What Is New in Combination TB Prevention?

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Treatment and Care (TAC) Team
HIV Department
WHO HQ
Outline

• Combination prevention for HIV
• Approaches to TB prevention
  – Individual
  – Household/key population
  – Population-level
• Conclusions and way forward
Lessons Learned from “Combination Prevention” for HIV

• Greater focus on evidence-based prevention
  – Elimination of mother-to-child transmission (EMTCT)
  – Voluntary medical male circumcision (VMMC)
• Focus on key populations (“know your epidemic”)
• Existing tools not fully scaled (e.g. condoms)
• Treatment of infectious cases (Treatment as Prevention (TasP))
• New tools (PrEP) and where they fit
Individual Risk of TB

Exposure

Infection

Disease

Latent TB infection (LTBI) ascertained by tuberculin skin test (TST) using PPD
Individual Risk of TB

Exposure

Infection

Disease

Latent TB infection (LTBI) ascertained by tuberculin skin test (TST) using PPD
Levels of Risk and Response

**Community/Environment**
- TB and HIV burden and distribution
- TB control efforts (e.g. timely case finding)
- Health infrastructure
- Poverty

**Household/Key population**

**Individual**
Individual Factors

• Increased risk of exposure in high TB burden settings
  – High HIV burden settings also high TB burden
  – Feminization of TB epidemic
• Elevated risk of infection if exposed
• WHO estimates that HIV+ persons have a risk of TB that is 21 times higher than HIV-negatives
• The risk of TB in PLHIV is CD4 dependent
  – The lower the CD4 count the greater the risk
Importance of Linking Intensified TB Case Finding (ICF) and Isoniazid Preventive Therapy (IPT)

- 2011 guidelines link these interventions
- Persons who are not TB suspects should be offered IPT
Isoniazid Preventive Therapy (IPT)

- Efficacy
- Durability
- IPT+ART
- Shorter or more efficacious regimens
- Challenges
IPT Reduces the Risk of TB among PLHIV

Akolo. 2010, Cochrane review
6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial

Taraz Samandari, Tefera B Agizew, Samba Nyirenda, Zegabriel Tedla, Thabisa Sibanda, Nong Shang, Barudi Mosimaneotsile, Oaitse I Motsamai, Lorna Bozeman, Margaret K Davis, Elizabeth A Talbot, Themba L Moeti, Howard J Moffat, Peter H Kilmarx, Kenneth G Castro, Charles D Wells

Lancet 2011
TB incidence during and following IPT
IPT Benefit on ART by LTBI Status

- RCT of added benefit of IPT while on ART in South Africa (Rangaka, AIDS2012)
- IPT (12months) vs. placebo
- TST or IGRA (QuantiFERON Gold In tube-QFT) performed on a subset

*Rangaka, CROI #189LB*
Figure 2. Antiretroviral therapy use and hazard of tuberculosis by baseline CD4 count.

<table>
<thead>
<tr>
<th>All baseline CD4 counts</th>
<th>ART</th>
<th>Control</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TB cases</td>
<td>PY at risk</td>
<td>TB cases</td>
</tr>
<tr>
<td>Badri (2002) [41] *</td>
<td>9</td>
<td>375.1</td>
<td>82</td>
</tr>
<tr>
<td>Cohen (2011) [42] *, †</td>
<td>17</td>
<td>1661.9</td>
<td>33</td>
</tr>
<tr>
<td>Golub (2007) [44]</td>
<td>221</td>
<td>11627</td>
<td>155</td>
</tr>
<tr>
<td>Golub (2009) [43]</td>
<td>44</td>
<td>952</td>
<td>200</td>
</tr>
<tr>
<td>Jerene (2006) [45]</td>
<td>6</td>
<td>162.6</td>
<td>9</td>
</tr>
<tr>
<td>Lannoy (2008) [46]</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Miranda (2007) [47]</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Samandari (2011) [48] †</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Santoro-Lopes (2002) [49]</td>
<td>1</td>
<td>42</td>
<td>-</td>
</tr>
<tr>
<td>Severe (2010) [50] †</td>
<td>18</td>
<td>-</td>
<td>36</td>
</tr>
<tr>
<td>Zhou (2009) [51]</td>
<td>57</td>
<td>5186</td>
<td>40</td>
</tr>
</tbody>
</table>

All studies: 0.35 (0.28 - 0.44)

Effect: Z = 9.19, p < 0.001; Heterogeneity: $I^2 = 31\%$ (22\% - 44\%), $p = 0.151$

