New horizons in treating latent TB infection

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New horizons: outline

• New regimens
• Duration of isoniazid preventive therapy (IPT): is more better?
• IPT and antiretroviral therapy (ART)
• Obstacles to implementation
  – and some solutions
First, the old horizons

- TB preventive therapy works for people with HIV.......
Effect of IPT on TB:
meta-analysis of clinical trials in PWHIV

Relative risk, 95% CI

Placebo
Overall
TST+
TST-

Akolo 2010, Cochrane review
New horizons: where low TB transmission

- treatment of latent TB important in TB control
- INH x 9 months is a long time, completion rates are poor
- shorter regimens are preferable if effective and safe
TBTC26: rifapentine (RPT)/isoniazid (INH) vs. INH

N=7544 (MITT)

RPT/INH weekly x3m

N=3895
89% US/Canada
3% HIV+
72% TB contacts

INH daily x 9m

N=3649
89% US/Canada
3% HIV+
70% TB contacts

Sterling IUATLD Berlin 2010
TBTC26: RPT/INH vs. INH

N=7544 (MITT)

RPT/INH weekly x3m
- N=3895
- 89% US/Canada
- 3% HIV+
- 72% TB contacts
- 82% completion
  At 33 m: 7 TB cases
  0.07/100pyrs

INH daily x 9m
- N=3649
- 89% US/Canada
- 3% HIV+
- 70% TB contacts
- 70% completion
  At 33m: 12 TB cases
  0.13/100 pyrs

non-inferior
TBTC26: RPT/INH vs. INH

N=7544 (MITT)

RPT/INH weekly x3m

- N=3895
- 16.2% discontinuation (any)
- 5% d/c any AE
- 0.5% any hepatotoxicity

INH daily x 9m

- N=3649
- 28.6% discontinuation (any)
- 3.6% d/c any AE
- 2.8% any hepatotoxicity

Sterling IUATLD Berlin 2010
New horizons: shorter regimens

• rifampicin x4m vs. INH x9m
  – adults, TST+ or IGRA+ (excluding HIV+ taking incompatible ART)
  – currently recruiting, high and low burden settings

• ACTG 5279
  – rifapentine/INH daily x1m vs. INH daily x 9m (self-administered)
  – HIV+, TST≥5mm OR IGRA+ OR resident in high burden country
  – due to start 2011
New horizons: high TB transmission

• shorter regimens preferable
• but where high risk re-infection, is longer duration more effective?
Soweto: novel TLTBI regimens

N=1148 HIV+, TST>5mm, not needing ART

- RPT/INH wkly x3m
  - N=329
  - 86% female
  - mean CD4 532
  - med FU 4.0y
  - LFU 19%

- RIF/INH twice wkly x3m
  - N=329
  - 82% female
  - mean CD4 548
  - med FU 4.0y
  - LFU 15%

- INH continuous
  - N=164
  - 85% female
  - mean CD4 532
  - med FU 3.8y
  - LFU 25%

- INH x6m
  - N=327
  - 83% female
  - mean CD4 537
  - med FU 3.8y
  - LFU 20%

Martinson CROI 2009
Time to TB or death: as treated

Censored
1. 60 days after last dose of INH-cont
2. <25% adherers in other 3 arms

Follow-up Time in Years

Cumulative TB or Mortality

- RPT:INH
- RIF:INH
- INH:6
- INH:Cont
Is longer duration IPT better?

- BOTUSA study, Botswana
  - for PWHIV, is 36 months of INH more efficacious than 6 months?

Samandari CROI 2010; Lancet in press
BOTUSA: INH 6 vs. 36m

N=1995 HIV+

INHx36m N=1006
- 71% female
- 26% TST>5mm
- Median CD4 307
- 46% started ART

INHx6m N=989
- 73% female
- 23% TST>5mm
- Median CD4 290
- 44% started ART

Samandari CROI 2010; Lancet in press
What was the duration of the benefit of 6 months IPT?
30H=30 additional months of IPT vs PL=placebo

43% reduction in TB
$P=0.03$

All received 6 months IPT (d0-d180)

Samandari *Lancet* in press
Continuous IPT benefited TST+ only not TST-
30H=30 additional months of IPT vs PL=placebo

TST+ had 92% efficacy, $P=0.01$

TST- effect of IPT $P=0.69$

Samandari *Lancet* in press
BOTUSA study

• In placebo arm, much higher TB incidence in TST+ vs. TST- over 30m
  – continuing higher TB exposure in TST+?
  – more ART in TST negatives?

Samandari CROI 2010; Lancet in press
IPT and ART for TB prevention?

