The evidence that isoniazid reduces the risk of developing active TB in PLHIV

Reuben Granich
WHO HIV/AIDS Department

Planning workshop to accelerate the implementation of HIV/TB collaborative activities in selected African countries
Addis Ababa, Ethiopia,
13-14 November 2008
Towards Universal Treatment Access

Number of people receiving antiretroviral therapy in low- and middle-income countries, 2002–2007

- North Africa and the Middle East
- East, South and South-East Asia
- Europe and Central Asia
- Latin America and the Caribbean
- Sub-Saharan Africa

People receiving antiretroviral therapy (in millions)

End 2002: 0.1
End 2003: 0.3
End 2004: 0.7
End 2005: 1.2
End 2006: 2.3
End 2007: 3.1
IPT Policy
WHO 2004 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
Different models of delivery will be appropriate in different settings and may governmental clinics, stand-alone VCT sites, NGOs, maternal health service among the range of services provided to those found to be living with HIV, should be included in the delivery of PT.
Those who have a positive HIV test should receive:
1. counselling on tuberculosis
2. screening for active tuberculosis
3. targeting of those most likely to benefit from PT
4. provision of preventive therapy to those without active tuberculosis
5. monitoring for adherence and toxicity
6. evaluation of outcome

1. Counselling on tuberculosis

People living with HIV are at risk of developing TB. They should be given encouragement to seek early diagnosis and treatment of cough and other symptoms.

2. Screening for active tuberculosis.

PT is inadequate treatment for active TB and could lead to the development of drug resistance. Active TB should therefore be excluded before PT is started. The setting of the size of the available capacity within government health services will determine which patients need to be referred. All people attending for HIV counselling and testing should have a cough, and those that do should be screened for TB. TB should be registered and treated by the TB control programme.

While it is recognised that most people with active TB will have symptoms, different screening tools or algorithms is established. It is recommended that examination from every individual before considering PT.

3. Targeting of those most likely to benefit.

PT is recommended for PPD-positive HIV-infected individuals who do not have active settings; it may not be feasible to perform PPD testing. Under these circumstances, these individuals may still be considered for preventive therapy if they are infected.

- 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
### 14.5.2 Role of isoniazid preventive treatment in HIV-positive individuals

The theoretical benefits of IPT are attractive. The 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 untreated 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 sputum microscopy</td>
</tr>
<tr>
<td>diversion of resources from NTP activities</td>
<td>funding must be from sources other than NTP (e.g., AIDS control programme, voluntary sector) or extra funding sources for the NTP must be found</td>
</tr>
</tbody>
</table>

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

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

- adequate capacity for HIV counselling, 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/failure rates at the end of treatment of less than 10%.

Recommendations for a preventive therapy service:

- Preventive therapy against TB should be 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 for 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

- 6H
- Evaluate for TB
- No treatment

If becomes symptomatic

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^a if TB is suspected, refer to Section 1.
^b isoniazid 5 mg/kg daily for 6 months.
^c 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 in 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_36meeting_report.pdf

Isoniazid preventive therapy (IPT) for people living with HIV
Implementation progress
Countries providing data on IPT prophylaxis to PLWHIV 2005

Countries reporting on IPT Prophylaxis activity

Key

- No reported activity
- Countries reporting IPT

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

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Countries providing data on IPT prophylaxis to PLWHIV 2006

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Countries providing data on IPT prophylaxis to PLHIV 2007 (provisional 7th Nov 2008)

Countries reporting on IPT Prophylaxis activity

Key

- No reported activity
- Countries reporting IPT

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Global progress in implementation of TB/HIV interventions (2002-2007)

Collaborative TB/HIV activities, 2002–2007, GLOBAL PROGRESS

Diagnosis and treatment of HIV in TB patients

- Tested for HIV
- HIV-positive
- CPT
- ART

Diagnosis, treatment and prevention of TB

- Screened for TB
- Diagnosed with TB
- IPT
AFRO progress in implementation of TB/HIV interventions (2002-2007)

