TB control in a sea of TB/HIV

Will IPT cut it?

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Interest 2014
Global TB in 2012

- 8.6 million new cases
- 13% co-infected with HIV.
- 1.3 million deaths
- SA: >300 cases notified annually (3rd largest number)
- 933/100 000 Largest number TB/HIV co-infected (65%)
TB incidence rates: 2012

- Fol <1%
  - Individualized

- Fol >10%
  - Generalized
Force of Infection

defined as the instantaneous per capita rate at which susceptibles acquire infection and reflects the degree of contact with potential for transmission between susceptibles and infecteds.
The numbers of tuberculosis notifications, stratified by 5-year age groups and HIV-status.
TB infection and disease

TB Infection

0.1% ARI

10% per lifetime

PTB

10% per lifetime

TB
Approach to TB

- DISEASED INDIVIDUALS
  - Management
  - SEEK, TEST, TREAT, CURE

- POPULATION CONTROL
  - SUSCEPTIBLE INDIVIDUALS
  - Management
  - MORE SEEK, TEST, TREAT, CURE
TB infection and disease

0.1% ARI

TB Infection

10% per lifetime

PTB

10% per lifetime

TB
TST reactions

TST Status, Accumulated TB Disease & Infections by Age in HIV-ve Population

- School entry: 20%
- Sexual debut: 60%
- Peak HIV Prevalence: 75%

**Proportion of population**

- TB disease & infection
- TB infected
- Accumulated TB disease

**Age (Years)**
High Force of Infection: HIV neg

7% ARI

20% per lifetime

30% per lifetime

PTB

TB

TB Infection
Risk factors for Childhood TB Infection & Disease

1. Association with TB notification on plot $p<0.001$
2. Quantitatively associated with TB exposure
3. HR: multiple TB cases > Sm+ve > PTB > TB
4. Not related to HIV status of adult index case
5. Child TB preceded adult notification in 36%

Therefore increased opportunities for ICF
HIV hyperendemic: HIV pos

15% per annum PTB

5% ARI

CRITICAL SITUATION

TB Infection

HIV infection
HIV prevalence/ new TB cases : 2012
Know your Epidemic-
Know your response.....
Many epidemics - ONE response???
TB Prevention strategies.


Stop TB Use DOTS
Approach to TB

- DISEASED INDIVIDUALS
- POPULATION CONTROL
- SUSCEPTIBLE INDIVIDUALS

Management: Type of Epidemic, Fol, HIV prev
TB Prevention strategies.

Susceptibles

TB Infection

TB Disease

TB Case

TB Cure

HIV - : nutrition
HIV + : ART

Safe Air

Vaccination

Force of infection

Active case finding

Diagnostics

Prophylaxis

μ

Death

Safe Air

Use DOTS

Infection Control

μ

Death

α

β₁

β₂
INH preventive therapy

- In animal models in 1950s
- Childhood contacts in 1960s
- Recommended for childhood contacts <5 yrs
- Meta analysis of studies in HIV neg from 1962-1994 showed decrease of 60% in recently exposed/infected.
- 12 RCTS in HIV+TST+ showed 62% reduction in TB (only 1 small RCT from RSA).
Impact of IPT on TB Incidence Rates and Mortality Risk

<table>
<thead>
<tr>
<th>Patient groups</th>
<th>TB Incidence</th>
<th>All-Cause Mortality</th>
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</thead>
<tbody>
<tr>
<td>HIV-negative</td>
<td></td>
<td></td>
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<tr>
<td>HIV+ all patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV+ TST+</td>
<td></td>
<td></td>
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<tr>
<td>HIV+ TST-</td>
<td></td>
<td></td>
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<tr>
<td>HIV+ TST unknown</td>
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</tbody>
</table>

Relative risk

Lawn et al. Lancet Infect Dis 2010
TST skin test

• Subject to physiologic and post treatment reversion
• +TST in childhood = recent infection
• +TST in adulthood = earlier/distant infection
  – Lowered risk of endogenous reactivation
  – Protection against TB reinfection (79% CI: 70-86%) progressing to active disease
  – TST+ declines as CD4 count declines
  – ART increases immunity but TST responses not well characterised.

