IPT INDABA:
Why the focus on IPT now?

04 September, 2013

Dr CI Azih
TB: Global Picture
## The Global Burden of TB - 2011

<table>
<thead>
<tr>
<th>Category</th>
<th>Estimated number of cases</th>
<th>Estimated number of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>All forms of TB</td>
<td>8.7 million (8.3–9.0 million)</td>
<td>1.4 million* (1.3–1.6 million)</td>
</tr>
<tr>
<td>HIV-associated TB</td>
<td>1.1 million (13%) (1.0–1.2 million)</td>
<td>430,000 (400,000–460,000)</td>
</tr>
<tr>
<td>Multidrug-resistant TB</td>
<td>Up to 0.5 million</td>
<td>Unknown, but probably &gt; 150,000</td>
</tr>
</tbody>
</table>

* Including deaths attributed to HIV/TB

Source: WHO Global Tuberculosis Report 2012
Who carries the burden of tuberculosis? …mostly, the most vulnerable

Poor, crowded & poorly ventilated settings

Half a million women and over 65,000 children die of TB each year; 10 million “TB” orphans

Migrants, prisoners, minorities, refugees face risks, discrimination & barriers to care

TB linked to HIV infection, malnutrition, alcohol, drug and tobacco use, diabetes
Incidence rates, 2011

Highest rates in Africa, linked to high rates of HIV infection
~80% of HIV+ TB cases in Africa
TB/HIV co-infection: 80% of burden in Africa

- 80% of all TB/HIV cases are in Africa
- TB leading cause of death in PLHIV
- ¼ of PLHIV worldwide die due to TB.
- PLHIV infected with TB 20-40 times more likely to develop active TB.
- Untreated, TB in PLHIV leads to death in weeks
Malawi – Less TB with more ART
IPT: Global Perspective
IPT: Definition

Use of an ATT drug called Isoniazid (INH), given to individuals with latent (dormant) mycobacterium tuberculosis infection, in order to prevent progression of the dormant infection to active disease.
People living with HIV receiving IPT 2009

*Data as per October 2010*
Background

- Among people living with HIV, TB is the most frequent life-threatening opportunistic infection and a leading cause of death.

- HIV care settings should implement the WHO Three I’s strategy:
  - intensified TB case-finding,
  - isoniazid preventive therapy (IPT)
  - infection control, at all clinical encounters.

- WHO Consolidated Guidelines, 2013 – Page 158
Rationale for IPT

- 10% **lifetime** risk of developing active TB if infected with M. tuberculosis alone
- 5-10% **annual** risk of developing active TB if co-infected with HIV and M. tuberculosis
- IPT is meant to prevent progression of latent TB to active disease
- INH shown to decrease incidence of TB among HIV-infected persons by about 40%
  - The protection period ranges from <1 year to 3 years*

Rationale for IPT

• Presence of an asymptomatic state in the patient infected with M. tuberculosis, prior to the development of active disease.

• The clinical manifestation of this asymptomatic state is a positive PPD or IGRA.

• The bacterial load at this time is several orders of magnitude lower than during active disease, and the patient may therefore be treated with a single agent, or for a reduced duration with two agents.
Number Needed to Treat (NNT)

• Among HIV + / PPD + patients
  – To prevent 1 death
    • 30
  – To prevent 1 incident case of TB
    • 20

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., T.B. Salome Chirumバンツ, M.D., M.B., T.B.
Katherine L. Delong, M.D.
John R. Boy, M.D., M.B.
Elizabeth L. Couttes, M.D., M.B.
Richard E. Chimes, M.D.
Kevin M. De Cock, M.D.
Richard J. Barlow, D.P.
Gavin J. Churchyard, M.D., M.B., T.B.