Collaborative TB/HIV activities, 2002–2007,
AFRICAN REGION

### Diagnosis, treatment and prevention of TB in people with HIV

<table>
<thead>
<tr>
<th></th>
<th>Screened for TB</th>
<th>Diagnosed with TB</th>
<th>IPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>9.6</td>
<td>0.1</td>
<td>4.4</td>
</tr>
<tr>
<td>2003</td>
<td>0.8</td>
<td>0.0</td>
<td>7.9</td>
</tr>
<tr>
<td>2004</td>
<td>60.9</td>
<td>11.2</td>
<td>12.0</td>
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<tr>
<td>2005</td>
<td>47.6</td>
<td>24.3</td>
<td>22.2</td>
</tr>
<tr>
<td>2006</td>
<td>128.6</td>
<td>51.6</td>
<td>23.1</td>
</tr>
<tr>
<td>2007</td>
<td>322.3</td>
<td>153.0</td>
<td>15.4</td>
</tr>
</tbody>
</table>
AFRO implementation of IPT, 2007

Countries with reported policy on IPT (N=17)

Countries reported provision of IPT (N=7)

• What's new in 2007?
  • One more country in AFRO reporting (8)
  • Only <1% of PLHIV put on IPT in AFRO (and globally)
  • Botswana reported 6042 (39%) of the AFRO PLHIV on IPT
  • Marked decrease from 19,034 in 2006
  • South Africa is next on leader board with 5,642 up from 2,512
  • Ethiopia Mozambique and South Africa all recorded increases (1.5 fold to 5 fold) in the numbers treated with IPT.
WHO Three I's Meeting
April 2008

• WHO HIV Department leadership
• *Three I's* are essential for quality HIV care
• Re-conceptualize WHO guidelines
  • Make *Three I's* central to HIV care
  • Develop new TB screening approach
  • TB screening leads to IPT and IC
  • IPT for those without TB symptoms
  • HIV care and treatment should include IC for TB
• WHO Three I's "push" and "pull" advocacy
Modeled Trends in Impact of Interventions with Increasing Coverage on TB Burden in Kenya, 1980 to 2030

• Currie et al. AIDS 2003, 17:2501-2508
TB Cases Averted Over 10 Years, 100% Coverage

Detection Rate | Cure Rate | TLTI to all HIV+ | Lifelong TLTI to all HIV+ | HAART 80% Adherence | HAART 100% Adherence | Reduction in HIV Incidence

Number of TB Cases Averted

Kenya
Evidence for IPT
What the evidence tells us…..

• IPT reduces risk of TB in people living with HIV:
  • 62% reduction in PPD+
  • 36% reduction overall
• IPT benefit may fade after 1-2 years in high prevalence settings
• HAART reduces TB risk, but still benefit of IPT
• Risk of selecting for resistance with IPT appears very low
• Active TB can be ruled out by clinical or laboratory screening in most patients
• No evidence of increased toxicity with IPT and HAART
1999 Bucher Systematic Review
Duration of Protective Benefit for IPT

**Results**

2,367 Persons in the intervention (7 Studies)

RR for developing TB: 0.58 (CI: 0.43 – 0.80);

For TB-related death: 0.94 (CI: 0.83 – 1.07).

In TST+/-, RR for TB incidence 0.40 (CI: 0.24-0.65) and 0.84 (CI: 0.54 – 1.30), respectively

Protective benefit ranged from 0.4 - 37 months

**Conclusion**

Prophylaxis with IPT provides a sustained reduction against the risk of contracting TB for persons with HIV infection

Cochrane Review:  
Aggregate of PPD+, PPD-, and Unknown


- **11 clinical trials including 8130 randomized participants**
- **Overall protective effect of RR 0.64 (95% CI 0.51, 0.81)**
  - Effect was greatest on those who were TST+ (RR 0.38; 95% CI 0.25, 0.57)
  - Effect on those who were TST negative was not significant (RR 0.83; 95% CI 0.58, 1.18)
- **The initial effect of INH does appear to decline over time**
How long does TB preventive therapy work after randomization?

