Tuberculosis Clinical Trials on the Horizon

C. Robert Horsburgh, Jr.
Boston University School of Public Health

Outline

• Current TB treatment and its theoretical basis
• New and “repurposed” drugs for TB treatment
• Goals of clinical trials for prevention and treatment of TB
• TB Clinical trials currently underway
• TB Clinical trials in planning stages

Schematic Time Course of TB Treatment
Current State of DS-TB Treatment

- Combination therapy essential to prevent emergence of resistance
- Current 6-month regimen validated in clinical trials in 1980s
- Average cure proportion of this regimen is 90-95%
- Emergence of additional resistance rare if taken as directed
- Regimens relatively well tolerated

Goals of TB Treatment Trials

- Shorten duration of treatment
- Increase cure proportion
- Decrease relapse
- Minimize emergence of resistance
- Optimize dosing
- Minimize adverse drug reactions
- Maximize compatibility with antiretrovirals
- Prevent progression from infection to disease

New and “repurposed” Drugs for TB Treatment
Global TB Drug Pipeline

Discovery

Preclinical Development

Clinical Development

Lead Optimization

Early Stage Development

GLP Tox.

Phase 1

Phase 2

Phase 3

Cyclopeptides
Diarylquinolines
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

TBI-166
CPZEN-45*
SQ609*
1599*
BTZ-043*
PBTZ169*
TBA-7371*
GSK-070*
Q203*

Sutezolid (PNU-100480)
Sutezolid EBA
High Dose Rifampicin for DS-TB
Bedaquiline (TMC207)-Pretomanid (PA-824) - Pyrazinamide Regimen
Levofoxacin with OBR for MDR-TB

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, diarylquinoline, benzothiazinone, imidazopyridine amide. New chemical class*

Details for projects listed can be found at [http://www.newtbdugs.org/pipeline.php](http://www.newtbdugs.org/pipeline.php) and ongoing projects without a lead compound series identified can be viewed at [http://www.newtbdugs.org/pipeline-discovery.php](http://www.newtbdugs.org/pipeline-discovery.php)

OBR = Optimized Background Regimen

[www.newtbdugs.org](http://www.newtbdugs.org)

Updated: May 2016
New Antituberculosis Drugs in Clinical Development, 2016

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Company</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifapentian</td>
<td>Rifamycin</td>
<td>Sanofi-Aventis</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>Fluoroquinolone</td>
<td>Bayer/GATB</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Bedaquiline</td>
<td>Diarylquinolone</td>
<td>Janssen</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Delamanid</td>
<td>Imidazooxazole</td>
<td>Otsuka</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Pretomanid</td>
<td>Imidazooxazine</td>
<td>GATB</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Sutezolid</td>
<td>Oxazolidinone</td>
<td>Sequella</td>
<td>Phase 2</td>
</tr>
</tbody>
</table>

Bedaquiline (TMC-207)

- Drug class: diarylquinolone
- Mode of action: inhibits proton pump for ATP synthase
- Half life: 165 days
- Toxicities: Nausea, QT prolongation
- Chemical Structure:

![Chemical Structure Image]
Bedaquiline Phase 2 Study
Time to sputum culture conversion

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Positive Culture (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
</tr>
<tr>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>18</td>
<td>0.5</td>
</tr>
</tbody>
</table>

---

**Bedaquiline Phase 2 Study**
**Final results**

<table>
<thead>
<tr>
<th></th>
<th>Bedaquiline+OBT</th>
<th>Placebo+OBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>79 patients</td>
<td>81 patients</td>
</tr>
<tr>
<td>Median Conversion</td>
<td>12 weeks</td>
<td>18 Weeks*</td>
</tr>
<tr>
<td>&quot;Cure&quot; at week 120</td>
<td>58%</td>
<td>32%*</td>
</tr>
<tr>
<td>Serious Adverse Events</td>
<td>23%</td>
<td>19%</td>
</tr>
</tbody>
</table>

*p<0.01

---

**Delamanid (OPC-67683)**

- **Drug class:** nitroimidazo-oxazole
- **Mode of action:** mycolic acid synthesis inhibitor
- **Half life:** 20-30 hours
- **Toxicities:** Nausea, QT prolongation
- **Chemical Structure:**

