Targeted TB Testing for Persons Infected with HIV

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Presentation Objectives:

- Participants will be able to understand clinical presentation of TB with and without HIV co-infection
- Participants will be able to identify options for LTBI diagnosis in HIV co-infection settings
- Participants will be able to list some pros and cons of different clinical intervention strategies for LTBI in HIV co-infection
Targeted TB Testing for Persons Infected with HIV

Thomas Hawn, MD-PhD
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Department of Medicine

WA State TB Educational Conference
October 4, 2017
1. Who to test
2. Diagnostic choices
3. Treatment options
4. Clinical Management: Who to treat
HIV-LTBI CASE

30 yo F with HIV+, CD4=XXX. Not on ART.
Immigrated from South Africa 1m ago
No symptoms
PE: Healthy appearing.

In clinic for routine care, what do you recommend for LTBI Testing & Rx?

1. Nothing
2. Rx w/ INH x 9m
3. Rx w/ INH x 9m if CD4<500
4. √TST & Rx w/ INH x 9m if +
5. √TST & Rx w/ INH x 3 years if +
What Might Matter?

- CD4
- ART
- Age
- Recent immigrant from high TB burden country
- Ongoing travel to high TB burden country
- Co-morbidities
Who to test?
Targeted Testing for LTBI
CDC LTBI Guidelines for US

Identify those at risk for developing TB based on:

A. Exposure Risk
   Close contacts of TB case
   Immigrant from high TB endemic country
   Work in facility with high TB risk

B. Risk of progression to ATBI
   HIV, IDU, CXR c/w healed TB, low body weight, silicosis, DM, ESRD,
   gastrectomy or jejunoilial bypass, SOT, head&neck cancer,
   immunosuppressants

LTBI in US: NHANES

2011-12 Survey N=9756
TST Skin Test Prevalence

US Born
1999 1.9%
2011 1.5%

Foreign Born
1999 18.1%
2011 20.5%

Mirmamontes PlosOne 2016
### Incidence of Active Tb In PPD+s

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>TB Cases/1000 person years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent Tb infection</td>
<td></td>
</tr>
<tr>
<td>&lt; 1yr</td>
<td>12.9</td>
</tr>
<tr>
<td>1-7 yr</td>
<td>1.6</td>
</tr>
<tr>
<td>HIV</td>
<td>35.0 - 162</td>
</tr>
<tr>
<td>IDU &amp; HIV+</td>
<td>76.0</td>
</tr>
<tr>
<td>IDU &amp; HIV- or unknown</td>
<td>10.0</td>
</tr>
<tr>
<td>Silicosis</td>
<td>68.0</td>
</tr>
<tr>
<td>CXR c/w prior Tb</td>
<td>2.0 – 13.6</td>
</tr>
<tr>
<td>Underwt by &gt;15%</td>
<td>2.6</td>
</tr>
</tbody>
</table>
LTBI Testing in HIV+
CDC, HIVMA, IDSA Guidelines for US

A. Test all for LTBI at time of HIV diagnosis (AII)

B. If negative & have low CD4 (e.g. <200), retest when on ART and CD4>200

C. Annual testing if at high risk for repeated exposure (AIII)

D. If +LTBI test, rule out ATBI with Sx screen & CXR

https://aidsinfo.nih.gov/guidelines
Can you get re-infected? **YES**

Molecular Fingerprint Studies

**Cape Town, South Africa**
1993-2001, area HIV rates 1-10%
N=612 pulmonary TB, Cx or smear+
N=61 recurrences after successful Rx

**Re-infections: 77% of recurrences**

**Malawi 1995-2003**
N=584 pulmonary TB, Cx+
N=53 recurrences after successful Rx

**Re-Infections: 52% in HIV+, 6.3% in HIV-**

High Burden Countries

WHO LTBI Guidelines

If HIV+ & unknown or +TST, recommend at least 6m INH:
Regardless of:
  ART status
  Degree of immunosuppression
  H/o treated TB
  Pregnancy

& Consider 36 months of INH (conditional recommendation)

Is this rational?
How does it affect immigrants in US?
Diagnostic Choices

Which LTBI test do you choose in HIV+?