Mwinga et al., AIDS 1998;12:2447
TB rates by ARV and INH treatment status
Rio de Janeiro, Brazil, 2003-2005

<table>
<thead>
<tr>
<th>Exposure category</th>
<th>Person-Years</th>
<th>TB cases</th>
<th>Incidence Rate (per 100 PYs) (95% CI)</th>
<th>Incidence Rate Ratio (95% CI)</th>
<th>Adjusted Hazard Ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naïve</td>
<td>3,865</td>
<td>155</td>
<td>4.01 (3.40-4.68)</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td>HAART only</td>
<td>11,627</td>
<td>221</td>
<td>1.90 (1.66-2.17)</td>
<td>0.48 (0.39-0.59)</td>
<td>0.41 (0.31-0.54)</td>
</tr>
<tr>
<td>Isoniazid only</td>
<td>395</td>
<td>5</td>
<td>1.27 (0.41-2.95)</td>
<td>0.32 (0.10-0.76)</td>
<td>0.57 (0.18-1.82)</td>
</tr>
<tr>
<td>Both</td>
<td>1,253</td>
<td>10</td>
<td>0.80 (0.38-1.47)</td>
<td>0.20 (0.09-0.91)</td>
<td>0.24 (0.11-0.53)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>17,140</td>
<td>391</td>
<td>2.28 (2.06-2.52)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for age, sex, CD4, prior history of TB

Effect of Routine Isoniazid Preventive Therapy on Tuberculosis Incidence Among HIV-Infected Men in South Africa: A Novel Randomized Incremental Recruitment Study

Alison D. Grant, M.D., M.B., B.S.
Salome Chandwana, M.B., B.S.
Katherine L. Fuld, M.B., B.S.
John H. Day, M.B., B.S.
Elizabeth L. Churchett, M.B., B.S.
Richard L. Hamilton, M.D.
Kevin M. De Cock, M.D.
Richard J. Hayes, M.D.
Gavin J. Churchyard, M.B., B.S.

A Markers of the increased incidence of tuberculosis (TB) in many countries are the increasing numbers of cases of HIV infection. The objectives of this study were to determine the impact of isoniazid preventive therapy on the incidence of TB in a group of HIV-infected men in South Africa. The study included 1,665 HIV-infected men aged 15-59 years who were enrolled in a randomized clinical trial of isoniazid preventive therapy versus placebo. The incidence of TB among the study participants was significantly lower in the group receiving isoniazid preventive therapy compared to the placebo group. The incidence of TB was 1.7% per year in the placebo group and 0.6% per year in the group receiving isoniazid preventive therapy. The study also showed that the incidence of TB was lower in men who had a history of TB infection than in those who did not. These findings suggest that isoniazid preventive therapy can effectively reduce the incidence of TB in HIV-infected men. The results of this study are important for the development of strategies to control the spread of TB in HIV-infected populations.
Fig. 1. Kaplan–Meier curves comparing survival according to the use of anti-tuberculosis chemoprophylaxis. The dashed vertical line indicates the median interval to the start of chemoprophylaxis.