SA History

- IPT in ART guidelines in 2005.
- Poor uptake: TST a barrier
- 2010 (following WHO) removed need for TST
- 2011/2012 : 375 000 SA commenced
- 2013: 36 months IPT for TST +, HIV+
- 6 months if TST unknown
- 12 months if ART+ and TST –
- HIV+, TST-, ART- : no IPT.
TST Status, Accumulated TB Disease & Infection by Age in HIV+ve Population

[Graph showing the proportion of population infected with TB and the accumulated TB disease by age in an HIV+ve population.]
Why the reticence?

- Short term trial efficacy evidence preceded MUCH more successful implementation of ART
- TST + patients are relatively small component of HIV+ population
- TST- patients get the intervention without any benefit?
- Durability low - reinfection rate high
- Lack of long term effectiveness limits epidemiological impact
- Implementation seen as a distraction from other pressing public health needs, eg ART initiation.
Data from South Africa: 5 RCTs

• 2 RCTs in paediatrics:
  263 sick HIV+ into daily/3x weekly INH vs placebo
  – Survival benefit and decrease in TB 72% intervention arm
  – No ART and due to difficult TB diagnosis? Benefit of treatment in undiagnosed TB.

  548 HIV+ and 804 HEU <4 months old
  – 99% commenced ART.
  – No difference in TB infection, disease, death
  – 23% INH resistance

  Zar H, et al.

  Madhi, et al.

Differed in age, severity of disease, nutritional status and ART use.
3 Adult RCTs

- **118 advanced HIV+, TST – , Pre-ART**
  - IPT 2x weekly
  - No effect (low statistical power since population screened for TB with sputum culture)

- **2000 patients – ART clinic, 12 mo IPT**
  - 1536 consented, 250 had active TB, 43% prior TB
  - 30% were TST+
  - Majority on ART prior to IPT.
  - Follow up 2.4 years: 37 /58 incident TB (IPT/Placebo)
  - HR 0.62. No difference in all cause mortality
  - INH resistance in 24%
  - No evidence that effect only restricted to TST +

Mohammed et al

Rangaka et al.

TST testing maybe more important before ART when immunity failing compared to post ART.
Large community wide RCT: Thibela

- **78 744 miners in RSA**
  - 8 mine shafts – 9 months of INH
  - 7 mine shafts – placebo
- PE: TB incidence in the first following year
- SE: TB prevalence at study end.
- Placebo men screened for TB in normal way
- Intervention mine shafts more intensively screened (6.9% more TB found at enrolment than control shafts).
- No difference in PE nor SE.
- Post hoc analysis of men in intervention arm- temporary reduction in TB incidence in 9 mo
- 12% incidence of INH resistance but no difference arms

Inter-study variability or trial design differences?

- 2 studies with TB culture screens had much lower TB incidence in control arms
- 6.9% more TB found in active arms in Thibela than control (SOC screening)
- 2 x more prevalent TB cases screened out than all the TB cases found in the IPT studies and far exceeded TB cases prevented by IPT.
- Much fewer TB clinical events in ART studies
What did INH do?

- Prophylaxis before and after known TB exposure
- Treatment of childhood active TB
- Sterilization of recent or distant latent TB (LTBI)
- Treatment of pauci/multi bacillary adult disease
- Anergic patients may **not** be a group without prior TB exposure
- INH before and after ART seems to act differently—may mean pre-ART studies less relevant now in today’s “universal access”.
Other considerations

• Safety:

  Important to screen out TB.
  – WHO recommends symptom screen- sensitivity?
  – Many trials have used CXR, culture, Xpert to screen where high rates of TB.

Toxicity

  IPT with ART: 2.13 x more likely to discontinue due to grade 3/4 events
  cIPT (V 6 mo) SAEs, Grade 3/4 and permanent discontinuation due to toxicity more common.