![](image)
New TB Clinical Trials on the Horizon

Figure 2. Proportion of Patients with Sputum-Culture Conversion by Day 57.
Delamanid Phase 2 Study

- Description: Addition of Delamanid (D) to OBT
- Regimens: OBT+D 100 mg bid
  - OBT+D 200mg bid
  - OBT+Placebo
- Target population: Adults with pulmonary MDR-TB, CD4>350 if HIV+
- Outcome: Sputum conversion at 8 weeks
- Size: 430 patients

Pretomanid (PA-824)

- Drug class: nitroimidazo-oxazine
- Mode of action: mycolic acid synthesis inhibitor
- Half life: 16-20 hours
- Toxicities: QT prolongation?
- Chemical Structure:
Sutezolid (PNU-100480)

- Drug class: oxazolidinone
- Mode of action: inhibition of protein synthesis by ribosomal binding
- Half life: 4-6 hours
- Toxicities: Unknown
- Chemical Structure:

\[ X = O, \text{Linzolid} \]
\[ X = S, \text{PNU 100480} \]
Clofazimine in MDR-TB Treatment

105 patients randomized to OBT+CFZ vs. OBT+Placebo.
Linezolid in the Treatment of XDR-TB

A Culture Conversion in Solid Medium

Cumulative Probability of Conversion

Days since Randomization

NEJM 2012;367:1508-18

Stable conversion, liquid, by RPT dose, MITT

Weeks on treatment

Probability that stable conversion has been observed

Data frozen on 2013-04-01. Analysis run on 2013-04-10

P1200
P900
P600
RIF600
New TB Clinical Trials on the Horizon

**Clofazimine in MDR-TB Treatment**

105 patients randomized to OBT+CFZ vs. OBT+Placebo

*Clin Infect Dis 2015;60:1361*

**Linezolid in the Treatment of XDR-TB**

*NEJM 2012;367:1508-18*
High Dose Rifampicin increases EBA
High Dose Rifampicin increases EBA

 AJRCCM 2015;191:1062

8 TB Trials to optimize dosing and Minimize DDI and Adverse Effects

- ACTG 5307 (Essentiality of INH)
- ACTG 5312 (High dose INH for inhA mutations)
- Opti-Q (optimization of levofloxacin dosing)
- ACTG 5356 (optimization of linezolid dosing)
- ACTG 5343 (BDQ and DLM QT interactions)
- C211 Study (Pediatric PK of BDQ)
- IMPAACT P1108 Trial (Pediatric PK of BDQ)
- Otsuka Pediatric PK Trial (Pediatric PK of DLM)

ACTG 5307 Trial (Phase 2)

- Description: EBA of RZE with/without INH in DS-TB
- Regimens: HRZE days 1-2, then HRZE days 3-14
  HRZE days 1-2, then RZE days 3-14
  HRZE days 1-2, then MRZE days 3-14
  RZE days 1-2, then RZE days 3-14
- Sponsor: ACTG
- Target population: Smear+ DS-TB, adults
- Outcomes: decline in CFU over 14 days
- Size: 60 patients
- Sites: South Africa
- Expected results: 2017
ACTG 5312 Trial (Phase 2)
- Description: EBA of High dose INH in patients with isolates with inhA mutations
- Regimens: INH 5 mg/kg + B6
  - INH 10 mg/kg + B6
  - INH 15 mg/kg + B6
  - INH 5 mg/kg + B6 (no inhA or katG mutation)
- Sponsor: ACTG
- Target population: Smear+ MDR-TB, adults, +/- HIV
- Outcomes: decline in CFU over 7 days
- Size: 198 patients
- Sites: South Africa
- Expected results: 2018

Opti-Q Study (Phase 2)
- Description: levofloxacin in 4 doses + OBT to identify most efficacious tolerable dose of levo for MDR-TB
- Regimens: Levo at 11, 14, 17 and 20 mg/kg, all plus OBT for 6 months
- Sponsors: NIH, CDC, Macleods
- Target population: pulmonary MDR-TB, adults, FQ susceptible
- Outcome: time to sputum culture conversion
- Size: 100 patients
- Sites: Peru, South Africa
- Expected results: 2017

Optimizing the dose of a TB drug

Drug Safety - Therapeutic Index

New TB Clinical Trials on the Horizon
ACTG 5356 Trial (Phase 2)

