IMPAACT TB SCIENTIFIC COMMITTEE UPDATE: 2018

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AMITA GUPTA
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TBSC core members

- Anneke Hesseling (chair) – DTTC, South Africa
- Amita Gupta (vice-chair) – JHU/India
- Kelly Dooley – JHU
- Bob Husson – Boston Children’s
- Anne-Marie Demers – DTTC, South Africa
- Vanessa Rouzier – Gheskio, Haiti
- Carol Onyango – Uganda
- Lindsay McKenna – TAG, NY
- Avy Violari – PHRU, South Africa
Aims

To evaluate novel approaches for TB prevention, treatment and diagnosis in HIV-infected infants, children, adolescents, and pregnant women regardless of DS and DR-TB status
Strategy

- Collaboration with industry
- Rapid uptake of findings into policy and practice
- Phase I/II trials where efficient
- Phase III as required
- Earlier inclusion of adolescents
- Inclusion of pregnant women
<table>
<thead>
<tr>
<th>Estimated total TB cases in children</th>
<th>1 000 000 (10% global burden)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood cases notified</td>
<td>360 000</td>
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<tr>
<td>TB deaths</td>
<td>136 000</td>
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<tr>
<td></td>
<td>(81 000 HIV-)</td>
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<tr>
<td></td>
<td>13.6% case fatality rate</td>
</tr>
<tr>
<td>TB infections</td>
<td>6.6 million</td>
</tr>
<tr>
<td>MDR-TB estimates</td>
<td>30-50 0000</td>
</tr>
<tr>
<td>MDR-TB infection</td>
<td>500 000</td>
</tr>
</tbody>
</table>
Global TB Drug Pipeline

Discovery

Lead Optimization
- Diaryquinolines
- DprE Inhibitors
- InhA Inhibitor, Ureas
- Macrolides, Azaindoles
- Mycobacterial Gyrase Inhibitors
- Pyrazinamide Analogs
- Ruthenium(II)Complexes
- Spectinamides
- Translocase-1 Inhibitors, Clp, Mmp13, Oxazolidinones, Pyrimidines DprE1, Aryl Sulfonamides, PKS13, Squaramides

Preclinical Development
- Early Stage Development
  - TBI-166
  - CPZEN-45*
  - 1599*
  - SATB-082*
- GLP Tox.
  - BTZ-043*
  - PBTZ-169
  - TBA-7371*
  - GSK-070*
- Phase 1
  - Q203*
  - PBTZ169*
- Phase 2
  - Sutezolid (PNU-100480)
  - Linezolid EBA
  - SQ-109*
- Phase 3
  - Rifapentine - Moxifloxacin for Drug Sensitive TB
  - Delamanid (OPC-67683) with OBR for MDR-TB
  - Pretomanid-Moxifloxacin-Pyrazinamide Regimen (STAND)
  - Bedaquiline-Pretomanid-Linezolid NiX-TB Regimen
  - Bedaquiline-STREAM MDR-TB Trial Stage 2 with oral OBR (9 mo) or OBR with injectables (6 mo)
  - Bedaquiline-Linezolid with OBR for MDR-TB (NExT Trial)

Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diaryquinolone, benzothiazinone, imidazopyridine amide. New chemical class*

1 Details for projects listed can be found at http://www.newtbdrugs.org/pipeline.php and ongoing projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline-discovery.php

2 OBR = Optimized Background Regimen

www.newtbdrugs.org

Updated: October 2016
Treatment considerations: children

- >75% pulmonary/intrathoracic TB
- Wide spectrum of disease
- Paucibacillary disease compared to adult pulmonary TB (fewer lung cavities)
- Severe and disseminated TB (TBM and miliary TB) especially in young
- Treatment outcome in children generally good provided initiated early (paucibacillary)
- All treatment data extrapolated from adult studies
MDR-TB in children

- Estimated 50,000 cases of paediatric MDR-TB annually worldwide\(^1\)
- Limited evidence base to inform MDR-TB treatment in children
  - Single systematic review; no paediatric IPD meta-analysis\(^2\)
- Guidelines for treatment of TB extrapolated from adults
- Specific paediatric considerations
  - Paucibacillary disease
  - Broad spectrum of disease
  - Study definitions: confirmed vs clinical cases; definition of treatment outcomes in absence of much culture data
- Good response to antituberculosis treatment (81.7% treatment success in children\(^2\) vs 54% in adults\(^3\))