- Early RCTs of IPT predated ART
- Soweto and BOTUSA studies started ART at CD4<200
- Need to re-evaluate role of IPT in context of wider use of ART, at higher CD4s
  - TB may be proportionally more important cause of morbidity in context of ART
  - IPT adherence may be less of an issue if given with ART
What is the effect of IPT combined with ART?
Association of IPT with mortality among patients taking ART

- Workplace HIV care programme, South Africa
- ART criteria:
  - CD4<250; WHO 4; WHO 3/CD4<350
- IPT recommended if no active or prior TB, but inconsistently implemented
- Retrospective cohort, prospectively-collected data
  - cohort entry: ART start
  - cohort exit: death, leaving employment, 12m post ART start
  - deaths ascertained from clinic and workforce records

Charalambous AIDS 2010;24(s5):S5
KM curve comparing survival among those who started or did not start IPT

Kaplan-Meier survival estimates

<table>
<thead>
<tr>
<th></th>
<th>Deaths</th>
<th>PYRS</th>
<th>RATE/100</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never started</td>
<td>227</td>
<td>2,047</td>
<td>11.08</td>
<td>(9.74-12.63)</td>
</tr>
<tr>
<td>Started INH</td>
<td>32</td>
<td>863</td>
<td>3.71</td>
<td>(2.62-5.24)</td>
</tr>
</tbody>
</table>

Charalambous AIDS 2010;24(s5):S5
## IPT vs. no IPT in ART programme – multivariable analysis

<table>
<thead>
<tr>
<th>INH</th>
<th>Rate /100py</th>
<th>Hazard Ratio (HR)</th>
<th>95% CI</th>
<th>P value</th>
<th>Hazard Ratio (HR)</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>11.10</td>
<td>1</td>
<td>(P&lt;0.001)</td>
<td></td>
<td>1</td>
<td>1</td>
<td>P=0.002</td>
</tr>
<tr>
<td>Yes</td>
<td>3.71</td>
<td><strong>0.34</strong></td>
<td><strong>0.24 - 0.49</strong></td>
<td></td>
<td><strong>0.51</strong></td>
<td><strong>0.32 - 0.80</strong></td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age group, baseline WHO stage, baseline CD4 count, year started on ART and individual company*
Effect of IPT on death in HIV+:
meta-analysis of clinical trials

Relative risk, 95% CI

Placebo
Overall
TST+
TST-

Akolo 2010, Cochrane review
Why have IPT trials not shown an effect on mortality?
## Screening for TB in IPT trials

<table>
<thead>
<tr>
<th>Author, country, study period</th>
<th>TB screen pre-enrollment</th>
<th>TB screen during follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pape, Haiti 1986-9</td>
<td>symptoms, CXR</td>
<td>3 monthly</td>
</tr>
<tr>
<td>Whalen, Uganda 1993-5</td>
<td>symptoms, physical examination, CXR, sputum M&amp;C x1</td>
<td>monthly, with CXR 6 monthly</td>
</tr>
<tr>
<td>Mwinga, Zambia 1992-4</td>
<td>if CXR abnormal, sputum M&amp;C x3</td>
<td>monthly for 6 months, then 3 monthly</td>
</tr>
<tr>
<td>Hawken, Kenya 1992-4</td>
<td>symptoms, CXR, sputum M&amp;C x1</td>
<td>monthly for 6 months, then 3 monthly, with CXR 12 monthly</td>
</tr>
<tr>
<td>Gordin, US 1991-6</td>
<td>symptoms, CXR</td>
<td>at months 1,2,4,6. If symptomatic, CXR and sputum examination</td>
</tr>
<tr>
<td>Rivero, Spain 1994-8</td>
<td>symptoms, physical examination, CXR</td>
<td>every 2 weeks for 2 months, then monthly</td>
</tr>
<tr>
<td>Fitzgerald, Haiti 1998-9</td>
<td>CXR, sputum microscopy and culture x1</td>
<td>monthly for 12 months, then 3-monthly</td>
</tr>
</tbody>
</table>
Active case finding reduces TB case-fatality

<table>
<thead>
<tr>
<th></th>
<th>Deaths/total</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>HIV status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>17/1628</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>64/608</td>
<td>11.15</td>
<td>6.3–20.1</td>
</tr>
<tr>
<td>How detected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSP</td>
<td>12/1225</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Self presentation</td>
<td>69/1011</td>
<td>7.4</td>
<td>3.9–14.6</td>
</tr>
</tbody>
</table>

Churchyard IJTL 2000;4:705
Why no effect on death in IPT trials?

- IPT trials have tested
  - intensified case finding vs.
  - intensified case finding plus IPT
- ICF does not reduce risk of TB
- but does reduce risk of TB death
  - equally in both study arms
- hence not detectable with this study design
- early RCTs may have underestimated benefits of IPT plus ICF programme

Grant AIDS 2010;24(s5):S15
What to do for MDR-TB contacts?

- investigate new agents?
- e.g. TMC 207: diarylquinoline, inhibits mycobacterial ATP synthetase
- phase 2 RCT of 5-drug second line regimen + TMC207 x8w vs. placebo reduced time to culture conversion
- also has activity in non-replicating mycobacteria

Figure 2. The Proportion of Patients with Positive Sputum Cultures and Time to Conversion.
Proportions of positive cultures were determined according to the mycobacteria growth indicator tube (MGIT) system.