Pinho, AIDS 2001
IPT and Drug Resistant TB (Balcell's 2006 meta-analysis)

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

Value of chest radiography in a tuberculosis prevention programme for HIV-infected people, Botswana

- 935 PLHIV in Botswana
- 692 (74%) no signs
- 123 (18%) lost during radiography
- 536/560 (96%) "normal"
- 24/560 "abnormal"
- 1 (0.2%) had TB

Botswana experience 2000-2001
Isoniazid-related Hepatotoxicity

United States Public Health Service 1971-1973
13,838 persons on IPT
8 Deaths (7 in Baltimore; 0.0005%)

Centers for Disease Control 1972-1988
1,084,760 started on IPT
152 reported IPT-related deaths (0.00014%)
32 confirmed IPT-related deaths (0.00002%)

Death reports could not be verified due to lack of diagnostic markers for hepatitis

Sources:
Benefit of IPT following treatment of active TB in PLHIV

Incidence Rate Ratios & 95% CI

Reference

Haller (1999) 0.3
Fitzgerald (2000) 0.18
Churchyard (2002) 0.45

Woldehanna and Volmink, Cochrane Review 2006
IPT is Cost-Effective

<table>
<thead>
<tr>
<th></th>
<th>Primary cases (per 100,000)</th>
<th>Secondary cases (per 100,000)</th>
<th>Medical care and social costsb (per person)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No preventive therapy</td>
<td>38,126</td>
<td>19,667</td>
<td>$111.88</td>
</tr>
<tr>
<td><strong>INH for 6 months</strong></td>
<td>30,020</td>
<td>15,463</td>
<td><strong>$87.71</strong></td>
</tr>
<tr>
<td>INH + RIF for 3 months</td>
<td>30,913</td>
<td>15,926</td>
<td>$106.76</td>
</tr>
<tr>
<td>RIF + PZA for 2 months</td>
<td>29,246</td>
<td>15,061</td>
<td>$103.72</td>
</tr>
</tbody>
</table>

aTB, tuberculosis; INH, isoniazid; RIF, rifampin; PZA, pyrazinamide. bIncludes cost of preventive therapy and treating adverse events of preventive therapy.

<table>
<thead>
<tr>
<th></th>
<th>TB medical care costs (per person)</th>
<th>TB medical care and social costs/person a (savings)</th>
<th>TB medical care and social costs (savings)/persona for primary and secondary cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INH for 6 months</strong></td>
<td>$13.01</td>
<td>($12.72)</td>
<td>($24.16)</td>
</tr>
<tr>
<td>INH + RIF for 3 months</td>
<td>$27.98</td>
<td>$5.08</td>
<td>($5.11)</td>
</tr>
<tr>
<td>RIF + PZA for 2 months</td>
<td>$32.55</td>
<td>$4.37</td>
<td>($8.16)</td>
</tr>
</tbody>
</table>

aIncludes cost of preventive therapy and treating adverse events of preventive therapy. Figures in parentheses represent savings. TB, tuberculosis; INH, isoniazid; RIF, rifampin; PZA, pyrazinamide.
Setting IPT Targets?
GLOBAL REPORTING of HIV positive TB case detection and provision of CPT and ART

2007

<table>
<thead>
<tr>
<th>Year</th>
<th>Estimated TB HIV</th>
<th>TB HIV detected</th>
<th>CPT provision</th>
<th>ART provision</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>699,156</td>
<td>28,432</td>
<td>9,174</td>
<td>10,186</td>
</tr>
<tr>
<td>2004</td>
<td>714,652</td>
<td>45,714</td>
<td>20,541</td>
<td>9,823</td>
</tr>
<tr>
<td>2005</td>
<td>712,555</td>
<td>103,741</td>
<td>57,986</td>
<td>28,864</td>
</tr>
<tr>
<td>2006</td>
<td>702,393</td>
<td>193,706</td>
<td>151,467</td>
<td>65,330</td>
</tr>
<tr>
<td>2007</td>
<td>695,755</td>
<td>291,596</td>
<td>195,295</td>
<td>70,939</td>
</tr>
</tbody>
</table>
## WHO-PEPFAR Collaboration: Setting and achieving targets

### Ethiopia
- HIV testing for 20,000 TB patients (>100% target)
- CPT to 5,000 HIV/TB patients (91% target)
- ART for 5,000 eligible HIV/TB patients (53% target)