Martinson, et al.
Other issues:

• Resistance
  – Metanalysis of IPT studies 1951-2005
  – Not associated with increased INH resistance
  – ? Outside of studies with less adequate screening

• Rapid rebound on stopping:
  – Botswana study: TB incidence incr 90% on stopping after 36 months IPT.
  – Thibela: TB incidence returned to pre-study rates on stopping.
Ability of preventive therapy to cure latent Mycobacterium tuberculosis infection in HIV-infected individuals in high-burden settings

Houben R, et al.
PNAS | April 8, 2014 | vol. 111 | no. 14
A simple deterministic compartmental model was created to reflect a closed cohort of individuals during and after TB-preventive therapy.
### Table 4. Estimated annual risk of infection (λ) and proportion cured (p) for the two placebo-controlled trials

<table>
<thead>
<tr>
<th></th>
<th>Annual risk of reinfection, %/y (IQR)</th>
<th>Proportion cured latent <em>M. tuberculosis</em> infection, % (IQR)</th>
<th>Proportion of disease due to lack of cure, % (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nairobi (Kenya)</strong></td>
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<tr>
<td>Placebo</td>
<td>4.9 (3.0–12.2)</td>
<td>0.0*</td>
<td>30.8 (17.3–46.3)</td>
</tr>
<tr>
<td>6 mo INH</td>
<td>4.9 (3.0–12.2)*</td>
<td>0.0 (0.0–0.0)</td>
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</tr>
<tr>
<td><strong>Kampala (Uganda)</strong></td>
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<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>3.7 (2.9–5.1)</td>
<td>0.0*</td>
<td>22.7 (8.6–40.1)</td>
</tr>
<tr>
<td>6 mo INH</td>
<td>3.7 (2.9–5.1)*</td>
<td>0.0 (0.0–30.9)</td>
<td></td>
</tr>
<tr>
<td>3 mo INH + RIF or 3 mo INH + RIF + PYR</td>
<td>3.7 (2.9–5.1)*</td>
<td>100 (95.0–100)</td>
<td>0.5 (0.4–1.0)</td>
</tr>
</tbody>
</table>

INH, isoniazid; RIF, rifampicin/rifampin; PYR, pyrazinamide; RPT, rifapentine; IQR, interquartile range.

*Values fixed during fitting (*Methods*). Tables 1 and 2 provide parameter values.
Conclusions

• HIV-positive, ART-naive individuals, TST+ : IPT is very unlikely to result in cure of LTBI,
• whereas rifampicin- or rifapentine-containing regimens cured between 19 and 100% of individuals.
• If IPT did not cure, individuals would immediately be at risk for tuberculosis through reactivation of preexisting infections.
• This large pool of individuals already at risk, in combination with a high risk of reinfection, could explain the rapid bounce back in incidence observed post therapy in IPT trials in sub-Saharan Africa.
Biological cause?

• INH is bacteriocidal and most effective against actively replicating mycobacteria
• Less likely to cure LTBI with few replicating organisms
• Rifamycins, however sterilize and therefore likely to be better at LTBI cure.
“Wekker” Conclusions: INH preventive therapy- can it contribute to TB control in RSA?

• Total lack of effect in a large community study
• Modest impact in ART clinics
• Rebound TB on stopping (even after 36 months)
  – Lack of cure/ removal of protection
  – Need for c IPT
• (Rifamycin based therapies for LTBI in low FoI settings)
• Active intensive screening pre-IPT more productive!
• Risk of resistance especially when screening relaxes
• Spending time and resources on this intervention with modest benefit should not divert us from meeting the treatment gap
• And thinking about transmission interruption......
How to control TB in Cape Town?

• TB is still endemic and generalised
• Decreasing the ECN is a priority
• HIV infection increases progression rate not ECN
• Active case finding in HIV+ does not address 1° driver of epidemic (ECN)

• Where and in whom is transmission taking place?
Way forward

• We need to tackle our **generalised** epidemic (HIV -)
• Turn our attention further upstream to tackle transmission
• Need to understand WHERE, WHOM and HOW
• Transmission Driver is within the HIV Negative population
• Also have a **localised** epidemic in HIV infected population and MUST CONTINUE to work hard to reduce mortality in this population
  – Intensified case finding, ART, diagnostics, IPT??.
SAMJ debate:

Pro: Churchyard G, etal. TB preventive therapy: an under-utilised strategy to reduce individual risk of TB and contribute to TB control.


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