A
n
1655 SA mineworkers with HIV

38% reduction in TB overall

46% reduction in face of no history of TB

TB incidence 9/100 person years afterwards

Conclusions Enrollment in a clinic offering primary isoniazid preventive therapy to HIV-infected adults reduced tuberculosis incidence by 38% overall and by 46% among individuals with no history of tuberculosis prior to the study. Tuberculosis incidence remained high despite isoniazid preventive therapy, and further work is needed to determine how to use additional interventions most effectively to reduce morbidity and mortality due to tuberculosis in HIV-infected persons.

JAMA. 2005;293:2719-2725
IPT Efficacy in HIV+ Children

Fig 2  Survival in children on isoniazid (INH) or placebo

Zar et al. BMJ. 2007 Jan 20;334(7585):136
IPT in HIV+ Children

• IPT had a greater protection on childhood TB, reducing chance of developing probable or definite TB by 72%.
  – This effect is greater than the 36% reduction in risk of active disease overall and the 60% reduction in PPD-positive found in adult (Woldehanna 2004).
  – The effect in children was the same irrespective of PPD status, probably reflecting the insensitivity of PPD testing in HIV-infected children or the efficacy of preventative therapy for primary TB disease.

• INH had a significant impact on all-cause mortality, reducing risk of death by 54% in contrast to the absence of effect on mortality in HIV-infected adults.

## Excess Occupational Risk

<table>
<thead>
<tr>
<th>Work location</th>
<th>TB incidence rate ratio (relative to rate in general population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient facilities</td>
<td>4.2 – 11.6</td>
</tr>
<tr>
<td>General medical wards</td>
<td>3.9 – 36.6</td>
</tr>
<tr>
<td>Inpatient facilities</td>
<td>14.6 – 99.0</td>
</tr>
<tr>
<td>Emergency rooms</td>
<td>26.6 – 31.9</td>
</tr>
<tr>
<td>Laboratories</td>
<td>42.5 to 135.3</td>
</tr>
</tbody>
</table>


## IPT Effectiveness

### South African Miners, 2003

<table>
<thead>
<tr>
<th>IPT usage</th>
<th>TB incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPT (n=338)</td>
<td>8.6/100 person years</td>
</tr>
<tr>
<td>No IPT (n=221)</td>
<td>19.1/100 person yrs</td>
</tr>
</tbody>
</table>


Overall 55% reduction in TB incidence
IPT Effectiveness

- IPT for PPD-reactive, HIV-infected patients reduces their lifetime risk of active TB to 4% or less [1].

- Although ART lowers risk of TB due to immune restoration, IPT further reduces the incidence of TB compared to ART alone [2].

## IPT Effectiveness Related to ART

TB Incidence in 11,026 HIV-infected patients in Brazil

<table>
<thead>
<tr>
<th></th>
<th>No INH</th>
<th>Yes INH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No ART</strong></td>
<td>4.01/100 person years</td>
<td>1.27/100 person years</td>
</tr>
<tr>
<td><strong>Yes ART</strong></td>
<td>1.90/100 person years</td>
<td>0.80/100 person years</td>
</tr>
</tbody>
</table>

76% reduction with both INH and ART when adjusted for age, previous TB diagnosis and CD4 count at baseline.

Schematic of Risk of TB and Change in CD4 Cell Count From Onset of HIV Seroconversion