### Kenya
- HIV testing for at least 80% of new TB patients (84%)
- CPT for 80% of HIV/TB patients (90%)
- 80% of HIV/TB patients access ART services (28%)

### Rwanda
- HIV testing of 75% of TB patients (88%)
- CPT for 80% of HIV/TB patients registered (61%)
- ART for 40% of HIV-infected TB patients (36%)
Towards Universal Access to High Quality HIV/TB Services

Number of people accessing high quality HIV/TB Services

Scaling up HIV/TB services in the health sector

Progress Report 2009

World Health Organization UNAIDS UNICEF
### Global Demand for CTX/INH Co-Formulation Based on 2004-2007 Data

<table>
<thead>
<tr>
<th>Countries with &gt; 1% of Global TB/HIV Burden</th>
<th># of People with HIV</th>
<th># of HIV/TB Cases</th>
<th>Total Eligibility for IPT/CPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>620,000</td>
<td>8,947</td>
<td>611,052</td>
</tr>
<tr>
<td>Cote d’Ivoire</td>
<td>750,000</td>
<td>9,863</td>
<td>740,137</td>
</tr>
<tr>
<td>DRC</td>
<td>1,000,000</td>
<td>23,123</td>
<td>976,877</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>1,000,000</td>
<td>18,488</td>
<td>981,511</td>
</tr>
<tr>
<td>India</td>
<td>5,700,000</td>
<td>26,989</td>
<td>5,673,011</td>
</tr>
<tr>
<td>Kenya</td>
<td>1,300,000</td>
<td>20,034</td>
<td>1,279,965</td>
</tr>
<tr>
<td>Lesotho</td>
<td>270,000</td>
<td>5,740</td>
<td>264,260</td>
</tr>
<tr>
<td>Malawi</td>
<td>940,000</td>
<td>15,548</td>
<td>924,451</td>
</tr>
<tr>
<td>Mozambique</td>
<td>1,800,000</td>
<td>26,304</td>
<td>1,773,696</td>
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<td>Nigeria</td>
<td>2,900,000</td>
<td>43,895</td>
<td>2,856,105</td>
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<td>Russian Fed.</td>
<td>940,000</td>
<td>8,312</td>
<td>931,687</td>
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<td>South Africa</td>
<td>5,500,000</td>
<td>178,624</td>
<td>5,321,376</td>
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<tr>
<td>Swaziland</td>
<td>220,000</td>
<td>6,280</td>
<td>213,720</td>
</tr>
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<td>Tanzania</td>
<td>1,400,000</td>
<td>24,600</td>
<td>1,375,399</td>
</tr>
<tr>
<td>Uganda</td>
<td>1,000,000</td>
<td>19,441</td>
<td>980,559</td>
</tr>
<tr>
<td>Zambia</td>
<td>1,100,000</td>
<td>23,322</td>
<td>1,076,678</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>1,700,000</td>
<td>29,762</td>
<td>1,670,238</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>28,140,000</strong></td>
<td><strong>489,271</strong></td>
<td><strong>27,650,728</strong></td>
</tr>
</tbody>
</table>
## Global CTX/IPT Demand Based on 2004-2007 Data