Low Treatment Success and High Mortality

**MDR TB**: 50% treatment success, 16% death

**XDR TB**: 24% treatment success, 30% death

*number of cases observed shown over the bars

WHO Global TB Report 2015
### Summary of treatment outcomes for children with multidrug-resistant tuberculosis

<table>
<thead>
<tr>
<th></th>
<th>Clinically diagnosed MDR-TB n=238</th>
<th>Confirmed MDR-TB without confirmed XDR-TB n=701</th>
<th>Confirmed XDR-TB n=36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cured</td>
<td>46 (19.3%)</td>
<td>327 (46.6%)</td>
<td>23 (64%)</td>
</tr>
<tr>
<td>Completed treatment</td>
<td>166 (69.7%)</td>
<td>209 (29.8%)</td>
<td>7 (19%)</td>
</tr>
<tr>
<td>Fail or relapse</td>
<td>0</td>
<td>14 (1.9%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Death</td>
<td>7 (2.9%)</td>
<td>73 (10.4%)</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Lost-to-follow-up</td>
<td>19 (8%)</td>
<td>77 (11%)</td>
<td>2 (6%)</td>
</tr>
</tbody>
</table>

*Harausz et al, in progress*
BDQ CRUSH: impact of dissolving on a typical bedaquiline PK profile

$T_{\text{max}}$: 4.3 to 5.2h
$C_{\text{max}}$: ↓ 5%

In press, Svensson
Levofloxacin: Simulated AUC
Assuming 20 mg/kg dosing

N=109, median age 2.1y (0.3-8.7), HIV+ 14.7%

Denti, Garcia-Prats, AAC, 2018
### PK STUDIES

<table>
<thead>
<tr>
<th>PK/safety studies</th>
<th>Study 35-</th>
<th>Rifapentine/isoniazid in HIV+/ -children &lt; 12 years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard first- and second-line drugs - Establishing doses that achieve adult-equivalent exposures</td>
<td>Study 35-</td>
<td>Rifapentine/isoniazid in HIV+/-children &lt; 12 years of age</td>
</tr>
<tr>
<td>DATiC: PK/safety first-line TB drugs (enrolment completed 2016):</td>
<td>NICHD R01:</td>
<td>McCilleron</td>
</tr>
<tr>
<td>MDR PK 1: PK, safety second-line drugs in children with/without HIV: levo, moxi, oflox, amik, HD INH, ethio, PAS, cycloserine) completed (NICHD R01) - Hesseling</td>
<td>MDR PK 2: Optimizing Levofloxacin, moxifloxacin, linezolid (NICHD Ro1): Garcia-Prats</td>
<td></td>
</tr>
<tr>
<td>OptiRIF Kids: high-dose rifampicin PK safety: opened 2017 (TB Alliance/Unitaid): Hesseling</td>
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</table>

### HIV/TB DDI studies

<table>
<thead>
<tr>
<th>HIV/TB DDI studies</th>
<th>DNDi: Ritonavir boosting of LPV/r in TB/HIV: completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICHD PK: first-line TB drugs with ART: completed</td>
<td></td>
</tr>
<tr>
<td>P1101: RAL-based ART with standard TB drugs: ongoing</td>
<td></td>
</tr>
<tr>
<td>EFFICACY STUDIES</td>
<td>ONGOING TRIALS</td>
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<td>--------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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<tr>
<td><strong>TB prevention</strong></td>
<td>• A5300 PHOENIX: delamanid vs. SD INH for MDR-TB prevention: 2018</td>
</tr>
<tr>
<td></td>
<td>• VQUIN: levo vs. placebo for MDR-TB prevention: open</td>
</tr>
<tr>
<td></td>
<td>• ACTG5279: one month of rifapentine+isoniazid daily for DS-TB prevention</td>
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<tr>
<td></td>
<td>• P4v9 Trial: 4 months RIF vs 9 months INH for DS-TB prevention: ongoing</td>
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<td></td>
<td>• TBTC 37: RPT 6 weeks vs. local SOC (RIF 4 mo or RPT/INH q week x 3 mo): planned</td>
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<td></td>
<td>• P1078: IPT in HIV-infected pregnant women</td>
</tr>
<tr>
<td><strong>DS-TB disease</strong></td>
<td>• TBM-KIDS: High-dose RIF +/- Levo for children with TBM (NICHD Ro1 - Dooley)</td>
</tr>
<tr>
<td>Reduce mortality, improve neurocognitive dysfunction</td>
<td>• SURE Kids: Gibb</td>
</tr>
<tr>
<td><strong>Non-severe DS-TB</strong></td>
<td>• SHINE: 4 vs. 6 months standard TB Rx (new FDCs, nested PK): open label (MRC CTU; Gibb)</td>
</tr>
<tr>
<td>Reduce treatment duration for children with non-severe disease</td>
<td>• N=1200 (accrual will be completed June 2018)</td>
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<tr>
<td></td>
<td>• SMART-KIDS: P2020</td>
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Data needed for MDR to inform regimens: rapid and efficient designs needed