## Joint Effects of ART & IPT on TB Incidence

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted RH (95% CI)</th>
<th>P value</th>
<th>Adjusted RH(^b) (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naive</td>
<td>1</td>
<td>&lt;0.01</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ART only</td>
<td>0.55 (0.45–0.68)</td>
<td>&lt;0.01</td>
<td>0.41 (0.31–0.54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IPT only</td>
<td>0.36 (0.15–0.89)</td>
<td>0.02</td>
<td>0.57 (0.18–1.82)</td>
<td>0.34</td>
</tr>
<tr>
<td>ART and IPT</td>
<td>0.23 (0.12–0.45)</td>
<td>&lt;0.01</td>
<td>0.24 (0.11–0.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous TB</td>
<td>1.26 (0.99–1.60)</td>
<td>0.06</td>
<td>1.19 (0.88–1.60)</td>
<td>0.25</td>
</tr>
<tr>
<td>CD4 cell count</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200–349</td>
<td>0.34 (0.26–0.46)</td>
<td>&lt;0.001</td>
<td>0.34 (0.25–0.45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>350–499</td>
<td>0.22 (0.15–0.31)</td>
<td>&lt;0.001</td>
<td>0.19 (0.13–0.27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥ 500</td>
<td>0.13 (0.09–0.19)</td>
<td>&lt;0.001</td>
<td>0.10 (0.07–0.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>1</td>
<td>0.15</td>
<td>0.98 (0.73–1.31)</td>
<td>0.88</td>
</tr>
<tr>
<td>30–39</td>
<td>0.84 (0.65–1.07)</td>
<td>0.15</td>
<td>0.98 (0.73–1.31)</td>
<td>0.88</td>
</tr>
<tr>
<td>40–49</td>
<td>0.61 (0.46–0.81)</td>
<td>&lt;0.01</td>
<td>0.69 (0.49–0.97)</td>
<td>0.03</td>
</tr>
<tr>
<td>≥ 50</td>
<td>0.42 (0.28–0.62)</td>
<td>&lt;0.01</td>
<td>0.53 (0.33–0.83)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

ART, Antiretroviral therapy; CI, confidence interval; IPT, isoniazid preventive therapy; RH, relative hazard; TB, tuberculosis.

\(^a\)Does not include 1524 patients with unknown CD4 cell counts at baseline.

\(^b\)Adjusted for all other variables in the table.

Golub et al. AIDS. 2007 Jul 11;21(11):1441-8
Evidence: Effect of IPT on TB

Meta-analysis of 7 randomised clinical trials (N=4134)

Relative risk, 95% CI

Placebo
Overall
TST+
TST-

Woldehanna 2004, Cochrane review
IPT provision for PLHIV, 2005-2009

* Data as per June 2010
Implementation challenges

• Ruling out TB is major barrier to implementing IPT
• Chronic cough alone is insensitive predictor of TB
• Screening tools are not standardised and vary
• Role of CXR is not clear and inconsistent
• Concerns that IPT causes drug resistance
• Demand from countries for TB screening algorithm
SWAZILAND
TB/HIV & IPT: Where are we?
Background

• High HIV burden – 26% prevalence
• High TB burden – 1370/100,000
  – High MDR burden  - 7.9% in new cases,
    - 33.6% in previously treated
• High TB/HIV co-infection rate – 73% (March)
• High mortality rate TB/HIV – 13%
HIV Testing and Counseling

HIV testing Uptake at TB clinics from October 2008 to March 2013

- Total # seen: 2041, 1917, 2497, 2949, 2747, 2698, 2566, 2822, 2903, 2243, 2018, 2368, 2277, 2497, 2147, 1804, 1438, 1324, 1602, 1300, 922, 1441, 1457, 1135
- # of tested: 1501, 1647, 2070, 2502, 2420, 2147, 2147, 2497, 2277, 2028, 1857, 1740, 2100, 1693, 1195, 1879, 1900, 1517
- # tested HIV positive: 1405, 1306, 1678, 2026, 2016, 1803, 1816, 1995, 1804, 1602, 1438, 1324, 1602, 1300, 922, 1441, 1457, 1135
- HTC Uptake among registered TB cases: 74, 86, 83, 85, 88, 80, 84, 88, 78, 90, 92, 73, 94, 95, 95, 91, 96, 99