Baseline CD4 count 0 - 199 cells/μL

| Badri (2002) [41] *     | 5    | 148     | 41        | 235        | 0.18 (0.07 - 0.47) |
| Lannoy (2008) [46]      | -    | -       | -         | -          | 0.11 (0.02 - 0.52) |

All studies: 0.16 (0.07 - 0.36)

Effect: Z = 4.39, p < 0.001; Heterogeneity: $I^2 = 0\%$, $p = 0.609$

Baseline CD4 count 200 - 350 cells/μL

| Badri (2002) [41] *     | 2    | 121.2   | 27        | 225        | 0.12 (0.03 - 0.53) |
| Golub (2007) [44]       | 143  | -       | 70        | -          | 0.46 (0.33 - 0.63) |
| Lannoy (2008) [46]      | -    | -       | -         | -          | 0.10 (0.02 - 0.45) |
| Severe (2010) [50] †    | 18   | -       | 36        | -          | 0.50 (0.28 - 0.83) |

All studies: 0.34 (0.19 - 0.60)

Effect: Z = 3.72, p < 0.001; Heterogeneity: $I^2 = 58\%$, $p = 0.069$

Baseline CD4 count > 350 cells/μL

| Badri (2002) [41] *     | 2    | 100.1   | 14        | 388.3      | 0.36 (0.10 - 1.74) |
| Cohen (2011) [42] *, †  | 17   | 1661.9  | 33        | 1641.8     | 0.51 (0.28 - 0.91) |
| Golub (2007) [44]       | 32   | -       | 33        | -          | 0.39 (0.23 - 0.66) |

All studies: 0.43 (0.30 - 0.63)

Effect: Z = 4.33, p < 0.001; Heterogeneity: $I^2 = 0\%$, $p = 0.774$

http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.1001270
Figure 3. Antiretroviral therapy use and pooled hazard ratios of tuberculosis by baseline CD4 count.

http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.1001270
IPT with ART: A Randomised Controlled Trial

- HR: 0.63 (95% CI 0.41-0.94)
- Deaths were similar between arms (3.0% vs. 2.1%, p=0.29)
- The risk of stopping IPT due to grade 3 or more raised ALT was 2.13 (95%CI 0.97-4.67)
Percent of reduction of TB risk with IPT, ART, and combined ART and IPT

<table>
<thead>
<tr>
<th>Studies</th>
<th>IPT alone</th>
<th>ART alone</th>
<th>ART plus IPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>68</td>
<td>52</td>
<td>80</td>
</tr>
<tr>
<td>South Africa</td>
<td>13</td>
<td>64</td>
<td>89</td>
</tr>
<tr>
<td>Botswana</td>
<td>65</td>
<td>67</td>
<td>97</td>
</tr>
</tbody>
</table>

AIDS 2007: 21: 1441-8;

ART has significant impact when combined with IPT
Conflicting Data on IPT in Children

Zar (2007) showed strong mortality benefit of IPT in South African children (pre-ART)

Madhi (2011) showed no benefit of IPT (HIV+ or HIV-) in young South African children
# Comparisons

<table>
<thead>
<tr>
<th></th>
<th>Zar et al N = 263</th>
<th>Madhi et al (HIV+) N = 547</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strategy</strong></td>
<td>“All comers”</td>
<td>Pre-exposure prophylaxis</td>
</tr>
<tr>
<td><strong>Exclusions</strong></td>
<td>Known TB exposure requiring INH</td>
<td>Any current TB contact</td>
</tr>
<tr>
<td><strong>ART</strong></td>
<td>Not available</td>
<td>Available</td>
</tr>
<tr>
<td>At baseline (%)</td>
<td>9</td>
<td>31</td>
</tr>
<tr>
<td>During trial (%)</td>
<td>22</td>
<td>98.9</td>
</tr>
<tr>
<td><strong>Baseline Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Age (m)</td>
<td>24.7</td>
<td>3-4</td>
</tr>
<tr>
<td>CDC N / A (%)</td>
<td>12</td>
<td>90</td>
</tr>
<tr>
<td>CD4% &lt;20</td>
<td>20 (14-28)</td>
<td>28 (6-58)</td>
</tr>
<tr>
<td></td>
<td>21.5%</td>
<td>74%</td>
</tr>
<tr>
<td>WAZ</td>
<td>-1.6 (-2.5 – 0.4)</td>
<td>-0.58 (-4.3 - 3.1)</td>
</tr>
<tr>
<td>Prior TB treatment</td>
<td>17%</td>
<td>None</td>
</tr>
<tr>
<td>TST +ve</td>
<td>9%</td>
<td>N/A</td>
</tr>
</tbody>
</table>
CHER Study Showed ART Benefit in Preventing TB in Children

