Regional Prospective Observational Research in TB

RePORT
South Africa

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IeDEA Africa

30 October 2019
RePORT - Model

- **Multi-country** initiative
- Collaboration: US and in-country PIs
- **Joint funding support** by host country gov and NIH
- **Enhance regional capacity for research**
- Focus on TB and comorbid conditions
- Implement the ‘Common Protocol’
  - Case definitions: **TB disease** and **High risk for TB**
  - Visit schedule for prospective cohort
  - Data and specimen collection
- **Global Consortium**: RePORT International Coordinating Center (RICC):
  - Data repository
  - Specimen repository (in-country but accessable)
  - Annual international meetings
  - Requests for proposals
RePORT International Consortia

- **RePORT India**: Common Protocol - Cohorts A & B; Site-specific Protocols
- **RePORT Brazil**: Common Protocol – Cohorts A & B
- **RePORT Indonesia**: Common Protocol – Cohort A (within TRIPOD Study)
- **RePORT South Africa**: Common Protocol – Cohorts TBD; Site-specific Protocols
RePORT International Consortia

RePORT India – 2012
RePORT Brazil – 2012
   Rio de Janeiro, Salvador and Manaus
RePORT Indonesia – 2013
RePORT South Africa – Initiated in 2016
   • Start Up: China and Philippines
   • Other countries interested in using RePORT Common Protocol
RePORT Terminology

Common Protocol

- **Prognosis of TB disease** (biomarkers of response to treatment)
- **Pathogenesis of progression** (biomarkers of progression to TB disease)
  - Standards and definitions
  - Data and specimens into repository (own research encouraged)

- **Cohort A**: Presumptive TB + culture positive for MTB + CXR suggestive
  - Baseline
  - M1, M2
  - End of Tx
  - 6 months post TB treatment

- **Cohort B**: Recent exposure in past 6 months, no TB disease, IGRA/TST result
  - Baseline
  - M4-6
  - M12
  - M24
  - TB Activation
RePORT South Africa

- **Partnership: NIH and SAMRC;** co-funded/co-managed
- SAMRC – host coordinating centre in SA
- PI’s from SA and US institutions
  - RePORT SA Representatives: Hatherill and Chaisson
- Developmental: PDI partners required (U Limpopo, Cecelia Makiwane Hosp)
- SAMRC funded units (broad definition)
- RFA 2015
- SA TB RePORT Funding 2016-2019.
- New SA RePORT RFA due any time
5 RePORT South Africa Sites

The Clinical Research Unit for Advancement of TB Biomarker-Targeted Interventions
Mark Hatherill, SATVI (UCT), Cape Town
Jerrold Ellner, Boston Medical Center (BMC), Boston, Cohorts A and B

TB in hot and cold spots in South Africa: researching index cases and their households
Neil Martinson, PHRU (WITS), Johannesburg
Richard E. Chaisson, Johns Hopkins University, Baltimore
Cohorts A and Cohort B

Highly sensitive cartridge-based nucleic acid amplification testing for the diagnosis of pulmonary tuberculosis in children
Mark Nicol & Heather Zar, UCT, Cape Town
Jeffrey Starke, Baylor College of Medicine, Houston
Cohort A (Pediatric TB)

Quantifying infectiousness of undiagnosed tuberculosis cases and impact of enhanced community-based active case-finding strategy using novel diagnostic tools
Keertan Dheda, Lung Institute (UCT), Cape Town
Tawanda Gumbo, Baylor Research Institute, Dallas
Cohorts A and Cohort B

Identifying Innovative Bacterial and Host-Mediated Biomarkers of Treatment Response to Tuberculosis Chemotherapy Relapse
Al Leslie, AHRI, Durban
Tim Sterling, Vanderbilt University, Nashville
Cohort A

- Biomarkers of triage and progression
- Community-level active surveillance
- Novel paediatric diagnostics
- Novel adult diagnostics
- Biomarkers of treatment response

Cohort A and B data & sample collection
Enrolment towards targets

COHORTS A & B
Years 2016 – 2019 (No-Cost Extension): Data up to August 2019
Table 1: Sample size targets and enrolment

<table>
<thead>
<tr>
<th>Site</th>
<th>Cohort A</th>
<th>Cohort B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>Target, n</td>
<td>Enrolled, n (%)</td>
</tr>
<tr>
<td>AHRI</td>
<td>75</td>
<td>100 (133%)</td>
</tr>
<tr>
<td>LI</td>
<td>60</td>
<td>42 (67%)</td>
</tr>
<tr>
<td>PHRU</td>
<td>300</td>
<td>189 (63%)</td>
</tr>
<tr>
<td>REACH</td>
<td>550</td>
<td>609 (110%)</td>
</tr>
<tr>
<td>UP*/SATVI</td>
<td>50</td>
<td>17 (34%)</td>
</tr>
<tr>
<td>Total</td>
<td>1,035</td>
<td>947 (91%)</td>
</tr>
</tbody>
</table>

