Kick TB Out.....
Using Isoniazid Prophylactic Therapy

IPT

Training slides provided by
Wits Reproductive Health and HIV Institute
The Case for IPT

What is the evidence that IPT works?
Do we need to be concerned about drug resistance?
Risk of TB

- **HIV negative persons**
  - 1 in 10 *lifetime* risk of developing TB

- **HIV positive**
  - 1 in 10 *annual* risk of developing TB
  - 20-37 times higher risk than HIV negative persons
  - Higher risk if skin test positive (ie latent TB infection)

- **HIV + on ART**
  - Risk much lower but still higher than that of general population
INH prophylactic therapy

- Recommended by WHO for HIV-infected persons since 1998
- Introduced in SA guidelines in 2004
- Reduces the risk of TB in HIV positive persons by 33% overall (ie TST positive and TST negative persons)
  - In persons with latent TB (TST positive), IPT has been shown to reduce the risk of TB by 64%*
  - Antiretroviral therapy reduces risk of TB by +/- 67%*

Understanding the studies that have shown the effectiveness of IPT

- The study design
  - Placebo controlled, randomised trials
  - Amongst HIV+ adults, one group got INH, one group got placebo. Neither group knew which drug they were getting
  - After two years or so, the number of cases of TB were measured in each group

- The relative risk or the ODDS ratio (OR)
  - The risk of INH recipients getting TB compared with placebo recipients
  - OR = 1  Identical risk
  - OR < 1  INH recipients are protected
  - OR > 1 INH recipients are more at risk
### Efficacy of primary IPT

IPT given to persons who have never had TB
All studies done in Africa, in HIV+ persons not on ART

<table>
<thead>
<tr>
<th>Author / year</th>
<th>PPD+</th>
<th>TB incidence</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative Risk</td>
<td>Relative Risk</td>
<td></td>
</tr>
<tr>
<td>Hawken 1997</td>
<td>0.64</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>Mwinga 1998</td>
<td>0.42</td>
<td>2.02</td>
<td></td>
</tr>
<tr>
<td>Pape 1993</td>
<td>0.22</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>Whalen 1997</td>
<td>0.29</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td><strong>Sub Total</strong></td>
<td><strong>0.36</strong></td>
<td><strong>0.74</strong></td>
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</tbody>
</table>

Efficacy of IPT (primary prevention)

TB incidence amongst IPT recipients

Placebo

Overall

TST+* 0.38

TST- 0.89

(RR & 95% CI)

1.00

Relative risk
95% confidence interval for relative risk

(Akolo C. Cochrane infectious disease group. 2009)

*4 trials; 2378 participants

Efficacy of secondary IPT among HIV+ individuals

(Incidence Rate Ratios & 95% CIs)

Reference
Haller (1999)
Fitzgerald (2000)
Churchyard (2002)

0.3
0.18
0.45

Duration of protective effect of IPT

- Studies revealed that the protective effect of IPT lasts 18-24 months only
  - Some patients who received IPT will still develop TB
  - Most likely this is because of early re-infection after killing of latent TB infection
  - Infection control is important.
- More recent studies demonstrate that IPT is best if given continuously or for at least 36 months!!
Retrospective studies amongst IPT and ART recipients - Brazil

A retrospective study done in Brazil, where INH and ART were implemented as part of routine primary health care services showed a decreased incidence of TB as follows

<table>
<thead>
<tr>
<th></th>
<th>Incidence rate of TB (per 100 person-years)</th>
</tr>
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<tbody>
<tr>
<td>Naïve</td>
<td>7.1</td>
</tr>
<tr>
<td>IPT only</td>
<td>5.2</td>
</tr>
<tr>
<td>HAART only</td>
<td>4.6</td>
</tr>
<tr>
<td>IPT &amp; HAART</td>
<td>1.1</td>
</tr>
</tbody>
</table>

A retrospective study done in Johannesburg, looking at incidence of TB amongst IPT recipients and non-recipients, from routine services, none of whom were on ART showed the following:

<table>
<thead>
<tr>
<th>Duration of IPT received</th>
<th>Incidence rate of TB per 100 person-years) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible for IPT but did not receive</td>
<td>3.8 (1.7-8.5)</td>
</tr>
<tr>
<td>Received 1-5 months of IPT (ie not adherent)</td>
<td>2.7 (0.88-8.4)</td>
</tr>
<tr>
<td>Received 6 or more months of IPT (ie completed course)</td>
<td>1.9 (0.7-5.2)</td>
</tr>
</tbody>
</table>
Two major concerns re IPT

• Drug resistance – theoretical, not supported by research*
• IPT and ART

IPT and drug resistance

• Uninfected
• Latent TB
• TB disease

INH kills latent (dormant TB)
• Therefore TB disease cannot occur
• Resistance to TB drugs (INH) cannot develop because the numbers of bacteria are VERY low in latent TB infection

Treatment of TB disease requires 4 drugs because
• Large numbers of TB bacilli mean that resistance can develop
IPT and drug resistance

- Uninfected
- Latent TB
- TB disease

If, in selecting a patient for IPT, we miss active TB disease, we may give IPT to someone who actually has TB disease. Then we run the risk of causing that person's TB to become resistant to INH.