Impact of early ART on TB

TB in 1st year of life (per 100 patient years)

Weekly High Dose 3HP is non-inferior to 9H

Study 26: High risk persons in US, Canada, Brazil & Spain

![Graph showing cumulative tuberculosis rate over time for 6H and 3HP treatments with N=7731.](image)
Weekly High Dose 3HP vs. 9H in HIV+ Persons not on ART  (N=393)

• In study 26, only 3% of participants were HIV+
• Enrolment of HIV+s extended to assess tolerability
• In MITT analysis, participants receiving 3HP
  – Had higher completion rates (89% vs 65%, p=0.04)
  – Fewer AEs (≥1) (22 vs. 40%; p=0.004)
  – Less hepatotoxicity (2% vs. 6%; p=0.03)

(Sterling et al, AIDS2012, MOAB0302)
Short-course Rifamycin-based Regimens Have Similar Efficacy as 6-month IPT 

TST+ South Africans

3RPT/INH (900mg/900mg weekly x12)

(Martinson NEJM. 2011)
Potential Drugs for Treating DR LTBI

**Available**
- Fluroquinolones (Moxi, Gati, Levo)
- Ethambutol
- Ethionamide
- PZA
- Clofazimine
- Linezolid

**New**
- Bedaquiline
- PA824
- Delamanid
- Sutezolid
- AZD5847
- SQ109
What Does a Positive TST Tell Us?

- Immune sensitization to mycobacterial antigens
- Marker of immune function
- Imperfect test for *M. tuberculosis* infection
  - Specificity (BCG, NTMs)
  - Reduced sensitivity in HIV+ ie false-negatives
- Marker of responsiveness to IPT
Challenges with IPT

• Ascertainment of latent TB infection (TST)
  – Challenges of using tuberculin skin test (TST)
  – Use of interferon-gamma release assays (IGRAs) not recommended in resource-limited settings

• Programme scale up

• Whether IPT alone is sufficient
Household and Other Key Populations

• Households and role of contact investigations
• Miners
• Healthcare workers
• Prisons and other congregate settings
Households and Role of Contact Investigations

- TB and HIV risk clustered at household level
- Contact investigation affords opportunity for TB and HIV case finding
- Importance of recent infection and timely diagnosis
RECOMMENDATIONS FOR INVESTIGATING CONTACTS OF PERSONS WITH INFECTIOUS TUBERCULOSIS IN LOW- AND MIDDLE-INCOME COUNTRIES

World Health Organization
## Table of Risk by Contact Status

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th># of TB cases/1000 person-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent TB infection</td>
<td></td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>12.9</td>
</tr>
<tr>
<td>1-7 years</td>
<td>1.6</td>
</tr>
<tr>
<td>HIV-infected</td>
<td>76.0</td>
</tr>
<tr>
<td>Silicosis</td>
<td>68</td>
</tr>
<tr>
<td>CXR consistent with prior TB</td>
<td>2.0-13.6</td>
</tr>
<tr>
<td>Underweight by &gt; 15%</td>
<td>2.6</td>
</tr>
</tbody>
</table>
## Yield (prevalence) of Active TB

<table>
<thead>
<tr>
<th>Contacts</th>
<th># Studies</th>
<th># Contacts investigated</th>
<th># Cases found</th>
<th>Prevalence (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>78</td>
<td>898,619</td>
<td>38,209</td>
<td>3.5 (2.3-5.4)</td>
</tr>
<tr>
<td>Children &lt; 5 yrs</td>
<td>21</td>
<td>6,617</td>
<td>856</td>
<td>9.6 (5.5-16.0)</td>
</tr>
<tr>
<td>Children 5-14 yrs</td>
<td>11</td>
<td>5,366</td>
<td>300</td>
<td>4.5 (1.6-12.3)</td>
</tr>
<tr>
<td>HIV infected</td>
<td>5</td>
<td>282</td>
<td>79</td>
<td>28.4 (9.8-59.2)</td>
</tr>
</tbody>
</table>
Key Recommendations

Recommendation 1: It is recommended that contact investigation be conducted for household and close contacts when the index case has any of the following characteristics:

- sputum smear-positive pulmonary tuberculosis,
- MDR-TB or XDR-TB (proven or suspected),
- is a PLHIV or
- is a child < 5 years of age.