1. PK and safety of BDQ (including in HIV+)
2. PK and safety of once-daily DLM
3. PK and safety of PA-824 in
4. PK and safety of DLM/BDQ co-treatment: 2020
5. PK and safety of linezolid, clofazimine in children: MDR PK 2
6. PK and safety: sutezolid
7. MDR TB and pregnancy: PHOENIX, 2026S
MDR TB 2 year plans: children, pregnant women

- Complete P1108 (Bedaquiline phase I, II) HIV+/-
- Implement P2005 (Delamanid Phase I, II) HIV+/-
- Implement A5300 and pregnancy sub study
- Implement P2020
- Complete Linezolid, clofazimine PK, safety
- Implement P1026 S (new MDR-TB arm with DLM, BDQ)
- TB trial registry: pregnancy
IMPAACT MDR-TB: 5 year plan

- Develop PA-824 phase I/II in children
- Develop Sutezolid phase I/II in children
- Complete PHOENIX, 2020
- Build capacity for paediatric MDR TB trials
<table>
<thead>
<tr>
<th>Gaps for children</th>
<th>Priority studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Prevention: RFTP INH 1 month</td>
<td>- PK and safety in children, pregnant women</td>
</tr>
<tr>
<td>- Optimal treatment for TB meningitis (levofloxacin, high dose rifampin)</td>
<td>- PK and outcome (TBM Kids; NICHD; Dooley): opened Q2 2017; SURE KIDS</td>
</tr>
<tr>
<td>- Rifampicin dose optimization (severe disease not addressed in SHINE, treatment shortening): OptiRif Kids</td>
<td>- Priority: building on SHINE, rifampin dose optimization</td>
</tr>
<tr>
<td>- Treatment shortening: non-severe and severe disease</td>
<td>- Opened Q1 2017; cohort 1 completed; cohort 2: n=12</td>
</tr>
<tr>
<td>- And need for treatment regardless of DST in future</td>
<td>- SHINE+: Priority – complementing SHINE and TBM Kids, Optirif Kids</td>
</tr>
</tbody>
</table>
NON-SEVERE TB

SEVERE TB
(INCLUDING DISSEMINATED)

Wiseman, Ped Infect Dis J 2014
Shorter treatment for minimal TB in children

A randomised trial of therapy shortening for minimal tuberculosis with new WHO-recommended doses/fixed-dose-combination drugs in African and Indian HIV+ and HIV- children

N=1200
1130 enrolled
New FDCs
<table>
<thead>
<tr>
<th><strong>Summary Information Type</strong></th>
<th><strong>Summary Details</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short Name Title of Trial</strong></td>
<td>SHINE (Shorter treatment for minimal TB in children)</td>
</tr>
<tr>
<td><strong>Long Title of Trial</strong></td>
<td>A randomized trial of therapy shortening for minimal tuberculosis with new WHO-recommended doses/ fixed-dose-combination drugs in African and Indian HIV+ and HIV- children</td>
</tr>
<tr>
<td><strong>Version</strong></td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Date</strong></td>
<td>24-Mar-2014</td>
</tr>
<tr>
<td><strong>ISRCTN #</strong></td>
<td>ISRCTNXXXXXXX</td>
</tr>
<tr>
<td><strong>Study Design</strong></td>
<td>Parallel group, randomised, non-inferiority, open label, 2 arm phase III clinical endpoint trial</td>
</tr>
<tr>
<td><strong>Type of Participants to be Studied</strong></td>
<td>Children &lt; 16 years with suspected minimal (limited) TB disease, with or without HIV infection, will be screened</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>South Africa (Cape Town); Zambia (Lusaka); Uganda (Kampala) and India (Chennai and Pune)</td>
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</tbody>
</table>
| **Interventions to be Compared** | **4-MONTH REGIMEN**<br>The experimental arm will be standard daily first-line anti-TB treatment for 16 weeks dosed according to revised WHO dosage recommendations: intensive 8 weeks Isoniazid (H), Rifampicin (R), Pyrazinamide (Z) with or without Ethambutol (E) according to local practice, HRZ(E), followed by continuation of 8 weeks HR.  