<table>
<thead>
<tr>
<th>Countries with &gt; 1% of Global TB/HIV Burden</th>
<th>Total Eligibility for IPT/CPT</th>
<th>CD4 &lt; 350 (40%)</th>
<th>CD4 &lt; 200 (25%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>611,053</td>
<td>244,421</td>
<td>152,763</td>
</tr>
<tr>
<td>Cote d’Ivoire</td>
<td>740,137</td>
<td>296,055</td>
<td>185,034</td>
</tr>
<tr>
<td>DRC</td>
<td>976,877</td>
<td>390,751</td>
<td>244,219</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>981,512</td>
<td>392,605</td>
<td>245,378</td>
</tr>
<tr>
<td>India</td>
<td>5,673,011</td>
<td>2,269,204</td>
<td>1,418,253</td>
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<td>Kenya</td>
<td>1,279,966</td>
<td>511,986</td>
<td>319,991</td>
</tr>
<tr>
<td>Lesotho</td>
<td>264,260</td>
<td>105,704</td>
<td>66,065</td>
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<tr>
<td>Malawi</td>
<td>924,452</td>
<td>369,781</td>
<td>231,113</td>
</tr>
<tr>
<td>Mozambique</td>
<td>1,773,696</td>
<td>709,479</td>
<td>443,424</td>
</tr>
<tr>
<td>Nigeria</td>
<td>2,856,105</td>
<td>1,142,442</td>
<td>714,026</td>
</tr>
<tr>
<td>Russian Fed.</td>
<td>931,688</td>
<td>372,675</td>
<td>232,922</td>
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<tr>
<td>South Africa</td>
<td>5,321,376</td>
<td>2,128,550</td>
<td>1,330,344</td>
</tr>
<tr>
<td>Swaziland</td>
<td>213,720</td>
<td>85,488</td>
<td>53,430</td>
</tr>
<tr>
<td>Tanzania</td>
<td>1,375,400</td>
<td>550,160</td>
<td>343,850</td>
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<tr>
<td>Uganda</td>
<td>980,559</td>
<td>392,224</td>
<td>245,140</td>
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<td>Zambia</td>
<td>1,076,678</td>
<td>430,671</td>
<td>269,170</td>
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<tr>
<td>Zimbabwe</td>
<td>1,670,238</td>
<td>668,095</td>
<td>417,560</td>
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<td><strong>TOTAL</strong></td>
<td><strong>27,650,729</strong></td>
<td><strong>11,060,292</strong></td>
<td><strong>6,912,682</strong></td>
</tr>
</tbody>
</table>
Next steps

- Fast-track implementation of new WHO IPT/ICF guidelines (2009)
- WHO and stakeholder technical support for national governments to support *Three I's* implementation
- Implement harmonized HIV/TB indicators
- Set national targets?
- Engage the community
- Strengthen engagement of country-level partners
IPT is Cost-Effective

Cape Town, South Africa

Measure ProTEST Package at Three Primary Clinics

Average cost/person completing IPT: US$92-183
Cost/TB case averted: US$486-962

Kampala, Uganda

Cost-Utility of Two IPT Programs in a VCT Center

IPT program with target testing: 11/100QALYs;
  treat all strategy: 30/100QALYs

ICER for target testing: US$102/QALYs;
  treat all strategy: US$106/QALYs gained

Source: Shrestha R. Cost-Utility of Tuberculosis Prevention among HIV-Infected Adults in Kampala, Uganda. INT J TUBERC LUNG DIS 11(7):747-754
Resource mobilization:
What about Global Fund? PEPFAR?
Percentage of TB and HIV proposals with TB/HIV component (R4-R6)

Any one of the 12 collaborative TB/HIV activities mentioned in objectives or SDA of the proposal.
Global Fund 18th Board Meeting: decision point 12 (Delhi 2008)

Decision Point GF/B18/DP12:

1. The Board acknowledges and commends the Stop TB Partnership’s Global Plan to Stop TB 2006-2015 (the “Global Plan”), which aims to have current tuberculosis prevalence and death rates by 2015. As the largest external financier of tuberculosis programs worldwide, the Global Fund is committed to ensuring that it is a key partner in supporting the implementation of the Global Plan.

2. The Board recognizes that almost 40% of the estimated 9.2 million new tuberculosis infections per year worldwide are not detected/diagnosed, posing a major risk to an increased transmission of tuberculosis. Therefore, the Board encourages applicants to the Global Fund and implementers of tuberculosis programs to develop innovative actions to accelerate case detection and effective treatment of these cases. This will require investment to: increase the speed and precision of tuberculosis diagnosis using new tools; strengthen in-country monitoring and evaluation (M&E) and surveillance systems; increase community-based responses. The Board specifically urges use of the dual track financing and other mechanisms to expand funded, well-trained community-based services for case detection and directly observed treatment (DOTS) provision.