Strong recommendation, very low-quality evidence
**Key Recommendations (2)**

**Recommendation 5:** It is recommended that all household contacts of an index case who is a PLHIV should be counselled and tested for HIV

*Strong recommendation, very low-quality evidence*

**Recommendation 6:** It is recommended that all household and close contacts of people with TB who have symptoms compatible with active TB should receive counselling and testing for HIV as part of their clinical evaluation

*Conditional recommendation, very low-quality evidence*

**Recommendation 7:** PLHIV who are household or close contacts of people with TB and who, after an appropriate clinical evaluation, are found not to have active TB should be treated for presumed LTBI as per WHO guidelines

*Strong recommendation, high-quality evidence*
Cluster-randomised trial in 24 communities in Zambia and Western Cape Province SA
- 962,000 people
- 4 arms factorial design

Primary endpoint: Prevalence of TB
- Enhanced case finding (ECF) Vs no ECF
- Household Intervention (HH) Vs no HH

Secondary Endpoint: Incidence of TB infection in school children
- Enhanced case finding (ECF) Vs no ECF
- Household Intervention (HH) Vs no HH

Risk and Rate ratios for intervention effect at the community level

Conclusions:
- There is a lot of undiagnosed TB in communities
- Household approach worked better than community approach
Household Intervention worked

- TB case identified at clinic (or via ECF)
- Request to go to home
- Consent from all HH members
- TB/HIV education
- TB screening
- HIV CT
- Linkage to care for TB, IPT, ART
Population-Level Factors

• Scale up of existing interventions
  – IPT scale up
  – ART scale up
  – Contact investigations

• New approaches
  – Vaccine
  – Targeted strategies for key populations
Community-Wide IPT Was Effective in Controlling Epidemic TB in Alaska

WHO TB Screening Guidelines (in press)

Strong recommendations

• **Recommendation 1**: Household contacts and other close contacts should be systematically screened for active TB
• **Recommendation 2**: People living with HIV should be systematically screened for active TB at each visit to a health facility
• **Recommendation 3**: Current and former workers in workplaces with silica exposure should be systematically screened for active TB
IPT promotion in 29 HIV clinics in Rio de Janeiro, Brazil reduced TB incidence/death at a clinic-level.

<table>
<thead>
<tr>
<th>Primary Analysis</th>
<th>% reduction</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB</td>
<td>475</td>
<td>0.87 (0.69-1.10)</td>
<td>0.24</td>
</tr>
<tr>
<td>TB/Death</td>
<td>1313</td>
<td>0.74 (0.64-0.85)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Diagram showing clinic number over time (months) with a control period, intervention period, and follow-up period.
Community-wide isoniazid preventive therapy does not improve tuberculosis control among gold miners in South Africa: the Thibela TB study

on behalf of the Thibela TB team

Mass 6/12 IPT in 40,000 people: no community impact

Effectiveness
TB incidence

Among employees in the primary outcome measurement

<table>
<thead>
<tr>
<th></th>
<th>TB</th>
<th>Person years</th>
<th>Rate/100 pyo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>893</td>
<td>29,352</td>
<td>3.04</td>
</tr>
<tr>
<td>Control</td>
<td>860</td>
<td>29,015</td>
<td>2.96</td>
</tr>
</tbody>
</table>

Incidence rate ratio

- Unadjusted: 1.02 (95% CI 0.77-1.34)
- Adjusted*: 1.00 (95% CI 0.77-1.31)

*Adjusted for gender, age, place of work

Effectiveness
TB prevalence

Among a sample of employees at study end

<table>
<thead>
<tr>
<th></th>
<th>TB  (n)</th>
<th>Total (N)</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>165</td>
<td>7,050</td>
<td>2.34</td>
</tr>
<tr>
<td>Control</td>
<td>119</td>
<td>5,557</td>
<td>2.14</td>
</tr>
</tbody>
</table>

Prevalence rate ratio

- Unadjusted: 1.04 (95% CI 0.60-1.80)
- Adjusted*: 0.95 (95% CI 0.83-1.10)

*Adjusted for gender, age, place of work, dwelling type, TB ever, active TB, silicosis, cluster size, baseline TB rate
Putting It All Together: IPT Scale Up in South Africa

![Chart showing the number of HIV+ screened for TB and those started on IPT from 2006 to 2011.](chart.png)
South Africa Example of National IPT Guidelines

Summary recommendations:

<table>
<thead>
<tr>
<th>TST status</th>
<th>PLHIV not eligible for ART</th>
<th>PLHIV on ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST negative</td>
<td>IPT optional (benefit limited)</td>
<td>IPT for 12 months</td>
</tr>
<tr>
<td>TST positive</td>
<td>IPT for at least 36 months</td>
<td>IPT for at least 36 months</td>
</tr>
<tr>
<td>TST not done*</td>
<td>IPT for 6 months</td>
<td>IPT for 12 months</td>
</tr>
</tbody>
</table>

*all facilities should work towards implementing TST.