Cohort A    Enrolled 947/1,035 (91%) (site range 34-133%)
Cohort B    Enrolled 639/1,575 (40%) (site range 13-100%)
RePORT RFAs: between consortia

- **Diabetes**
  - Molecular Signatures of Tuberculosis-Diabetes Interaction
    - HbA1C as diagnosis of diabetes in TB patients.
  - Pediatric RFA: Diagnosis (not response to therapy)
    - **EDICT**: PI Sanjay Lala: collecting specimens from TB v non-TB LRTI
      - Nested in R01
      - Plasma, blood, tongue swab, urine, clinical data
  - Maternal TB: PI: Martinson/Mathad (Pune and Soweto): immune markers of susceptibility to TB.
  - MDR TB meningitis: PI: Jeff Thornheim (India and SA)

- **RO1: Neel Gandhi**: Characterization of Genomics and Metabolomics among Individuals Highly-Exposed, but Resistant to Mtb Infection.
  - India, SA, Brazil RePORT sites

Data science: NIH TB Portal
Advice for prospective RePORT’ers

1. Plan for secular improvements:

Higher CD4 counts, earlier diagnosis of TB, more and better PT, more better ART/adherence, TB vaccine....

New cases of lab confirmed TB, SA
2. Anticipate late exclusions (culture negatives)

TB Report Cohort A ➔

Consider:

a. \( \geq 2 \) baseline specimens for culture; large volume, early morning oysters
b. Clinical case definitions plus routine lab Mtb pos
c. Ultra Trace?

<table>
<thead>
<tr>
<th></th>
<th>Culture-Negative [N=26]</th>
<th>Culture-Positive [N=80]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Age (IQR)</strong></td>
<td>41 [29 - 53]</td>
<td>34 [15 - 44]</td>
</tr>
<tr>
<td><strong>% Female</strong></td>
<td>61.5%</td>
<td>36.3%</td>
</tr>
<tr>
<td><strong>% with smear positive (+, ++ or ++++)</strong></td>
<td>0%</td>
<td>26.25%</td>
</tr>
<tr>
<td><strong>% HIV+</strong></td>
<td>61.5%</td>
<td>54.0%</td>
</tr>
<tr>
<td>If HIV+ % on ART</td>
<td>62.5%</td>
<td>27.5%</td>
</tr>
<tr>
<td>If on ART median duration</td>
<td>351 days</td>
<td>1314 days</td>
</tr>
<tr>
<td>If HIV+ median CD4 count (IQR)</td>
<td>100 [53 - 110]</td>
<td>75 [31 - 113]</td>
</tr>
<tr>
<td><strong>% with TB symptom/s</strong></td>
<td>96%</td>
<td>96%</td>
</tr>
<tr>
<td><strong>% with X-ray changes</strong></td>
<td>54%</td>
<td>65%</td>
</tr>
<tr>
<td><strong>% with symptom AND X-ray changes</strong></td>
<td>50%</td>
<td>61%</td>
</tr>
<tr>
<td><strong>% with symptom AND X-ray changes AND smear pos</strong></td>
<td>0%</td>
<td>17.5%</td>
</tr>
<tr>
<td><strong>% with a close contact of TB</strong></td>
<td>23.1%</td>
<td>33.8%</td>
</tr>
<tr>
<td><strong>% with prior episode of TB in past two years</strong></td>
<td>19.2%</td>
<td>7.5%</td>
</tr>
</tbody>
</table>
## 3. No Binary Universes: Symptoms v no Symptoms
Test+ v Test-

**TB RePORT** – Universal testing of HH Contacts irrespective of symptoms:
Xpert Ultra v MGIT

<table>
<thead>
<tr>
<th></th>
<th>Contam</th>
<th>Negative</th>
<th>MTB+</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTB+</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>5 (2.5%)</td>
</tr>
<tr>
<td>Neg for MTB</td>
<td>38</td>
<td>152</td>
<td>11</td>
<td>204</td>
</tr>
<tr>
<td>TOTAL</td>
<td>41</td>
<td>153</td>
<td>12</td>
<td>206</td>
</tr>
</tbody>
</table>

### Additional Table

<table>
<thead>
<tr>
<th></th>
<th>Sx Pos</th>
<th>IGRA Pos</th>
<th>HIV pos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra MTB</td>
<td>2/5</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Cult pos MTB</td>
<td>4/12</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Either or both pos</td>
<td>6/16</td>
<td>11</td>
<td>11</td>
</tr>
</tbody>
</table>
Pooling Sputum Specimens