- Description: Linezolid dose optimization with delamanid
- Regimens: DEL+OBT
  - DEL+LZD300QD+OBT
  - DEL+LZD600QD+OBT
  - DEL+LZD1200QOD+OBT
- Sponsor: ACTG
- Target population: Smear/Xpert+ MDR-TB, adults, +/- HIV
- Outcomes: Discontinuation of assigned LZD dose
- Size: 180 patients
- Sites: Global
- Expected results: 2018

ACTG 5343 Trial (Phase 2)

- Description: BDQ and DEL alone and in combination
- Regimens: BDQ for 6 months + OBT (20-24 months)
  - DEL for 6 months + OBT (20-24 months)
  - BDQ + DEL for 6 months + OBT (20-24 mos)
- Sponsor: ACTG
- Target population: Smear/Xpert+ MDR-TB, adults, +/- HIV
- Outcomes: Mean change in QTcF
- Size: 84 patients
- Sites: South Africa
- Expected results: 2018

5 Clinical Trials for DS-TB

Goal: Shorten treatment while maintaining ~95% relapse-free cure
Outcomes of 4-month DS-TB Treatment Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Relapse Rate in 6-month Arm</th>
<th>Relapse Rate in 4-month Arm</th>
<th>Non-inferiority?</th>
</tr>
</thead>
<tbody>
<tr>
<td>ReMox</td>
<td>2.4%</td>
<td>8.2%</td>
<td>Inferior</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11.7%</td>
<td>Inferior</td>
</tr>
<tr>
<td>Oflotub</td>
<td>7.3%</td>
<td>14.8%</td>
<td>Inferior</td>
</tr>
<tr>
<td>Riflaquin</td>
<td>3.2%</td>
<td>14.1%</td>
<td>Inferior</td>
</tr>
<tr>
<td>NIRT</td>
<td>5.0%</td>
<td>8.9%</td>
<td>Inferior</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14.5%</td>
<td>Inferior</td>
</tr>
<tr>
<td>TBRU</td>
<td>1.5%</td>
<td>6.6%</td>
<td>Inferior</td>
</tr>
</tbody>
</table>

NIRT Trial 000024

- Description: Non-inferiority trial of two four-month regimens for DS-TB
- Regimens: 2HRZEM + 2HRM
  2HRZEM + 2HRM₃
  2HRZE+ 4HR
- Sponsor: NIRT
- Target population: Pulmonary DS-TB, adults
- Outcome: Failure/Relapse
- Size: 1650 patients
- Sites: India
- Expected completion: ?

TBTC 31/ACTG 5349 Trial

- Description: Non-inferiority trial of 4-month Rifapentine and Rifapentine/Moxifloxacin regimens for DS-TB
- Regimens: 2HPZE + 2HP
  2HPZM + 2HPM
  2HRZE+ 4HR
- Sponsors: TBTC/ACTG
- Target population: Pulmonary DS-TB, adults
- Outcome: Failure/Relapse
- Size: 2450 patients
- Sites: Global
- Expected completion: 2019
<table>
<thead>
<tr>
<th><strong>STAND Trial</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description:</strong> 4-6 month trial of Pretomanid in combination with moxifloxacin and PZA</td>
</tr>
</tbody>
</table>
| **Regimens:** PA\textsubscript{100-M-Z} for DS-TB (4 months)  
PA\textsubscript{200-M-Z} for DS-TB (6 months)  
HRZE for DS-TB  
PA\textsubscript{200-M-Z} for MDR-TB (FQ & Z susceptible) |
| **Sponsors:** GATB |
| **Target population:** smear+ MDR-TB, adults |
| **Outcome:** quantitative sputum cultures |
| **Size:** 1300 patients |
| **Sites:** Global |
| **Expected results:** Doubtful |

<table>
<thead>
<tr>
<th><strong>Rifashort Trial</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description:</strong> Non-inferiority trial of 4-month High-dose Rifampicin regimens for DS-TB</td>
</tr>
</tbody>
</table>
| **Regimens:** 2HR\textsubscript{1800ZE} + 2HR\textsubscript{1800}  
2HR\textsubscript{1200ZE} + 2HR\textsubscript{1200}  
2HR\textsubscript{900ZE} + 4HR\textsubscript{600} |
| **Sponsors:** MRC/Wellcome Trust/DFID |
| **Target population:** Pulmonary DS-TB, adults |
| **Outcome:** Failure/Relapse |
| **Size:** 654 patients |
| **Sites:** Botswana, Uganda, Peru, Bolivia |
| **Expected completion:** 2019 |

