Ongoing Research on LTBI and Research priorities in India

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1. Epidemiology: Research Priorities

- What is the prevalence of LTBI in general population and in high-risk group (HIV infected, Contacts of TB cases, Diabetics, Elderly) and in congregate settings (Prison, Shelters)

- What would be the probable epidemiological impact of widespread LTBI diagnosis and treatment on TB transmission in high-burden countries?
Burden of LTBI

• Prevalence of LTBI observed according to QFT-G and TST was 48% and 42% respectively,

• Of the 401 women in a cross-sectional study, 150 (37%) had a positive QFT, compared to 59 (14%) for the TST

• Among 206 HCW, TST results suggested that 36.8% (76/206) were infected with TB using a TST induration ≥10 mm as a cut-off. None showed evidence of active TB in clinical & CXR eval.

• Overall TB incidence rate (among 76 subjects with LTBI) was 2.14 per 1,000 person-years. The highest TB and lowest TB incidence rates were observed among contacts, who were QFT+ve TST–ve [3.70 (95% CI: 2.54–5.36)] and QFT-ve TST-ve [0.64 (95% CI: 0.29–1.42)]
Prevalence of TB infection among Pediatric HHC of MDR-TB patients

Nair et al. NIRT [ICMR]

- Prospective Cohort study
  - To measure the prevalence of LTBI among pediatric HHC (<15 years) of MDR-TB patients
  - To identify risk factors for disease progression in pediatric HHC

- Sample size: 600
- Study ongoing
2. Basic Research : Research Priority

• Which biomarker or combinations of biomarker will help distinguish the various stages of spectrum of TB infection (from sterilizing immunity to active disease)
  – allow accurate identification of patients at each level, including detection of latently infected people who are at highest risk for progression to disease?
  – Which specific platform and which human samples – sputum, blood or urine will be most useful
  – QFT and -------
Evaluation of additional cytokines in QFT supernatants may be valuable for identification of LTBI

Rv2204c & Rv0753c specific IFN-γ & IFN-γ/ TNF-α responses: promising accuracy in identifying LTBI

Pathakumari et al. Cytokine 76 (2015) 496–504
RePORT INDIA CONSORTIUM
(RePORT INDIA COMMON PROTOCOL)

• Purpose: To establish a biorepository in India with an associated
database of well-characterized specimens and standardized data
for future tuberculosis research

• Primary objective of the study is to provide specimens to Indian &
international biomarker researchers and their collaborators over
the next decade to achieve a better understanding of:
  – prognosis of TB disease; and
  – pathogenesis of progression from latent TB infection (LTBI) to
disease.

• Multiple sites involved

• Saliva, Sputum, urine, Blood & components from DS-TB and DR-
TB patients are stored

• Study is Ongoing
3. Diagnosis of Latent TB Infection

• WHO Symptom Screening Algorithm
  – Effectiveness & Feasibility of adopting WHO Algorithm for targeted diagnosis and treatment of LTBI in individuals from risk groups screening?

• Diagnostic Tests: TST vs QFT-GIT assay
  – To generate evidence on predictive utility of IGRA among specific high-risk vs non high-risk groups

• Development of better diagnostic tools to identify individuals with LTBI (POC diagnostic)
  – Discriminate recent from remote LTBI
3. Diagnostics : Research Priority

• Can fundamental studies identify bacteria and/or host molecules that differentiate between people with active TB disease and those with LTBI using a POC test?

• How can novel tools for diagnosis, such a measurement of metabolites, RNA, lipids in sputum, urine and/or blood and volatile compounds in breath, be simplified and validated for use as POC diagnostics in high-burden settings?
Effectiveness of Symptom Screening and Incidence of Tuberculosis among Adults and Children Living with HIV Infection in India


9859 PLHIV screened for the study

6214 agreed to participate in study

6099 PLHIV enrolled

Unwilling to attend for monthly follow-up as required by the study

115 had recent history of TB/ATT hence excluded from study

1815 (30%) had symptoms suggestive of TB

634 referred to RNTCP

5723 (94%) of those enrolled to the study completed 6 months of follow-up

(203 transfer out; 56 died; 117 diagnosed to have TB)

97 patients of TB diagnosed in RNTCP and 20 patients diagnosed outside RNTCP

Total: 117 TB

PLHIV TB Incidence: 2.4/100 person-years
Prevalence: 8/10000

- PLHIV administered WHO symptom screen
- Presumptive TB: any (current) cough, fever, drenching night sweats, unintentional weight loss & failure to thrive in children
- Trained staff did symptom screen
- If symptomatic: sputum microscopy and CXR
Need to strengthen regular symptom screening of TB at ART centers

- **Prevalence of TB**
  - Adult: 0.84%
  - Children: 0.5%

- **Incidence of TB**
  - Adult: 2.4/100 p-y (95% CI 1.9-3.10)
  - Children: 2.7/100 p-y (95% CI 1.60-4.30)
Progression of LTBI to TB