Proportion of TB patients receiving HIV testing
Cotrimoxazole Preventive Therapy

Cotrimoxazole Preventive Therapy uptake among TB/HIV coinfected patients

<table>
<thead>
<tr>
<th>Month</th>
<th># of all HIV +ve TB patients</th>
<th># on CPT</th>
<th>CPT Uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oct-Dec 08</td>
<td>1816</td>
<td>1713</td>
<td>81%</td>
</tr>
<tr>
<td>Jan-Mar 09</td>
<td>1678</td>
<td>1678</td>
<td>88%</td>
</tr>
<tr>
<td>Apr-Jun 09</td>
<td>2026</td>
<td>2016</td>
<td>92%</td>
</tr>
<tr>
<td>Jul-Sep 09</td>
<td>2016</td>
<td>1995</td>
<td>97%</td>
</tr>
<tr>
<td>Oct-Dec 09</td>
<td>1816</td>
<td>1804</td>
<td>94%</td>
</tr>
<tr>
<td>Jan-Mar 10</td>
<td>1804</td>
<td>1602</td>
<td>96%</td>
</tr>
<tr>
<td>Apr-Jun 10</td>
<td>1602</td>
<td>1438</td>
<td>81%</td>
</tr>
<tr>
<td>Jul-Sep 10</td>
<td>1438</td>
<td>1324</td>
<td>97%</td>
</tr>
<tr>
<td>Oct-Dec 10</td>
<td>1324</td>
<td>1240</td>
<td>97%</td>
</tr>
<tr>
<td>Jan-Mar 11</td>
<td>1240</td>
<td>1270</td>
<td>95%</td>
</tr>
<tr>
<td>Apr-Jun 11</td>
<td>1270</td>
<td>1276</td>
<td>96%</td>
</tr>
<tr>
<td>Jul-Sep 11</td>
<td>1276</td>
<td>1257</td>
<td>99%</td>
</tr>
<tr>
<td>Oct-Dec 11</td>
<td>1257</td>
<td>1276</td>
<td>98%</td>
</tr>
<tr>
<td>Jan-Mar 12</td>
<td>1276</td>
<td>1257</td>
<td>97%</td>
</tr>
<tr>
<td>Apr-Jun 12</td>
<td>1257</td>
<td>1257</td>
<td>98%</td>
</tr>
<tr>
<td>Jul-Sep 12</td>
<td>1225</td>
<td>1225</td>
<td>98%</td>
</tr>
<tr>
<td>Oct-Dec 12</td>
<td>1225</td>
<td>1225</td>
<td>97%</td>
</tr>
<tr>
<td>Jan-Mar 13</td>
<td>1225</td>
<td>1225</td>
<td>98%</td>
</tr>
</tbody>
</table>
ART uptake among TB-HIV coinfected patients

Number of TB patients on ART vs. Proportion of TB patients on ART from Oct-Dec 2008 to Jan-Mar 2013.

- **# of all HIV +ve TB patients**
  - Oct-Dec 08: 1816
  - Jan-Mar 09: 1713
  - Apr-Jun 09: 1678
  - Jul-Sep 09: 1678
  - Oct-Dec 09: 2026
  - Jan-Mar 10: 2016
  - Apr-Jun 10: 1995
  - Jul-Sep 10: 1804
  - Oct-Dec 10: 1602
  - Jan-Mar 11: 1438
  - Apr-Jun 11: 1324
  - Jul-Sep 11: 1602
  - Oct-Dec 11: 1300
  - Jan-Mar 12: 922
  - Apr-Jun 12: 1646
  - Jul-Sep 12: 1457
  - Oct-Dec 12: 1135

- **# on ART**
  - Oct-Dec 08: 296
  - Jan-Mar 09: 254
  - Apr-Jun 09: 402
  - Jul-Sep 09: 653
  - Oct-Dec 09: 562
  - Jan-Mar 10: 586
  - Apr-Jun 10: 781
  - Jul-Sep 10: 827
  - Oct-Dec 10: 780
  - Jan-Mar 11: 933
  - Apr-Jun 11: 1209
  - Jul-Sep 11: 1602
  - Oct-Dec 11: 1300
  - Jan-Mar 12: 922
  - Apr-Jun 12: 1646
  - Jul-Sep 12: 1457
  - Oct-Dec 12: 1135