DANGER
IPT and drug resistance

• So, screening for TB is CRITICALLY IMPORTANT in selecting patients for INH prophylaxis
  – If we miss patients with active TB, we run the risk of treating TB with one drug (INH), and causing resistance

• How do we screen for TB disease?
  – Symptoms ONLY (cough, fever, night sweats, LOW)
  – If the patient is not well, they are NOT SUITABLE candidates for IPT
IPT and drug resistance

• INH prophylaxis is an intervention for the WELL HIV+ person, only
  – Just like CPT!
  – IPT is prevention for well persons
IPT & Drug Resistance

• Meta-analysis of studies looking for drug resistance amongst persons who have received IPT concluded that the provision of IPT is not associated with the development of resistance.

• Regular screening for TB whilst on IPT will identify patients who develop TB as soon as possible therefore reducing the chance that someone with TB is treated with mono-therapy.

Balcells ME et al. Isoniazid preventive therapy and risk for resistant tuberculosis. Emerging Infectious Diseases, 2006, 12:744–751
TB and ART

- If a person is eligible for both ART and IPT (ie HIV+, well, CD4<200 cells/mm3), ART is ALWAYS the priority.

- Start ART (refer for ART) first.

- What about IPT then?
  - The risk of TB is highest in the first 3-6 months after initiating ART
  - We don’t want to treat TB disease with INH alone.
  - Therefore, once ART started, IPT can be commenced after 3-6 months

  **AFTER excluding active TB!**
Additional concerns re IPT

• Side effects
  – Peripheral neuropathy, hepatitis
  – Prior counselling is important re management
• Availability and accessibility of IPT
  – Important that stock outs don’t occur
• Lack of knowledge amongst HCW and patients leads to poor delivery, uptake and adherence

Conclusion

• IPT is an effective intervention to reduce the incidence of TB in HIV positive persons
• Drug resistance is a theoretical risk
• IPT and ART in combination provided added benefit
• IPT may reduce TB mortality in those on ART
ISONIAZID PREVENTIVE THERAPY (IPT) FOR HIV INFECTED INDIVIDUALS: SA National Guidelines
1. IPT is considered BEST PRACTICE for PLWA

SA National Guidelines on IPT

- Revised in 2010
- Part of the ART guidelines as approved by the National Health Council
- Based on evidence based research results
- Recommended duration- 6 months but can go up to 9 months
- Adult dose: 300mg daily given with Pyridoxine 25 mg daily
2. Who can get IPT?

- HIV positive patients, adults and children
  - Including pregnant women, persons recently having completed TB treatment, persons on ART already
  - Any CD4 count – regardless of stage of HIV

- TB contacts, especially <5 years, regardless of HIV status
IPT and ART

- High CD4 – IPT
- Low CD4 – ART
- If patient on IPT is ready for ART, do not delay ART
- Patient on ART
  - ART protective to an extent
  - Still at risk for TB
  - Risk for IRIS
  - IPT well tolerated (Caution d4T and NVP)
  - But **EXCLUDE ACTIVE TB FIRST!**
3. Exclude active TB disease in all potential IPT recipients

- TB symptom screen: ask the following
  - Cough > 24 hours
  - Fever
  - Drenching night sweats
  - Loss of weight
- No CXR or sputum screen required to exclude IPT if the patient is well
- If patient is symptomatic
  - Investigate for TB—smear, CXR and culture as necessary
  - Do NOT give IPT under any circumstances, even if smear comes back negative (smear is a terrible test!)
  - If TB cannot be proven, re-evaluate patient after 3 months.
    - If well at that stage, IPT can be given
Screening Algorithm for IPT

1. HIV + Client
2. Complete Patient Chart
3. Clinical status and screening for suitability for IPT
   - Alcohol abuse
   - Active Liver disease
     - Not eligible for IPT
   - TB symptoms or signs (use TB screening tool)
     - NO
       - Thorough counselling
         - Inform patient on benefits of IPT – ask patient consent
         - Commence IPT
         - Client refuses IPT
     - YES
       - Sputum smear & culture
         - Smear Negative
           - Antibiotics
         - Smear Positive or culture
           - TB Treatment Cotrimoxazole bacteriostatic
4. Who is not eligible for IPT?

- Persons with active TB disease on treatment
- Persons with unexplained symptoms, possibly due to TB
  - Can re-evaluate after 3 months, if still well.
- Alcoholic liver disease
- Hepatic disease
5. Monitor and evaluate

- Always record in patients record
  - Use BANC card for ANC, or patient handheld record, and clinic card
  - Document that symptoms of TB not observed
- Use facility monitoring tools
  - GDH 1.1 (standard headcount tool)
  - If in ANC, use Ante-natal register
- If facility has WRHI register – use it to monitor completion and adherence
- Consider continuity of care esp in ANC
  - Explain to clients that they need a minimum of 6 months, and they will need to obtain this from post natal or HIV wellness clinics after delivery.
  - Be sure that your facility has arranged for referral for moms to receive IPT with the above clinics
5. Monitor and evaluate

• What to do if persons are not adherent?
  – Remember, IPT is prophylaxis NOT treatment
  – Interrupting IPT is not as serious as interrupting TB treatment
  – The goal is to give the person their 6 months of IPT within 9 months
    • Ie there can be some allowances made for interruptions
  – Always counsel patients as to benefit of IPT before initiation – understanding leads to adherence
  – Counsel interrupters to establish reasons and commitment to adherence.
    • If persons are not committed, don’t push the matter. Allow them to refuse to take.