- Neither TST nor IGRA predicted subsequent development of active TB among HHC of pulmonary TB patients during follow-up
  - TST [HR: 1.14, 95% CI: 0.72±1.79, p= 0.57] / QFT-GIT assay [HR: 1.66, 95% CI: 0.97±2.84, p = 0.06]
4. Progression of LTBI

• Identification of Risk factors – clinical & biomarkers for progression of LTBI to active disease

• Identification of factors and mechanisms responsible for
  – maintaining latency / Correlates of protective immunity
  – activation of LTBI to active disease among HRG

• Explore latency in context of possible exposure to drug-resistant strains of *M. tb*
Predictors of LTBI progression: Malnutrition

• Malnutrition (BMI <18 kg/m²), tobacco smoking & poor household ventilation were significantly associated with active TB development among HHCs of PTB patients

• LTBI coexistent with Low BMI has diminished protective cytokine responses [IFN-γ, TNF-α, IL-4, IL-22] & heightened regulatory cytokine responses [IL-10], providing potential biological mechanism for increased risk of developing active TB
Type 2 diabetes mellitus coincident with Latent tuberculosis


- Plasma levels of adiponectin, adipsin, leptin, resistin, visfatin, PAI-1 measured by ELISA in LTB-DM (n=44) and LTB (n=44).
- Systemic levels of adiponectin (Geometric Mean of 60.56 ng/ml in LTB-DM vs 98.21 ng/ml in LTB) and adipsin (GM of 3.31 ng/ml vs. 6.23 ng/ml) were significantly lower in LTB-DM compared to LTB.
Modulation of pro- and anti-inflammatory cytokines in latent tuberculosis by coexistent *Helminthic* infection

*George PJ et al. Tuberculosis (Edinb). 2015;95(6):822-8*

<table>
<thead>
<tr>
<th>Cytokines</th>
<th>LTB (n=44)</th>
<th>ATB (n=46)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-γ</td>
<td>693.9 (300.66–5486.29)</td>
<td>1066 (140.08–5574.88)</td>
<td>0.0007</td>
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<tr>
<td>TNF-α</td>
<td>938.5 (437.56–2960.7)</td>
<td>945.2 (307.32–4537.08)</td>
<td>NS</td>
</tr>
<tr>
<td>IL-2</td>
<td>238.1 (88.66–2150.32)</td>
<td>249.6 (89.6–1094.62)</td>
<td>NS</td>
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<tr>
<td>IL-17A</td>
<td>446 (108.56–955.3)</td>
<td>102.2 (17.49–388.6)</td>
<td>&lt;0.0001</td>
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<tr>
<td>IL-17F</td>
<td>7.505 (3.15–42.21)</td>
<td>19.06 (6.56–184.55)</td>
<td>&lt;0.0001</td>
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<tr>
<td>IL-22</td>
<td>31.79 (8.36–211.38)</td>
<td>76.24 (51.8–295.8)</td>
<td>&lt;0.0001</td>
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<tr>
<td>IL-4</td>
<td>35.9 (4.38–100.92)</td>
<td>29.89 (3.24–206.55)</td>
<td>NS</td>
</tr>
<tr>
<td>IL-5</td>
<td>137.4 (53.78–452.71)</td>
<td>154.1 (63.23–1542.03)</td>
<td>NS</td>
</tr>
<tr>
<td>IL-13</td>
<td>25.67 (7.64–92.23)</td>
<td>289.3 (67.52–1604.89)</td>
<td>&lt;0.0001</td>
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<td>IL-10</td>
<td>121.4 (28.29–421.08)</td>
<td>181.5 (28.29–716.57)</td>
<td>0.0022</td>
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<tr>
<td>TGF-β</td>
<td>82.89 (51.02–180.02)</td>
<td>51.14 (10.12–357.36)</td>
<td>NS</td>
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<tr>
<td>IFN-α</td>
<td>0.7166 (0.17–11.12)</td>
<td>66.25 (40.34–219.32)</td>
<td>&lt;0.0001</td>
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<tr>
<td>IFN-β</td>
<td>50.85 (10.71–537.68)</td>
<td>1781 (162.89–92354.94)</td>
<td>&lt;0.0001</td>
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<tr>
<td>IL-1α</td>
<td>2.458 (0.97–15.44)</td>
<td>1.559 (0.58–15.01)</td>
<td>0.0027</td>
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<td>IL-1β</td>
<td>235.7 (100.39–654.02)</td>
<td>174.1 (80.64–470.37)</td>
<td>0.0039</td>
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<tr>
<td>IL-6</td>
<td>576 (96.37–4196.09)</td>
<td>799.8 (193.81–2019.38)</td>
<td>0.0062</td>
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<tr>
<td>IL-12</td>
<td>487.7 (341.68–1112.30)</td>
<td>476.7 (193.81–1233.11)</td>
<td>NS</td>
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<tr>
<td>GM-CSF</td>
<td>370.2 (104.08–1671.36)</td>
<td>39.9 (3.40–250.45)</td>
<td>&lt;0.0001</td>
</tr>
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</table>
Blood biomarker to predict progression to active TB disease among recently exposed adult and pediatric HHCs of TB patients