- **ART uptake**
  - Oct-Dec 08: 16%
  - Jan-Mar 09: 15%
  - Apr-Jun 09: 24%
  - Jul-Sep 09: 32%
  - Oct-Dec 09: 28%
  - Jan-Mar 10: 33%
  - Apr-Jun 10: 39%
  - Jul-Sep 10: 46%
  - Oct-Dec 10: 49%
  - Jan-Mar 11: 52%
  - Apr-Jun 11: 57%
  - Jul-Sep 11: 60%
  - Oct-Dec 11: 67%
  - Jan-Mar 12: 67%
  - Apr-Jun 12: 72%

**Notes:**
- The graph shows the number of TB patients on ART and the proportion of TB patients on ART from Oct-Dec 2008 to Jan-Mar 2013.
- The number of HIV +ve TB patients is shown at the bottom of the graph.
- The ART uptake percentage is shown at the bottom of the graph.
Background

• Adoption of the 3-Is strategy
• Successful IPT pilot
• High ICF through TB screening at facilities
• Roll-out of IPT at some HIV-care sites
  – But lack sustainability
• Need for intervention—
  – Core Team meeting
  – Root-cause identification
  – Institution of intervention
Identified Challenges

- Lack of leadership
- Minimal information/awareness
- Issues of documents & documentation
- Weak implementation strategy
- Poor monitoring & supervision
- Issues of ordering & supply
- Training and support
What next . . . ?

• Visit selected sites
  – Mbabane VCT, Mbabane TB, RFM VCT, Mawhalala
  – Identify challenges

• Meet with facility managers
  – All HIV care sites
  – Present IPT update

• Work together to forge way forward
  – Met 15 May, 2013
IPT Progress Report 1

• 9 sites trained by Aug 2011
  – Only 7 started implementation in 2011
  – All 7 had on-site follow-up mentoring before start
  – Of the 7, only 3 still actively enrolling patients
  – All site have had recurrent challenges
So, why IPT now?
WHO GLOBAL TB PROGRAMME

VISION:

A World FREE of TB

MISSION:

The WHO Global TB Programme aims to advance **universal access to TB prevention**, care and control, guide the global response to threats, and promote innovation.
Targets for 2025/2030

Target 1

75%-80% reduction in deaths due to TB (compared with 2015)

Target 2

40%-60% reduction in TB incidence rate (compared with 2015)

Target 3

No catastrophic expenditures for families affected by TB
TB crosses borders

THE END – THANK YOU!
SUPPORT SLIDES
IPT Progress Report 2

• Hlathikulu:
  – 363 patients enrolled Sept 2011- March 2012
  – 6 stopped (2 pregnant, 3 s/e & 1 t/o)
  – Most completed Rx (poorly documented)
  – No major issues met--Patient uptake was good
  – Stopped in March 2012 due to communication issues.
  – 7 baby sites continue to provide IPT, (MSF supported)
  – Data collected by MSF & not with facility.
IPT Progress Report 3

• Mbabane:
  – Started IPT mid 2012
  – 500 patients ever enrolled
  – Doctors & nurses initiating IPT
  – Had challenges with documentation in register.
  – Used electronic database initially but have reverted to paper
  – No outcome data available as system not providing report
  – Patient uptake not good as IPT pick up does not linked to ART
  – Patients completing TB Rx not started on IPT in TB clinic
  – Staff turnover is another challenge difficult to address.
  – Lack of patient information
Pigg’s Peak:
• Started January 2012.
• 300 pts initiated but only 125 reflected in system
• Of the 125, 1 died, 1 TB, 2 had S/E, 80 completed.
• The rest were not evaluated.
• Staff left and program stopped in March 2012.
• Restarted in January 2013, 70 patients on IPT.
• Patient uptake not good (same as Mbabane).
• Recording is an issue as there are no registers or log books.
• The electronic system is being used currently and the data clerk is proficient, but reports cannot be generated.
• 12 baby clinics are willing to start IPT program.
Nhlangano:

- Started October 2011
- 500 patients to date
- Outcomes are not documented
- No real time entry but added column in register to record IPT status.
- Poor program performance due to high staff turnover
- Patient uptake was good initially but due to system issues, patient education and enrolment has declined
- Additional recording seen as hindrance
- Challenges with initiating IPT post TB treatment
IPT Progress Report 6

Emkhuzweni:
• Started September 2011,
• 500 patients enrolled to date.
• Mid last year the IPT ran out and this affected the implementation of the program.
• Documentation is a challenge as with other sites
• Continuity of care is a challenge, hence patients miss out medications.
• INH not linked to ART refill
• Reliance on patient health card affects documentation. Long term: cohorting of patients, advocacy for IPT.
IPT Progress Report 7

Mankayane:

• Not started IPT yet.
• Staff trained 19th March 2013.
• IPT ordered and have enough for 400 patients.
• Currently working on SOPs and patient flow.
• TB/HIV integration going well—headed by same person.
• Are including FP integration and
• Addressing the data collection as well.
Stock update

• INH 300mg: 670,000 exp 2016 and 2017
• Pyridoxine 180,000 exp Nov 2013, 150,000 Nov 2014
• INH for PLWHIV should be ordered from the ART CMS
  – The ordering process should follow the current procedure for ARV ordering.
• INH for the “U5” is to be ordered along with TB drugs
  – TB clinics need to be reminded of this.
Interventions

• Leadership
  – SNAP to take lead → policies, guidelines, implementation
  – In collaboration with NTBCP & Partners

• Appropriate & consistent messaging
  – To facilities & all healthcare providers
  – To clients at TB & HIV care settings (+ demand creation)

• Site sensitization, motivation & mentoring
  – Meetings, orientations, refresher trainings
  – Mentorship & supportive supervision
Interventions

What information are we giving our clients on IPT as they visit care sites?

Can uptake be as client-driven and as high as for CPT?
Interventions

• Sites to adopt IPT (3Is) policy
  – Form IPT (3Is) MDT Committee (+ Regional Mentors)
  – Develop IPT plans with set targets
    • Proportion of pre-ART & ART clients per quarter
    • Number of baby sites to decentralize to per period
  – Develop IPT roll-out plan to baby sites (in collaboration)
  – Share roll-out plan with SNAP & partners
  – MDT meets regularly to review progress
  – Report monthly to M&E unit (Mother + Baby sites)
  – Report bi-annually at NAHSAR meetings (cascade)
Stock Ordering

Challenges

• Where to order?
• What tool to use to order?
• Ordering by baby sites?
• What to do when orders go to the wrong CMS?
• Having proper consumption data
• How TB clinic can dispense to patients – following completion

Solutions

• From ART CMS – not the main CMS
• Different order form (LIMS form)
• Babies to order from mother sites
• Right data capture and recording
• Include pharmacists in training
Reporting /Electronic / IPT tools

Challenges

• Stock Recording
  – Use the LMIS form?

• Patient Recording
  – Too many tools to enter?
  – Computer recording?
  – File card is repetition

Solution

• Use of Rx Solution
  – For hospitals & health centre
  – Fix problem with data entry
  – Update S/E issues on the system
  – Log book for each Dr but problem is having to consolidate – those completed, educate the patients computer system
  – Have a register in one place then one focal person per day to consolidate at the end of the day
  – Have a system to flag number of patients expected to complete each month
  – Sites without electronic system to continue with HIV care tools
Interventions

Mother site

Phase 1

Mother site
Plus IPT

Phase 2

Baby sites

Phase 3

IPT
THANK YOU!