New Directions for TB Prevention
Seminar on Global TB/HIV Research
3 August, 2018

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TB: Variable Outcomes

Transmission
Primary Tuberculosis
Latent Tuberculosis
“Reactivation” Tuberculosis

Prevent progression to TB
Prevent infection
Decrease progression by addressing risk factors

Prevent exposure
Skin-test conversion in 6 to 8 weeks
Spontaneous healing in 6 months
Progression after 2 years, 10%
Progression within 2 years, 5%
Progression with concurrent HIV infection, 10% each year

Small NEJM 2001
TB is a Spectrum

- Clinical disease
- Bacterial replication maintained at a subclinical level by the immune system
- Infection controlled with some bacteria persisting in non-replicating form
- Infection eliminated in association with T cell priming
- Infection eliminated without priming antigen-specific T cells
- Disease
- Active infection
- Quiescent infection
- Acquired immune response
- Innate immune response

Effect of HIV infection

Pai Clin Microbiol Rev. 2014
Importance of TB Prevention

- LTBI treatment key to global TB control
- Increased focus on LTBI – US & Global

Abu-Raddad PNAS 2009
Independent Benefits of TB Preventive Treatment & ART

Early ART & IPT beneficial regardless of LTBI status
36.7 million PLHIV
- 25.5 million in sub-Saharan Africa

FIG. 5.2
Provision of TB preventive treatment to people living with HIV, 2005–2016

WHO Global Report 2017
LTBI Cascade – Controlling Leaks

Alsdurf *Lancet ID* 2016
LTBI Treatment Adherence

Percent Completion

Months of LTBI Treatment

9H 6H 4R 3HR

Chest 2010;137:401
### TB Prevention Regimens

<table>
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<tr>
<th>Regimen</th>
<th>Months</th>
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<tbody>
<tr>
<td>INH [9H]</td>
<td>0, 3, 6, 9</td>
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<tr>
<td>INH [6H]</td>
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<td>RIF [4R]</td>
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<tr>
<td>INH/rifapen [3HP]</td>
<td>0, 3, 6, 9</td>
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<td>[1HP]</td>
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Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection


Planned trial
- ASTERoiD (TBTC 37, TBESC Part D) – 6 wks, daily Rpt

Sterling NEJM 2016; Swindells CROI 2018
Self-administered 3HP: I-Adhere

Need: Implementation studies of TB prevention regimens
TB After TB Prevention

- IPT: Limited durability
- Better with ART

South Africa →

Ivory Coast →

**Figure 1:** Cumulative hazard plot for antiretroviral therapy versus antiretroviral therapy plus isoniazid

**Figure 2:** 6-year probability of death

- No IPT: 6.9% (95% CI 5.1-9.2)
- IPT: 4.1% (95% CI 2.9-5.2)

Log-rank p = 0.039

Rangaka *Lancet* 2014; Badje *Lancet Glob Health* 2017
Re-treat with Preventive Tx

- WHIPP TB – annual 3HP
- A5365 – annual 1HP

If effective…
- Does everyone require?
Diagnosing LTBI

*Tuberculin Skin Test (TST)*

*Interferon Gamma Release Assays (IGRAs)*
LTBI Tests Show Mtb exposure

1. Clinical disease
   - Bacterial replication maintained at a subclinical level by the immune system
2. Infection controlled with some bacteria persisting in non-replicating form
3. Infection eliminated in association with T cell priming
4. Infection eliminated without priming antigen-specific T cells

Disease
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Effect of HIV infection

Bacterial load?

Pai Clin Microbiol Rev. 2014
Risk Stratifying Risk of Progression

TST/QFT to identify progressors
- 7500 rural Chinese, followed 2 yrs
  - Cumulative TB Incidence:
    0.3% (TST+/QFT-); 2.0% (TST-/QFT+)
    1.6% (TST+/QFT+)

• S. African Study, >6000 participants to identify transcriptional signatures associated with TB progression
• Validated in other settings

Thompson – Response to treatment?
• 130 HIV-negative adults w/ PTB Cape Town
• Signatures that predicted treatment responses/failures using baseline/week 1/week 4 mRNA
• Also signature that normalized at week 24 in patients with cure.

Fiore-Gartland TB 2018; Thompson TB 2017; Malherbe Nat Med 2016
Interventions that act by host-mediated responses rather than direction action on pathogen
- Augment abx efficacy, shorten treatment length, reduce disease severity
- Novel agents or repurposed approved drugs

Much excitement for active TB…TB prevention?

Metformin – widely used oral diabetic agent
- Decreased LTBI positivity in diabetics in Singapore
- Decreased active TB in Taiwanese diabetics

Lansoprazole (Prevacid) – unique activity vs. Mtb thru inhibition of mycobacterial cytochrome bc1 complex
- Study - UK registry (>500k lansoprazole initiators, 923k other PPIs
- Lansoprazole – decreased active TB, aHR 0.68 (0.52-0.89)

**Host-directed Therapeutics (HDT)**

Conclusions

• TB leading cause of death in PLHIV & TB prevention is key intervention

• ART & TB Preventive therapy independently beneficial

• Need to look at care continuum
  – Shorter regimens
  – Need to improve TB preventive treatment uptake, evaluate delivery strategies
  – Annual retreatment?

• Need for improved risk stratification
Thank you!