Kennedy Otwombe
Katlego Motlogelwa
Anthony Kinghorn

TB MGIT Test

NHLS standard process (6 minutes per sample)
- 50 TB +ve
- 950 No TB

NHLS process with sputum homogenization (6.27 minutes per sample)
- 13 TB +ve
- 237 No TB

Process for 52 contacts separately, 13 by 4
- 312 minutes

Total:
- Standard NHLS process: 6000 Minutes
- NHLS + Pooling Process: 1880 Minutes
3. Focus on DR or DS TB. Not both?

a. Delays to confirm resistance patterns
b. Novel diagnostics
c. Rif R on Xpert ≠ MDR

<table>
<thead>
<tr>
<th>Drug resistance on Hain testing in adults with R resistance on Xpert</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rif Mono</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>206</td>
</tr>
</tbody>
</table>

Data from Matlosana prescreening of index MDR patients for TB CHAMP, a trial of LVX for child contacts of MDR index patients (2017-2018).
4. Use biological markers

<table>
<thead>
<tr>
<th>Prevalence of Smoking Population survey v HIV+</th>
<th>SANHANES\textsuperscript{a} 2015</th>
<th>PLWH\textsuperscript{b} 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>18%</td>
<td>28%</td>
</tr>
<tr>
<td>Men</td>
<td>29%</td>
<td>52%</td>
</tr>
<tr>
<td>Women</td>
<td>7%</td>
<td>13%</td>
</tr>
<tr>
<td>Tried to quit in past year</td>
<td>48%</td>
<td>80%</td>
</tr>
</tbody>
</table>

Reddy P, et al. SAMJ; 105 (8), 2015
Smoking prevalence in adolescents and men requesting male circumcision at five clinics in South Africa - 2017

Urinary cotinine
Urinary THC
Prevalence of current smoking among HIV infected men and women

Smoking defined by CO+ and Urinary Cotinine+

304/705 women reported snuff use: (cotinine+ but CO negative)
Prevalence of cotinine+ in HIV-infected, non-smoking women
**Snuff use**

**Non-smoking, HIV-infected women**: urine cotinine and current TB

<table>
<thead>
<tr>
<th></th>
<th>Total ((n = 606))</th>
<th>No TB ((n = 547))</th>
<th>Current TB ((n = 59))</th>
<th>Univariate OR (95% CI)</th>
<th>p-value*</th>
<th>Multivariate OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No cotinine</strong></td>
<td>330 (56)</td>
<td>319 (59)</td>
<td>11 (23)</td>
<td>REF</td>
<td></td>
<td>REF</td>
</tr>
<tr>
<td><strong>Any cotinine</strong></td>
<td>263 (44)</td>
<td>226 (41)</td>
<td>37 (77)</td>
<td>4.7 (2.4, 10.0)</td>
<td>&lt; 0.0001</td>
<td>5.7 (2.6, 14.0)</td>
</tr>
</tbody>
</table>
Interactions: BMI, TB, Diabetes

Diabetic Clinic Bara

- Symptom screened
- 27 (4%) reported symptoms of TB
- **0 (Zero) cases of TB diagnosed**
- Prior TB: 10% - 1% TB after diagnosis of DM.
- Record review of 828 clinical files in the diabetic clinic (2013)
- 1% of files had TB treatment (ever) recorded in their files – most prior to diabetes diagnosis.

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<table>
<thead>
<tr>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>African/Black</td>
</tr>
<tr>
<td>Median BMI (IQR)</td>
</tr>
<tr>
<td>Type II Diabetes</td>
</tr>
<tr>
<td>Median HbA1c (IQR)</td>
</tr>
<tr>
<td>Ever smoker / Current</td>
</tr>
<tr>
<td>HIV +</td>
</tr>
<tr>
<td>Hypertensive</td>
</tr>
<tr>
<td>On Insulin</td>
</tr>
</tbody>
</table>
BMI protective against TB

Lonroth et al Int J Epi 2010

Hanrahan et al AIDS 2010
Innovation: BMI
Aknowledgements

Limakatso Lebina
Minja Milovanovic
Firdaus Nabeemeeah
Azra Ghoor
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Sanjay Lala

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• Molefi Tladi
• Abraham Pattamukkil
• Andrew Ratsela
• Pinky Motsomi
• Bavesh Kana
• Charity Leeuw

• Peter Kim
• Sudha Srinavasan*
• Roxana Rustomjee
• Fareed Abdullah
• Bavesh Kana
• Candice Roux
• Thuli Mthiyane