Additional Approaches Adopted by South Africa

- Roll out of Xpert MTB/Rif promotes earlier and more sensitive case detection
- Widespread scale up of ART
Thibela TB: what will it take to control TB control in gold mines?

A Reid, A Grant, R White, C Dye, E Vynnycky, K Fielding, G Churchyard, Y Pillay
Accelerating progress towards TB elimination: the need to combine treatment & prevention

General population - Rapid scale up

- No intervention
- ART
- Doing the basics better
- Improved diagnostics
- Treat. latent MTB in HIV+s
- Treat. latent MTB in HIV-s

A Reid, A Grant, R White, C Dye, E Vynnycky, K Fielding, G Churchyard, Y Pillay
Status of TB Vaccine

• First TB Vaccine Efficacy Study in Almost a Century Provides Key Insights
• Vaccine Safe but Does Not Confer Protection, calls for Redoubling Efforts on Global TB Vaccine Portfolio

February 4, 2013 - Results of a first-of-its-kind clinical trial of a novel TB vaccine candidate announced today show the candidate vaccine was safe and well tolerated, but did not confer efficacy in prevention of TB disease when administered as a boost to Bacille Calmette-Guerin (BCG), the currently used TB vaccine. The clinical trial of the TB vaccine candidate MVA85A was a Phase IIb safety and efficacy trial in 2,797 infants living in the Western Cape province of South Africa. The candidate was safe and well tolerated in the population tested.
## Combination Prevention

<table>
<thead>
<tr>
<th>Intervention</th>
<th>HIV Prevention</th>
<th>TB Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART scale up</td>
<td>Essential</td>
<td>Essential</td>
</tr>
<tr>
<td>Better use of existing tools</td>
<td>Condoms</td>
<td>IPT</td>
</tr>
<tr>
<td>Focus on evidence-based strategies</td>
<td>Male circumcision</td>
<td>Contact investigations</td>
</tr>
<tr>
<td>Target interventions to key populations using local epidemiologic data</td>
<td>Key populations (IDU, SW, MSM)</td>
<td>Contacts, PLHIV, miners, prisoners, HCWs</td>
</tr>
<tr>
<td>Refinement of existing strategies</td>
<td>PrEP</td>
<td>IPT</td>
</tr>
<tr>
<td>Need for new tools</td>
<td>Vaccine</td>
<td>Vaccine Test for latent TB infection</td>
</tr>
<tr>
<td></td>
<td>Functional cure</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

• Need to scale up what we know works to have population-level impact
• New tools and additional research needed
• Future efforts should focus on preventing TB in those at greatest risk of developing disease
Acknowledgements

• Jonathan Golub
• Haileyesus Getahun
• Gavin Churchyard
• Steven Lawn
Additional Slides
ART benefit in TB Prevention in Children

Objective: To investigate the combined effect of IPT and ART on TB risk in children infected with HIV.

Methods: A cohort analysis was done within a prospective, double-blinded, placebo-controlled trial of isoniazid (INH) compared with placebo in children infected with HIV in Cape Town, South Africa, a high TB incidence setting. In May 2004 the placebo arm was terminated and all children were switched to INH. ART was not widely available at the start of the study, but children were started on ART following the establishment of the national ART program in 2004. Data were analyzed using Cox proportional hazard regression.

Results: After adjusting for age, nutritional status and immunodeficiency at enrolment, INH alone, ART alone and INH combined with ART reduced the risk of TB disease by 0.22 (95% CI 0.09 to 0.53), 0.32 (95% CI 0.07 to 1.55) and 0.11 (95% CI 0.04 to 0.32) respectively. INH reduced the risk of TB disease in children on ART by 0.23 (95% CI 0.05 to 1.00).

Frigati et al. Thorax. 2011
ART Reduces Risk of TB

TB risk reduced by 67% (61%-73%)

- Jones et al. 2000, USA
- Girardi et al. 2000, Italy
- Santoro-Lopes et al. 2002, Brazil
- Badri et al. 2002, South Africa
- Golub et al. 2007, Brazil
- Miranda et al. 2007, Spain
- Muga et al. 2007, Spain
- Moreno et al. 2008, Spain
- Golub et al. 2009, South Africa

Summary estimate (n=37,879)