3. The Board recognizes that the slow progress in implementing core TB-HIV collaborative services is a risk to achieving successful outcomes under current and future Global Fund tuberculosis and HIV grants. Given the large gap in tuberculosis screening in HIV settings and vice versa, the Board emphasizes that all applicants should include and implement significant, robust tuberculosis interventions in their HIV/AIDS proposals and HIV/AIDS interventions in their tuberculosis proposals. The Board requests the Secretariat to review the guidelines for phase 2 requests to require that, in respect of continued funding for tuberculosis or HIV grants, CCMs explain their plans for scale up to universal TB-HIV collaborative services and explicitly articulate what TB-HIV activities, funding, and milestones will be included in each proposal.

4. Noting the upcoming Ministerial meeting on MDR-TB in Beijing, the Board of the Global Fund urges substantive proposals be submitted to support MDR- and XDR-TB plans and that countries make use of budget and planning flexibilities to ensure programs utilize emerging technologies. The Board recognizes that the first line in reducing the risk of MDR- and XDR-TB is through effective DOTS treatment programs with high cure rates. In addition to expanding quality DOTS to prevent MDR-TB, a successful response will necessarily include a major scale up of drug susceptibility testing for all people suspected of having drug-resistant tuberculosis and effective treatment of these cases by expanding community-based DOTS-Plus programs. As such, the Board urges applicants to scale up laboratory capacity, and community-based management of MDR- and XDR-TB cases.

5. Recognizing that, according to the Global Plan to Stop TB, there is a gap between estimated needs and available resources, the Board urges countries to undertake a comprehensive situational gap analysis and to submit ambitious proposals that are appropriate to the specific country context through future funding Rounds, or the Rolling Continuation Channel, or national strategy applications, which requests for funding are particularly aimed at achieving major and rapid expansion of case detection with high cure rates, universal coverage of TB-HIV collaborative services, as well as scaling up laboratory and care capacities to expand DOTS and to address MDR- and XDR-TB, and at
PEPFAR’s TB/HIV Investments

• TB/HIV is a priority program area in PEPFAR

• PEPFAR support for TB/HIV programs has increased almost 700% over four years – from $18.8 million in 2005, to $48.6 million in 2006, to $130.9 million in 2007 and $169 million in 2008.

• Support efforts to mitigate the impact of TB/HIV need to be integral across technical areas

• As of September 2007, PEPFAR had supported care for approximately 367,000 TB/HIV co-infected people in the 15 focus countries
## Cochrane Review: Isoniazid vs. Placebo in PLHIV (PPD-)

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Relative Risk (Fixed) 95% CI</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>02 PPD-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fitzgerald 2001</td>
<td>6/126</td>
<td>4/111</td>
<td></td>
<td>2.8</td>
<td>1.32 [0.38, 4.56]</td>
</tr>
<tr>
<td>Gordin 1997</td>
<td>4/260</td>
<td>6/257</td>
<td></td>
<td>4.0</td>
<td>0.66 [0.19, 2.31]</td>
</tr>
<tr>
<td>Hawken 1997</td>
<td>11/235</td>
<td>8/224</td>
<td></td>
<td>5.4</td>
<td>1.31 [0.54, 3.20]</td>
</tr>
<tr>
<td>Mwinga 1998</td>
<td>27/351</td>
<td>17/166</td>
<td></td>
<td>15.3</td>
<td>0.75 [0.42, 1.34]</td>
</tr>
<tr>
<td>Pape 1993</td>
<td>2/20</td>
<td>5/35</td>
<td></td>
<td>2.4</td>
<td>0.70 [0.15, 3.28]</td>
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<tr>
<td>Rivero 2002</td>
<td>7/242</td>
<td>4/77</td>
<td></td>
<td>4.0</td>
<td>0.56 [0.17, 1.85]</td>
</tr>
<tr>
<td>Whalen 1997- anergy</td>
<td>9/395</td>
<td>10/323</td>
<td></td>
<td>7.3</td>
<td>0.74 [0.30, 1.79]</td>
</tr>
</tbody>
</table>