<table>
<thead>
<tr>
<th><strong>SHINE Trial</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description:</strong> Non-inferiority trial of 4-month regimen for DS-TB in children with non-severe disease</td>
</tr>
</tbody>
</table>
| **Regimens:** 2HRZ(E) + 4HR  
2HRZ(E) + 2HR |
| **Sponsors:** MRC/Wellcome Trust/GATB/UKAID |
| **Target population:** non-severe DS-TB, ages 0-15 |
| **Outcome:** Failure/Relapse |
| **Size:** 1200 patients |
| **Sites:** India, South Africa, Uganda, Zambia |
| **Expected completion:** ? |
7 Clinical Trials for MDR-TB

Goal: Shorten treatment and improve upon ~65% relapse-free cure

STREAM Trial Stage 1 (Phase 3)

- Description: Modified Bangladesh regimen (with moxifloxacin in place of gatifloxacin) compared to "standard" MDR-TB regimen
- Regimens: 7-drug regimen (9 months)
  4-5 drugs (18-24 months)
- Sponsors: IUATLD, USAID
- Target population: smear+ MDR-TB, adults
- Outcome: Failure, relapse, default or death
- Size: 400 patients – 100% enrolled
- Sites: Ethiopia, Vietnam, South Africa
- Expected completion: 2017

STREAM Trial Stage 2 (Phase 3)

- Description: Addition of two new arms to STREAM
- Regimens:
  SOC (continues both WHO and Bangladesh)
  BDQ+CFZ+EMB+LFX+PZA+4(INH,+PTO) – 9 mos
  BDQ+LFX+CFZ+PZA+2(INH,+KM) – 6 mos
- Sponsor: USAID, others
- Target population: smear+ MDR-TB, adults
- Outcome: Failure, relapse, default or death
- Size: 1100 patients
- Sites: Ethiopia, Vietnam, South Africa, Mongolia
- Expected completion: 2019
### NeXT Trial (Phase 3)
- **Description:** 6-9 month trial of bedaquiline in combination with other oral agents (duration dependent on culture conversion)
- **Regimens:** BDQ+LZD+LFX+ETA/INHH+PZA (6-9 Mo) MXF+ETH+TER+KM+PZA (21-24 Mo)
- **Sponsors:** MCC
- **Target population:** MDR-TB, adults
- **Outcome:** “favorable outcome” at 24 months
- **Size:** 300 patients
- **Sites:** South Africa
- **Expected results:** 2020

### Delamanid Confirmatory Trial (Phase 3)
- **Description:** Addition of D to OBT
- **Regimens:**
  - OBT+D 100 mg bid (6 months/OBT 18 months)
  - OBT+D 50 mg bid (6 months/OBT 18 months)
  - OBT+Placebo (24 months)
- **Sponsor:** Otsuka Pharmaceutical Development
- **Target population:** Adults with pulmonary MDR-TB, CD4>350 if HIV+
- **Outcome:** Time to sputum conversion through 6 months
- **Size:** 430 patients
- **Duration:** 2017
- **Status:** 100% enrolled

### MDR-END Trial (Phase 2c)
- **Description:** Injectable-free DLM-based regimen vs SOC
- **Regimens:**
  - SOC (WHO 20-24 months)
  - DLM+LZD+LFX+PZA for 9-12 months
- **Sponsor:** Korean government
- **Target population:** smear+ MDR-TB, adults 18+
- **Outcome:** Failure, relapse, default or death
- **Size:** 96 Patients
- **Sites:** Korea
- **Expected completion:** 2019
NiX-TB Trial (Phase 2/3)
- Description: 6 month trial of Pretomanid in combination with bedaquiline and linezolid
- Regimen: BDQ-PRT-LZD (Single Arm)
- Sponsor: GATB
- Target population: XDR-TB, adults
- Outcome: relapse-free cure
- Size: 100 patients
- Sites: South Africa
- Expected results: 2017

endTB Trial (Phase 3)
- Description: Combination regimens, adaptive randomization
- Regimens: WHO SOC (20-24 months)
  - BDQ+LZD+MXF+PZA for 9 months
  - BDQ+CF+LZD+LFX+PZA for 9 months
  - BDQ+DEL+LZD+LFX+PZA for 9 months
  - DEL+CF+LZD+LFX+PZA for 9 months
  - DEL+CF+MXF+PZA for 9 months
- Sponsor: MSF/Unitaid
- Target population: smear+ MDR-TB, adults 15+
- Outcome: Failure, relapse, default or death
- Size: 750 Patients
- Sites: Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru
- Expected completion: 2021