• This project aims to determine if the identified blood-based signatures in South African cohorts can predict progression to active TB disease in other TB endemic countries like India
  – To estimate the prevalence of persons positive for the recently identified 16-gene correlate of risk of TB signature among adult and pediatric household contacts (HHC) of TB and HIV-TB coinfected patients in India
  – To explore change over time in 16-gene signature among recently TB-exposed household contacts who subsequently do and do not develop active TB

• To compare the full mRNA transcriptomes in a subset of adults and children
5. Treatment : Research Priority

• What is the optimal TB preventive therapy in terms of efficacy, safety, tolerability and duration of protection that can be used in HIV infected adults and children particularly those receiving ART?

• Can novel drugs rapidly kill latent or persisting bacilli in people with LTBI? How should they be optimally combined to introduce a safer, shorter, more efficacious preventive drug regimen for adults and children?
Effectiveness of Isoniazid Preventive Therapy on Incidence of TB under Programme Settings in PLHIV

Padmapriyadarsini et al. NIRT (ICMR), India

- 3841 were on ART
- 622 were pre-ART
- 65 started ART soon after IPT

4528 PLHIV initiated on IPT

4015 PLHIV completed 6 months of IPT

PLHIVs followed for 6-months post-IPT

3533 (96%) completed 6-months of Post-IPT follows up

IPT discontinued due to:
- Adverse events: 121
- Pill burden: 68
- Transferred out: 282
- Deaths: 17
- Tuberculosis: 25

Incidence of TB pre IPT - 2.4/100 p-y
Incidence of TB during IPT - 1.17/100 p-y
Incidence of TB post-IPT - 0.64/100 p-y

Body mass index <18 (OR=1.99, 95% CI 0.85-4.61)
Patients not on ART (OR=1.52, 95% CI 0.57-4.08)
were at risk of developing TB
Randomized, Pragmatic, Open-Label Trial to Evaluate the Effect Of 3-months Of high Dose Rifapentine Plus Isoniazid Administered As A Single Round Or Given Annually In HIV-Positive Individuals

Indian Council of Medical Research & Aurum Institute, SA

Part A: To compare treatment completion in HIV-positive participants taking a three-month round of weekly Rifapentine plus isoniazid to those taking six months of daily isoniazid
  – to compare a single round of 3HP to 6H with respect to
    • TB incidence / All-cause mortality / Permanent discontinuation of therapy due to TEAE / at end of 1-year compare occurrence of IGRA conversions and IGRA reversions

Part B: To compare the effectiveness of a single round of 3HP to two periodic (annual) rounds of 3HP (p3HP) in preventing TB disease among HIV-positive persons.
  – to compare 3HP and p3HP with respect to
    • Effectiveness 13-24 months after randomization / Treatment completion / All-cause mortality / Permanent discontinuation of therapy due to TEAE / Incremental cost and cost-effectiveness

• 1800 participants (750:750:300)
Community Rifapentine Study : Cluster Randomized trial

• Study to determine Effectiveness of 12 dose Rifapentine + Isoniazid in preventing TB among HHCs of patients diagnosed with Pulmonary TB
• All HHCs of newly diagnosed TB patients, aged > 2 years

• Tuberculin units under the National Programme will be randomized
• Interventions:
  – Standard Arm: Child contacts of index TB patients receiving 6 months of daily Isoniazid Prophylaxis
  – Intervention Arm 1: All the contacts of index TB patients receiving 12 doses of Rifapentine and Isoniazid Prophylaxis given every week for 12 weeks
    • Isoniazid-15 mg/kg 900 mg maximum
    • Rifapentine  10.0–14.0 kg 300 mg / 14.1–25.0 kg 450 mg / 25.1–32.0 kg 600 mg / 32.1–49.9 kg 750 mg / ≥50.0 kg 900 mg maximum
  – Intervention Arm 2: All adult contacts of index TB patients receiving 6 months of daily Isoniazid

• Sample size: 2100 with 21 clusters
• Outcome: Development of Tuberculosis disease as assessed based on smear, culture and Radiology / Death due to any cause
Research Priorities

• Identify methods & means to optimize LTBI case-finding
• Develop methods & means to scale up PT under field condition

• Genetic basis for resistance to *M.tb* infection
  – *Genome-wide association study (GWAS) of individuals with TB exposure but who remain TST and IGRA negative*
  – *Identify metabolomic markers associated with resistance to M.tb infection*

• Create awareness among private practitioners about the Utility of the diagnostic tests currently available in India
  – *its specificity, sensitivity and interpretation of results*

• Determine efficacy of TB infection control measures / monitor and evaluate TB infection control in health facilities
THANK YOU

Dr. Wallace Fox  Prof. D.A. Mitchison  Dr. Hugh Stott

Founders of TCC...TRC...NIRT