A. Nothing
B. TST
C. QFT
D. QFT-Plus
E. T-SPOT
F. TST + IGRA
G. TST + RNA whole blood assay
Diagnosis: Immune Tests

*Does not distinguish active vs latent
Does not correlate with sterilization (cure)*

**I. Skin Test**

**TST or PPD**

Purified protein derivative (PPD) has crude antigens shared among MTb, BCG, & other mycobacteria.

**II. IGRA**

Quantiferon-TB Gold, T-SPOT

IFN-γ Release Assay

Synthetic Tb peptides (ESAT-6, CFP-10, TB-7.7)

CDC recommends as substitute for PPD


### Which Test in HIV+? TST vs IGRA

#### Impact of CD4 Count on Test Positivity

Difference in % Positive = comparing CD4 < 200 vs > 200

#### Conclusion

All tests impaired at low CD4 count
No preferred test

---

### Table

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Difference in % Positive (95% CI)*</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Low/middle-income Countries</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSPOT</td>
<td>Hoffmann (b) 2007</td>
<td>-26 (-53, 0)</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Jiang 2009</td>
<td>-27 (-41, 2)</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Leid (a) 2009</td>
<td>5 (-15, 25)</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Mandalakis 2008</td>
<td>-18 (-62, 26)</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Oni 2010</td>
<td>-31 (-53, -0)</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Pooled Estimate (I-squared 44%, p=0.13)</td>
<td>-18 (-34, -2)</td>
<td>10</td>
</tr>
<tr>
<td>OFT-GIT</td>
<td>Baccells 2008</td>
<td>-2 (-20, 17)</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>Leid (b) 2009</td>
<td>-23 (-43, -4)</td>
<td>49</td>
</tr>
<tr>
<td>TST</td>
<td>Jiang 2009</td>
<td>-35 (-59, -11)</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Oni 2010</td>
<td>-15 (-41, -11)</td>
<td>50</td>
</tr>
<tr>
<td>B. High-income Countries</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSPOT</td>
<td>Clark 2007</td>
<td>-18 (-45, 9)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Dheda 2005</td>
<td>-4 (-34, 26)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Hoffmann (a) 2007</td>
<td>0 (-19, 39)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Roskold (a) 2009</td>
<td>1 (0, 11)</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Rivas (a) 2009</td>
<td>-11 (-45, 22)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Stephan 2008</td>
<td>-8 (-21, 5)</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Talati (a) 2009</td>
<td>-3 (-7, 1)</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>Pooled Estimate (I-squared 0%, p=0.70)</td>
<td>-3 (-7, 0)</td>
<td>10</td>
</tr>
<tr>
<td>OFT-GIT</td>
<td>Achterburg 2009</td>
<td>-4 (-6, -1)</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Brook 2005</td>
<td>-3 (-7, 1)</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Jones 2007</td>
<td>-7 (-12, -2)</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Laukemeyer 2007</td>
<td>-9 (-14, -4)</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Richel (b) 2009</td>
<td>-5 (-12, -3)</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Rivas (b) 2009</td>
<td>-18 (-52, 16)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Talati (b) 2009</td>
<td>0 (-3, 4)</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Pooled Estimate (I-squared 45%, p=0.07)</td>
<td>-4 (-7, 2)</td>
<td>10</td>
</tr>
<tr>
<td>TST</td>
<td>Jones 2007</td>
<td>-8 (-14, -3)</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>Laukemeyer 2007</td>
<td>-6 (-12, -4)</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Richel (b) 2009</td>
<td>-6 (-15, 2)</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Stephan 2008</td>
<td>-2 (-12, 9)</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Pooled Estimate (I-squared %, p=0.87)</td>
<td>-7 (-10, -3)</td>
<td>10</td>
</tr>
</tbody>
</table>

* Difference = (% positive CD4 < 200 cells/μl) – (% positive CD4 > = 200 cells/μl)

Cattamanchi JAIDS 2011
Which Test? TST vs IGRA

IGRA & TST both acceptable
Most groups (including HIV+)

IGRA preferred
BCG vaccinated
Unlikely to return for 2\textsuperscript{nd} visit

TST Preferred
<5 yrs old*
(*less data overall, especially <2)
(but IGRA may be preferred if BCG vaccinated)
Does Magnitude Matter?