TB-PRACTECAL Trial (Phase 2/3)
- Description: Staged trial of BDQ/PTM/LZD regimens:
  - SOC (WHO 20-24 month regimen)
  - BDQ+PTM+LZD+MFX for 6 months
  - BDQ+PTM+LZD+CF for 6 months
  - BDQ+PTM+LZD for 6 months
- Sponsor: MSF
- Target population: smear/Xpert+ MDR-TB, adults 18+
- Outcome: Failure, relapse, default or death
- Size: 630 Patients
- Sites: Uzbekistan, Swaziland
- Expected completion: ?
7 Clinical Trials for Prevention of TB

Goal: Identify shorter treatment for Latent TB
While maintaining 90% reduction in TB Disease

4RIF vs. 9INH Trial
- Description: Rif daily versus 9 INH for TB prevention
- Regimens: RIF daily for 4 months
  INH daily for 9 months
- Sponsor: CIHR
- Target population: TST+ adults (HIV+ if not on PI)
- Outcome: TB Disease
- Size: 5720
- Sites: Australia, Benin, Brazil, Canada, Ghana, Guinea, Indonesia, Korea, Saudi Arabia
- Expected Results: 2017

ACTG 5279 Trial (Phase 3)
- Description: 1 month daily INH + Rifapentine for prevention of TB disease
- Regimens: RPT+INH daily for 4 weeks
  INH daily for 9 months
- Sponsor: ACTG
- Target population: TST+ persons with HIV infection
- Outcome: TB Disease
- Size: 3000
- Sites: South Africa
- Expected Results: 2017
<table>
<thead>
<tr>
<th>MDR-TB prevention trials</th>
<th>PHOENix</th>
<th>V-QUIN</th>
<th>TB-CHAMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>DLM vs standard dose INH daily for 26 weeks</td>
<td>LVF vs placebo daily for 6 months</td>
<td>LVF (novel paediatric formulation) vs. placebo daily for 6 months</td>
</tr>
<tr>
<td>Design</td>
<td>Cluster randomized; superiority Community-based</td>
<td>Cluster randomized; superiority Community-based</td>
<td>Cluster randomized; superiority Community-based</td>
</tr>
<tr>
<td>Target Population</td>
<td>HIV+ Children 0-5 yrs TST/IGRA+ &gt; 5 y Paediatric enrolment on hold</td>
<td>LVF decreases TB incidence from 3% untreated 80% power</td>
<td>0-5 y regardless of TST or HIV status</td>
</tr>
<tr>
<td>Assumptions</td>
<td>DLM decreases TB incidence by 50% from 5% to 2.5% 90% power</td>
<td>LVF decreases TB incidence from 7 to 3.5% 80% power</td>
<td>LVF decreases TB incidence from 7 to 3.5% 80% power</td>
</tr>
<tr>
<td>Sample size</td>
<td>1726 Households 3452 contacts</td>
<td>1326 Households 2785 contacts</td>
<td>778 Households 1556 contacts</td>
</tr>
<tr>
<td>Sites, funder</td>
<td>ACTG &amp; IMPAACT sites DAIDS Churchyard, Swindells, Gupta, Hesseling</td>
<td>Viet Nam Australian MRC Fox/Nguyen</td>
<td>South Africa BMRC/Wellcome Trust Hesseling/Seddon</td>
</tr>
<tr>
<td>Timelines to open</td>
<td>Q4 2017</td>
<td>Open (Q1 2016)</td>
<td>Q4 2016</td>
</tr>
</tbody>
</table>
## MDR-TB prevention trials