Diacon NEJM 2009;360:2397
IPT implementation for PLHIV
IPT implementation is limited among PLHIV where there is most TB

*Numbers under years show the number of countries reporting data followed by the percentage of total estimated HIV-positive people without active TB accounted for by reporting countries.*

WHO TB report 2010
..implementation limited because...

- clinicians (in HIV care programme in SA)
  - lack experience of using IPT
  - uncertain how to exclude active TB
  - worried about side effects
  - worried about promoting resistance

- patients
  - don't know about IPT
  - but think it's a fine idea when you tell them

Lester AIDS 2010;24(s5):S45
Improving IPT implementation
Screening for active TB

Development of a Standardized Screening Rule for Tuberculosis in People Living with HIV in Resource-Constrained Settings: Individual Participant Data Meta-analysis of Observational Studies

Haileyesus Getahun¹, Wanitchaya Kittikraisak², Charles M. Heilig³, Elizabeth L. Corbett⁴, Helen Ayles⁴,⁵, Kevin P. Cain⁴, Alison D. Grant⁴, Gavin J. Churchyard⁶, Michael Kimerling⁷, Sarita Shah⁸, Stephen D. Lawn⁴,⁹, Robin Wood⁹, Gary Maartens¹⁰, Reuben Granich¹, Anand A. Date³, Jay K. Varma²,³

• Excluding active TB: symptom screen with any of:
  – cough (any duration)
  – night sweats
  – fever
  – weight loss
  79% sensitivity, 50% specificity vs. culture pos TB
  NPV 98% at 5% prevalence, 90% at 20% prevalence

• add CXR: sensitivity 91%, specificity 39%

New WHO guidelines for TB ICF and IPT for PLHIV

- regular TB screening
- IPT x at least 6m if no active TB
  - regardless of CD4
  - regardless of ART
  - regardless of past history of TB
- Conditional recommendation for 36m IPT if TST pos or unknown
- TST not essential prior to IPT
  - but can identify those who will benefit most
- similar recommendations for children
Improving IPT implementation: experience from large-scale IPT delivery in Thibela TB

Adverse events

Effect of IPT on resistance to INH
Thibela TB

- Aim: to evaluate community-wide IPT in setting of very high TB incidence and high HIV prevalence
- Cluster randomised trial
- 15 clusters = gold mine shafts, all employees (total N= 80,000 approx)
- Randomised to:
  - Intervention (community-wide TB screening, then IPT x9m) vs.
  - Control (routine TB control programme activities)
- Primary outcome: TB incidence
Thibela TB: adverse events

• AE reporting included these study-defined events:
  – hepatitis (based on clinical monitoring)
  – hypersensitivity
  – peripheral neuropathy
  – convulsions
  – psychosis
  – death from any cause

• occurring between
  – first IPT dispensing date
  – two months after last IPT dispensing date
Thibela TB: adverse events

• 24221 participants started IPT
  – 95% male, median age 40 years

• 130 individuals had 132 possible AEs (0.54%)
  – 61 (0.25%) suspected hypersensitivity
  – 50 (0.21%) suspected peripheral neuropathy
  – 17 (0.07%) clinical hepatotoxicity [2 SAEs]
  – 4 (0.02%) convulsions [2 SAEs]

• One hepatotoxicity AE resulted in death: overall risk of death 4 per 100,000 (0.004%)
Isoniazid resistance after IPT

- case series from Thibela TB
  - 126 gold miners (125 men, median 43y) developing active TB after receiving IPT
  - 89/103 (86.4%) had HIV infection
  - median CD4 (n=51) 196 cells/mm$^3$
  - drug susceptibility results available for 71 (58 new, 13 retreatment)

van Halsema AIDS 2010;24:1051
Prevalence of any isoniazid resistance in TB episodes after IPT (bars=95% CI)

van Halsema AIDS 2010;24:1051
Experience of IPT delivery in Thibela TB

- IPT can be safely delivered by nurses using clinical criteria for adverse event monitoring
- No excess of isoniazid resistance among individuals developing active TB after IPT

Grant AIDS 2010;24(s5):S29
van Halsema AIDS 2010;24:1051
New horizons: low TB transmission

• prospects for effective, shorter, tolerable regimens to treat latent TB
New horizons: high TB transmission

- longer duration of IPT looks better, particularly in TST+
- TB screening simplified to facilitate IPT implementation
- new data support safety of IPT
- need to determine how best to use IPT and ART to maximise TB prevention for PLHIV
Acknowledgements

Collaboration, data, slides, discussion:

• Dick Chaisson
• Salome Charalambous
• Gavin Churchyard
• Katherine Fielding
• Rebecca Lester
• Taraz Samandari
• Tim Sterling
• Clare van Halsema

Funding:

• CREATE consortium
• Bill and Melinda Gates Foundation
New horizons in treating latent TB infection

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**Effect of IPT on prevalence of resistance**

- **Latent TB**
  - **Isoniazid**
    - Prevalence of resistance: 50%
    - Incidence of resistance: 10% individuals exposed to INH
  - **Control**
    - Prevalence of resistance: 25%
    - Incidence of resistance: 10% individuals exposed to control

- **Active TB**
  - INH-resistant
  - INH-sensitive