1. PPD—yes
   5mm cutoff in HIV+ vs 10-15mm cutoff in HIV-

2. IGRA—no
   … sort of
   A. Low values
   B. High values
The Dynamics of QuantiFERON-TB Gold In-Tube Conversion and Reversion in a Cohort of South African Adolescents

Jason R. Andrews¹, Mark Hatherill²,³, Hassan Mahomed⁴,⁵, Willem A. Hanekom²,³, Monica Campo⁶, Thomas R. Hawn⁶, Robin Wood⁷, and Thomas J. Scriba²,³

Cape Town, SA
Compare QFT-GIT & TST
N=5357
Reversion: 4.1-5% per year
Correlation: $K = 0.74$

Values:
TST: bimodal
QFT: not bimodal

Hard to establish cutoff for QFT
N=2563 HCWs in USA
Baseline & q6month tests TST/QFT/TSPOT
4 institutions

<table>
<thead>
<tr>
<th>Test</th>
<th>TST</th>
<th>QFT</th>
<th>TSPOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Positivity:</td>
<td>1.8%</td>
<td>3.8</td>
<td>5.0</td>
</tr>
<tr>
<td>Conversions</td>
<td>0.9%</td>
<td>6.1</td>
<td>8.3</td>
</tr>
</tbody>
</table>

Exposure: conversion not associated with exposure

Short term repeatability: 33 to 52.6%
(change QFT/TSPOT positive to negative within 2 weeks)

Reproducibility: 23.7% of QFT conversions did not reproduce
N=2563 HCWs in USA
Baseline & q6month tests
TST/QFT/ TSPOT

More reversion at lower values
Most converters & transience at lower values
# IGRA Variability: Many Reasons

## Table 1: Potential Sources of Variability and Their Impact on Results in IGRA's

<table>
<thead>
<tr>
<th>Source of Variability</th>
<th>Impact on QFT</th>
<th>Impact on T-SPOT.TB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Manufacturing Sources</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between-lot variability</td>
<td>↑↓</td>
<td>↑↓</td>
</tr>
<tr>
<td><strong>Preanalytical Sources</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time of blood draw (a.m. vs p.m.)</td>
<td>↑ p.m.</td>
<td>?</td>
</tr>
<tr>
<td>Skin disinfection</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Traumatic blood draw</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Blood vol (0.8–1.2 ml)</td>
<td>↓ NA</td>
<td>NA</td>
</tr>
<tr>
<td>Shaking of tubes (gentle to vigorous)</td>
<td>↑ NA</td>
<td>NA</td>
</tr>
<tr>
<td>T-cell and APC counts</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Transportation temp</td>
<td>?</td>
<td>↓</td>
</tr>
<tr>
<td>Delay in incubation (0–16 h)</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Incubation time (16–24 h)</td>
<td>Possible effect</td>
<td>?</td>
</tr>
<tr>
<td>Plasma separation delays (seconds to hours)</td>
<td>?&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NA</td>
</tr>
<tr>
<td>Plasma storage (+4–80°C)</td>
<td>No effect</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Analytical Sources</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within-run imprecision</td>
<td>↑↓</td>
<td>↑↓</td>
</tr>
<tr>
<td>Between-run imprecision</td>
<td>↑↓</td>
<td>↑↓</td>
</tr>
<tr>
<td>Between-operator imprecision</td>
<td>↑↓</td>
<td>↑↓</td>
</tr>
<tr>
<td>Between-laboratory imprecision</td>
<td>↑↓</td>
<td>↑↓</td>
</tr>
<tr>
<td><strong>Immunological Sources</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boosting by PPD</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Modulation by PAMP</td>
<td>↑↓</td>
<td>?</td>
</tr>
</tbody>
</table>

*Source: Pai, Clin Micro Review 2014*
Does High IGRA Magnitude Matter?