<table>
<thead>
<tr>
<th>Intervention</th>
<th>TB-CHAMP</th>
<th>V-QUIN</th>
<th>PHENIX</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td>LVF (novel paediatric formulation) vs. placebo daily for 6 months</td>
<td>LVF vs. placebo daily for 6 months</td>
<td>LVF vs standard dose INH daily for 26 weeks</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Cluster randomized, superiority Community-based</td>
<td>Cluster randomized, superiority Community-based</td>
<td>Cluster randomized, superiority Community-based</td>
</tr>
<tr>
<td><strong>Target Population</strong></td>
<td>0-5 y regardless of TST or HIV status</td>
<td>All ages</td>
<td>TST +</td>
</tr>
<tr>
<td><strong>Target Population</strong></td>
<td>Paediatric enrolment on hold</td>
<td>TST +</td>
<td>HIV +</td>
</tr>
<tr>
<td><strong>Assumptions</strong></td>
<td>LVF decreases TB incidence from 7 to 3.5% 80% power</td>
<td>LVF decreases TB incidence by 70% from 3% untreated 80% power</td>
<td>DLM decreases TB incidence by 50% from 5% to 2.5% 90% power</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>1759 Households 1558 contacts</td>
<td>1389 Households 2786 contacts</td>
<td>1720 Households 3452 contacts</td>
</tr>
<tr>
<td><strong>Sites, funder</strong></td>
<td>South Africa</td>
<td>Viet Nam Australian MRC Fox/Nguyen</td>
<td>ACTG &amp; IMPAACT sites DAIDS Churchyard, Swindells, Gupta, Hesseling</td>
</tr>
<tr>
<td><strong>Timelines to open</strong></td>
<td>Q4 2016 Open (Q1 2016)</td>
<td>Q4 2017</td>
<td>Q4 2017</td>
</tr>
</tbody>
</table>

### SATVI POI Vaccine Trial

- **Description:** VPM 1003 (listerialysin containing BCG) versus placebo for TB prevention
- **Regimens:** VPM 1003
  - Placebo
- **Sponsor:** SII
- **Target population:** High-risk adolescents
- **Outcome:** TB Disease
- **Size:** 2000
- **Sites:** South Africa
- **Expected Results:** ?

### Dar-901 POI Vaccine Trial

- **Description:** Dar 901 (killed NTM vaccine) versus placebo for TB prevention
- **Regimens:** Dar-901
  - Placebo
- **Sponsor:** Dartmouth Medical School
- **Target population:** High-risk adolescents
- **Outcome:** TB Disease
- **Size:** 2000
- **Sites:** Tanzania
- **Expected Results:** ?
TB Clinical Trials in Planning Stages

- TRUNCATE Ultrashort treatment strategy trial
- DAZZLE Duration of treatment trial
- VPM 1003 Prevention of reinfection trial
- ID93 Prevention of infection trial
- WHIP Prevention of progression trial

Schematic Time Course of TB Treatment

TRUNCATE Trial

- Description: Non-inferiority MAMS trial of 2-3 month combination regimens for DS-TB
- Regimens: HRZE (6 months)
  5-drug combinations of isoniazid, high-dose rifampicin, linezolid, bedaquiline, delamanid, rifapentine, ethambutol and PZA
- Target population: Pulmonary DS-TB, adults
- Outcome: Failure/Relapse
  - Size: 1300 patients
  - Sponsors: MRC/Wellcome Trust/DFID
- Sites: Asian TB Trial Network
- Completion: ?
Multi-Arm Multi-Stage Design (MAMS)
Multi-Arm Multi-Stage Design (MAMS)

DAZZLE Trial (Phase 2/3)
- Description: Duration-randomized Injectable-free DLM-based regimen vs SOC
- Regimens: SOC (WHO 9-month or 20-24 month) DLM+LZD+LFX+PZA for 24,32,40,48,or 56 wks
- Target population: smear+ MDR-TB, adults 18+
- Outcome: Failure, relapse, default or death
- Size: 350 Patients
- Sites: TBD
- Expected completion: ?
Conclusions

- A broad spectrum of TB clinical trials are in the field and in planning stages
- New and repurposed TB drug classes may increase TB disease treatment responses and shorten treatment duration
- Tolerability of a number of the new and repurposed agents remains to be defined, especially when used in combination
- TB vaccines may also prove useful in improving treatment outcomes