**6-MONTH REGIMEN**<br>The control arm will be standard daily first-line anti-TB treatment for 24 weeks dosed according to revised WHO dosage recommendations: intensive 8 weeks HRZ(E), followed by continuation of 16 weeks HR. |
<table>
<thead>
<tr>
<th>Group</th>
<th>AUC\textsubscript{0–24h} (h · mg/L)</th>
<th>C\textsubscript{max} (mg/L)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg/kg (control)</td>
<td>26.3 (21.3–40.9)</td>
<td>7.4 (6.1–9.9)</td>
</tr>
<tr>
<td>20 mg/kg</td>
<td>113 (77.5–162)</td>
<td>21.6 (16.0–31.9)</td>
</tr>
<tr>
<td>25 mg/kg</td>
<td>135 (91.5–228)</td>
<td>25.1 (16.3–34.6)</td>
</tr>
<tr>
<td>30 mg/kg</td>
<td>190 (84.7–436)</td>
<td>33.1 (17.6–55.8)</td>
</tr>
<tr>
<td>35 mg/kg</td>
<td>235 (166–321)</td>
<td>35.2 (28.6–44.2)</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: AUC\textsubscript{0–24h} = area under the time versus concentration curve up to 24 h after dose; C\textsubscript{max} = peak plasma concentration. Data are shown as geometric means and range.

*Serial venous blood samples were taken just prior to and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 h after the investigational products were taken under direct supervision and with a standardized meal.

Table 1. Steady state pharmacokinetics of RMP on day 14 in adults (n=68 patients) (50)
OptiRif Kids

- **Dosing cohorts**: n=20 per cohorts: A minimum of 60 (20 children per cohort) (i.e. 3 dosing cohorts) enrolled
- Demonstrate exposures in children similar to those achieved in adults receiving 35-40 mg/kg in HIGHRIF1 over 15 days
- No age de-escalation. Children enrolled in 3 age groups, with children in all 3 age groups included in each dosing cohort:
  - Age group 1: Age ≥ 6 to < 12 years
  - Age group 2: Age ≥ 2 to < 6 years
  - Age group 3: Age ≥ 0 to < 2 years
  - Status: Dosing cohort 1 completed (15-20 mg/kg)
  - Dosing cohort 2 open: 35 mg/kg – up to 50 mg/kg
Children

- Complete P2001
- Develop 1 month RFPRT/INH for DS-TB prevention: PK, safety: separate paediatric and pregnant studies
- Develop phase 3 treatment shortening treatment trial (full spectrum of TB disease)
- Work towards TB treatment regardless of DST
Diagnostics and biomarkers: DS-TB and DR-TB

- Support nested diagnostics, biomarker studies
- Support expansion of site and TB lab capacity: MDR-TB
- Use IMPAACT and other lab platforms
- Work with ITBSL
- Work with other investigators: serum, urine biomarkers
- Evaluate novel commercial molecular tests (Xpert Ultra), DST methods, WGS, correlates of risk
- Ideal cohorts through planned protocols: SMART-Kids, P1108, PHOENIX, diagnostic studies: prognostic markers, treatment response and diagnostic markers
TB vaccines

- Collaborate with HVTN to design and conduct studies in infants and adolescents
- P1113
Milestones

- P1078 completed
- P2001: completion 2018
- P1113 completed
- Opened to accrual: P1108, P2005
- BDQ CRUSH completed
- PHOENIX: Version 1.0; maternal sub study
- IMPAACT 2020: Version 1.0 by July 2018
- P1026S: new TB arms
Mentored investigator graduates

- Adrie Bekker: P1106, 20126S
- Jyothi Mathad: P2001
- Vidya Mave: BJMC
- Anthony Garcia-Prats: P2005, 2020
New mentored investigators

- Ethel Weld: JHU
- Yael Hirsch-Moverman: CU
- Sylvia LaCourse: UW
- Lisa Cranmer: Emory
- Jeff Tornheim: JHU
- Mandar Paradkar: BJMC
- Pauline Howell: Sizwe
- Christy Beneri: Stonybrook
- Jennifer Hughes: SU
- Nicole Salazar-Austin: JHU
- Louvina van der Laan: SU