Generally NO
But one recent study suggests QFT>4 associated with increased progression to active TB in children

Andrews JR, Lancet Respir Med. 2017
N=2512
Cape Town, South Africa
Enroll at 18-24 weeks
Follow up to 2y
What’s New? CD8 vs CD4

Do CD8 Cells distinguish latent from active disease?

Lancioni et al. AJRCCM 2012
QFT-Plus: Will it be better?

QFT Plus
- ELISA as per current product
- Nil (grey) = as per current product
- TB1 (green) = ESAT-6 and CFP-10 CD4 peptides
- TB2 (yellow) = ESAT-6 and CFP-10 CD4 and CD8 peptides
- Mitogen (purple) = as per current product

Research Questions
- Latent vs Active TB Disease
- HIV+
- Children
- Predicting progression from latent to active disease
- Treatment response for LTBI
QFT-Plus & HIV

QFT-Plus similar to QFT with HIV
Performance decreased with CD4<100

Table 4: Comparing the performance of QGIT assay, the TST and QFT-Plus among adult (age ≥ 18 years) pulmonary TB patients

<table>
<thead>
<tr>
<th>Study features</th>
<th>Raby et al.</th>
<th>QGIT (n=112)</th>
<th>TST (n=92)</th>
<th>QFT-Plus (n=108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case definition</td>
<td></td>
<td>Smear +ve; within 1 month of treatment</td>
<td>Smear or Xpert +ve within 2 days of treatment</td>
<td></td>
</tr>
<tr>
<td>TB-HIV co-infection, %</td>
<td></td>
<td>61</td>
<td>212</td>
<td>63</td>
</tr>
<tr>
<td>Median CD4 cell count among PLHIV, cells/μL</td>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>74 (66-82)</td>
<td>67 (58-77)</td>
<td>83 (75-90)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td></td>
<td>12 (6-19)</td>
<td>NA</td>
<td>10 (5-17)</td>
</tr>
<tr>
<td>Quantiferon-negative</td>
<td></td>
<td>14 (8-22)</td>
<td>NA</td>
<td>6 (3-13)</td>
</tr>
<tr>
<td>Quantiferon-indeterminate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity by HIV-positive</td>
<td></td>
<td>63 (50-74)</td>
<td>55 (40-70)</td>
<td>85 (75-93)</td>
</tr>
<tr>
<td>HIV-negative</td>
<td></td>
<td>84 (71-96)</td>
<td>81 (62-92)</td>
<td>80 (64-91)</td>
</tr>
<tr>
<td>CD4 cell count, cells/μL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100</td>
<td></td>
<td>23 (5-54)</td>
<td>—</td>
<td>50 (16-84)</td>
</tr>
<tr>
<td>100-199</td>
<td></td>
<td>70 (46-88)</td>
<td>—</td>
<td>91 (59-99)</td>
</tr>
<tr>
<td>200-349</td>
<td></td>
<td>74 (52-90)</td>
<td>—</td>
<td>85 (62-97)</td>
</tr>
<tr>
<td>≥350</td>
<td></td>
<td>88 (75-95)</td>
<td>—</td>
<td>92 (64-99)</td>
</tr>
</tbody>
</table>

QGIT = Quantiferon-TB Gold In-Tube assay; TST = tuberculin skin test; QFT-Plus = Quantiferon-TB Gold Plus; TB = tuberculosis; +ve = positive; PLHIV = people living with HIV; CI = confidence interval; NA = not applicable.
Predicting Progression

TLR

Latent TB Infection (LTBI)

Clinical Features
• No symptoms
• Dormant bacilli
• 90% of infections remain latent
• Reactivation occurs with risk factors

