HAART by Updated CD4 cell count

Lawn et al. AIDS. 2009 May 20. [Epub ahead of print]
54%-90% reduction in TB risk during ART
Waiting may be bad for your health


Mortality at one year

CD4\(^+\) cell count

HIV-positive

HIV-negative

Data: Hargrove *AIDS* 2010; Model: Williams *JID* 2006.
Four Key Messages

1) **Start ART earlier**
   - Put more people on ART by increasing the CD4 threshold to 350 cells/mm³

2) **Use less toxic and more patient-friendly options**
   - Reduce the risk of adverse events and improve adherence by using less toxic drugs

3) **Improve management of TB/HIV and HBV/HIV**
   - Start ART in all PLHIV who have active TB and chronic active hepatitis B disease irrespective of CD4 cell count

4) **Promote better and strategic use of laboratory monitoring**
   - Expand the role of laboratory monitoring with CD4 and viral load to improve the quality of HIV treatment and care
Recommendations translated to action

• Understand the evidence
• Understand the recommendations
• Understand how they will impact your program and patients
• Understand how to implement
• Implement and monitor benefits for your patients and community!

Prikaz rain
The first photo of a human being at Boulevard du Temple, Paris (Louis Daguerre, 1839)
Exposure time: 10 minutes
Thank you

Review Team:
Anand Date (CDC/CCID/NCHHSTP)
Martina Penazatto
Georgina Russell (NHS)
Abhishek Sharma

Co-Chairs:
Kevin De Cock, Holger Schunemann, Suzanne Hill

WHO Committee
Haileyesus Getahun (STOP TB Co-lead)
Siobhan Crowley (HIV/AIDS)
Andrew Doupe (HIV/AIDS)
Christian Gunneberg (STOP TB)
Reuben Granich (HIV/AIDS)
Malgorzata Grzemska (STOP TB)
Lulu Mussa Muhe (HIV/AIDS and CAH)
Delphine Sculier (STB TB)
Caoimhe Smyth (HIV/AIDS)