**Subtotal (95% CI)**

|                          | 1629         | 1193        | 41.2                              | 0.83 [0.58, 1.18] |

**Total events:** 66 (Treatment), 54 (Control)

**Test for heterogeneity chi-square:** 2.33 df=6 p=0.89 P =0.0%

**Test for overall effect z=1.03 n=0.3**

---

Cochrane Review: Isoniazid vs. Placebo in PLHIV (PPD Unknown)

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Relative Risk (Fixed) 95% CI</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed) 95% CI</th>
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</thead>
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<tr>
<td>03 PPD unknown</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hawken 1997</td>
<td>9/40</td>
<td>7/49</td>
<td></td>
<td>4.2</td>
<td>1.58 [0.64, 3.85]</td>
</tr>
<tr>
<td>Mwinga 1998</td>
<td>19/251</td>
<td>16/124</td>
<td></td>
<td>14.2</td>
<td>0.59 [0.31, 1.10]</td>
</tr>
<tr>
<td>Subtotal</td>
<td>291</td>
<td>173</td>
<td></td>
<td>18.3</td>
<td>0.81 [0.49, 1.34]</td>
</tr>
</tbody>
</table>

Total events: 28 (Treatment), 23 (Control)
Test for heterogeneity chi-square=3.13 df=1 p=0.08 P =68.0%
Test for overall effect z=0.82 p=0.4

Currie et al.

## Total annual effects:

<table>
<thead>
<tr>
<th>Intervention</th>
<th>DALYs Gained vs. Baseline Scenario</th>
<th>Deaths Averted vs. Baseline Scenario</th>
<th>TB Cases Averted vs. Baseline Scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline scenario†</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Improve TB Detection Rate</td>
<td>551,184</td>
<td>26,015</td>
<td>59,436</td>
</tr>
<tr>
<td>Improve TB Cure Rate</td>
<td>220,939</td>
<td>10,087</td>
<td>43,378</td>
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<tr>
<td>Improve TB Cure Rate and Case Detection Rate</td>
<td>676,748</td>
<td>31,769</td>
<td>97,795</td>
</tr>
<tr>
<td>TLTI, 6 months</td>
<td>7,366</td>
<td>549</td>
<td>2,119</td>
</tr>
<tr>
<td>TLTI, Lifetime</td>
<td>20,178</td>
<td>2,075</td>
<td>5,480</td>
</tr>
<tr>
<td>ART, 50% dropout rate</td>
<td>585,232</td>
<td>7,390</td>
<td>4,025</td>
</tr>
<tr>
<td>ART, 20% dropout rate</td>
<td>834,071</td>
<td>23,794</td>
<td>12,183</td>
</tr>
<tr>
<td>ART, 5% dropout rate</td>
<td>1,205,912</td>
<td>56,872</td>
<td>27,446</td>
</tr>
<tr>
<td>ART to TB patients</td>
<td>152,604</td>
<td>5,089</td>
<td>1,126</td>
</tr>
</tbody>
</table>
Community-wide IPT
Bethel district, Alaska

Passive CFT
INH RCT: 42% pop INH
12mos

INH all residents

ARI
TB incidence
(Per 100 pyrs)
TB Cases Averted Over 10 Years, 1% Increase in Coverage

Kenya

Detection Rate, Cure Rate, TLTI to all HIV+, Lifelong TLTI to all HIV+, HAART 80% Adherence, HAART 100% Adherence, Reduction in HIV Incidence

Number of TB Cases Averted