Active TB Disease

Clinical Features
• Cough
• Fever
• Weight Loss
What’s new? Targeted IPT?
Predicting Progression: RNA

A blood RNA signature for tuberculosis disease risk: a prospective cohort study

Adolescent Cohort Study, South Africa
N=6363
Prospective cohort study
Serial whole blood RNA signature
Test & Validation Sets

16 gene signature predicts progression
12m prior to symptoms
Sensitivity 66.1%, Specificity 80.6%

Zak et al Lancet 2016
1. TST less specific than IGRA
2. TST & IGRA similar sensitivity
3. IGRA reproducibility problems at low assay values
4. HIV status does not affect choice of test
5. All LTBI tests impaired at low CD4 counts
6. QFT-Plus data mostly pending—early data does not show improvement in HIV+
7. Whole blood RNA profile: new method to detect high risk of progression (not in clinical use yet)
Treatment
LTBI with HIV co-infection

45 yo M HIV+, CD4=400, h/o BCG vaccination, 11 mm PPD.
What do you recommend?

A. Nothing
B. INH x 9m
C. PZA/ETB x 6m
D. PZA/RIF x 2m
E. RIF x 4m
F. INH/Rifapentine x 3m

A. Recommendation is to Rx
B. **Class A recommendation**
C. Not needed, maybe with MDR
D. Class D, Not advised, hepatitis
E. **Class B recommendation**
F. HIV-: Class A recommendation
HIV+: Not formally recommended yet
Challenging drug interactions

Other Points: BCG hx does not matter
## Latent TB Treatment Guidelines

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Duration</th>
<th>Rating HIV-</th>
<th>Rating HIV+</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>9 months, daily*†</td>
<td>A(II)</td>
<td>A(II)</td>
<td>Standard and preferred regimen— or INH/RIFP</td>
</tr>
<tr>
<td>Isoniazid/Rifapentine</td>
<td>3 months, weekly</td>
<td>A</td>
<td></td>
<td>DOT, HIV-, &gt;12 yrs, not pregnant</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>9 months, 2x/wk**†</td>
<td>B(II)</td>
<td>B(II)</td>
<td>Must use DOT</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>6 months, daily</td>
<td>B(I)</td>
<td>C(I)</td>
<td>Not for HIV+, children, or those with fibrotic lesions</td>
</tr>
<tr>
<td>Rifampin</td>
<td>4 months, daily</td>
<td>B(II)</td>
<td>B(III)</td>
<td>For HIV+, rifabutin may be substituted to avoid drug interactions</td>
</tr>
<tr>
<td>Rifampin-PZA</td>
<td>2 months, daily</td>
<td>D(II)</td>
<td>D(II)</td>
<td>Avoid this regimen due to liver toxicity</td>
</tr>
</tbody>
</table>

*Recommended for persons < age 18.  
† Recommended for pregnant women.


Rifapentine/INH x 3 months update: Sterling NEJM 2011, MMWR 60: 1646-1671 (2011)
LTBI Rx: PREVENT TB Trial

PREVENT TB Study (Sterling et al NEJM 2011)
Randomized, open label, non-inferiority trial
N=8053
INH 300 qday x 9 m (9H) vs INH 900/Rifapentine 900 q week x 3m (3HP)
No difference in TB rate
Did not include HIV+ or <13

Adverse Events
Hepatotoxicity higher in 9H (2.7% vs 0.4%)
Systemic drug reaction higher in 3HP (3.5% vs 0.4%)
Flu-like illness accounted for majority
No deaths (4 hospitalized)
3HP vs 9H

Completion Rates
Moro et al CID 2015
1406 did not complete Rx
  317 adverse event: similar in both arms 6.4% vs 5.9%
  1089 other reason for non-completion:
  3HP lower non-completion rate (12.7% 3HP vs 24.5%)

Missing ≥1 early clinic visit associated with non-completion

HIV Infected
Sterling et al AIDS 2016
N=403; non-inferiority trial
median CD4=495; ~3 years follow-up
3HP non-inferior to 9H (TB rates 1% vs 3.5%)
3HP lower non-completion rate: 11% 3HP vs 36%
### Rifamycin Drug Interactions

Rifampin: most potent known inducer of Phase I. Also induces Phase II.

<table>
<thead>
<tr>
<th>Cyto P450 Induction</th>
<th>Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin: 1A2, 2C9, 2C19, 3A4, 2D6</td>
<td>1</td>
</tr>
<tr>
<td>Rifabutin: 3A4</td>
<td>0.4</td>
</tr>
<tr>
<td>Rifapentine: 2C9, 3A4</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Rifabutin substitution can be useful to minimize needs for drug dose changes with: HIV protease inhibitors, methadone, cyclosporine (with drug level monitoring)

BCP: add barrier method for any rifamycin
Treatment Summary

1. 3HP & 9H similar efficacy with different adverse event profiles
2. 3HP with less hepatotoxicity than 9H
3. 3HP higher completion rates than 9H
4. HIV+
   3HP non-inferior to 9H
   Higher completion rates for 3HP
   Drug interactions with rifapentine & ART
   (efavirenz & raltegravir OK)
Clinical Management

Who to treat?

What Might Matter?

- TST/IGRA result
- h/o TB
- CD4
- ART
- Age
- Previous Rx for LTBI
- Recent immigrant from high TB burden country
- Ongoing travel to high TB burden country
- Co-morbidities
LTBI In HIV+: Major RCTs in Adults

1. THIBELA: “INH for all”: no sustained benefit (community RCT, mixed HIV- and HIV+)

2. Samandari Botswana: “INH forever”: (6m vs 42m, low ART usage) benefit for TST+ only

3. Rengaka Cape Town:
   INH vs placebo x 12m on ART: benefit for INH group (IGRA- > IGRA+)

4. TEMPRANO …
TEMPRANO: INH + ART

TEMPRANO, 2x2 design, Ivory Coast
1. Deferred ART
2. Deferred ART+IPTx6m
3. Early ART
4. Early ART+IPTx6m
N=2056, median CD4~460

Outcomes
1° end point: composite of AIDS-defining illness, non–AIDS-defining cancer, non–AIDS-defining invasive bacterial disease, or death from any cause at 30m

NEJM 2015
TEMPRANO: INH + ART

Early ART & IPT beneficial

NEJM 2015
TEMPRANO: INH + ART

Benefit for high & low CD4

No difference in AEs

TB prevention main driver of outcome

IPT vs no IPT:
- TST+ 0.43 (0.19-0.99)
- TST- 0.58 (0.21-1.61)
**What is next? Assess Durability**

**WHIP3TB**
Evaluation of the Effect of 3HP vs Periodic 3HP vs 6H in HIV-Positive Individuals

Rationale: durability of IPT in high burden settings is modest. 3HP better tolerated with higher completion rates than 6H or 9H.

Study design: compare annual 3HP vs one time 3HP vs one time 6H. N=4000
Summary: LTBI in HIV+

Resident of Low TB Endemic Country

- **Who to test:**
  - A. Baseline IGRA/TST on all
  - B. If CD4 low, repeat when CD4>200
  - C. Annual screen based on exposure risk

- **Who to treat:** Positive LTBI test or exposure of active case

- **How to Rx:**
  - Class A: 9m INH
  - Class B: Rifampin x 4m
  - Not in guidelines: 3HP non-inferior to 9H in 1 trial, but has drug interaction challenges
Summary: LTBI in HIV+

Resident of High TB Endemic Country
• Recommend LTBI Rx regardless of known exposure, age, TST/IGRA, CD4, ART usage
• Protection wanes after discontinuation
• Benefit of long-term Rx not settled

Immigrants from High TB Endemic Country
• No standard practice on how immigration status changes decision
• Variables to consider: time since immigration, ongoing travel, level of TB burden in country, CD4 count
LTBI:HIV Future Priorities

Re-infection & Long term Rx in high burden countries
Test of cure for LTBI
Predicting Progressors: role of new RNA signature
