TB SCIENTIFIC COMMITTEE
ACTIVITY UPDATE

ANNEKE C. HESSELING
AMITA GUPTA

13 JUNE 2016
TBSC MEETING
TBSC Aims

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

Model: close collaboration with other networks, pharma, academic community, other partners
TBSC core members

- Anneke Hesseling (chair): SA
- Amita Gupta (vice-chair): USA
- Kelly Dooley (clinical pharmacology): USA
- Bob Husson (diagnostics/biomarkers): USA
- Gerhard Walzl (biomarkers): SA
- Anne-Marie Demers (ITBSL, TB microbiologist): SA
- Lyndsay McKenna (Advocacy): USA
- Vanessa Rouzier (treatment trials): Haiti
- Carol Onyango (diagnostics, PK): Uganda
- Avy Violari (treatment trials, vaccines): SA
Extensive mentored investigator program


- Lisa Cranmer (maternal infant TB): Emory
- Elin Svensson (pharmacometrics): Uppsala
- Adrie Bekker (maternal infant PK): Stellenbosch
- Vidaye Mave (PK, MDR-TB): Pune
- Ethel Weld (PK): JHU
- Vanessa Rouzier (MDR-TB, PK): Gheskio, Haiti
- Kathryn Snow (epi, pregnancy, adolescents): Melbourne
- Heather Draper (biostats): Stellenbosch
- Sylvia La Course (maternal immunology): Seattle
- Jyothi Mathad (maternal TB, immunology): Cornell
- Liz Walters (Diagnostics): Stellenbosch
- Tony Garcia-Prats (MDR-TB): Stellenbosch
- Christ Beneri (TB prevention): Stonybrook
Current IMPAACT sites and TB burden

FIGURE 2.5

Estimated TB incidence rates, 2012
<table>
<thead>
<tr>
<th>Estimated total 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>
</tr>
<tr>
<td>TB deaths</td>
<td>136 000</td>
</tr>
<tr>
<td></td>
<td>(81 000 HIV-)</td>
</tr>
<tr>
<td></td>
<td>13.6% case fatality rate</td>
</tr>
<tr>
<td>TB infections</td>
<td>6.6 million</td>
</tr>
</tbody>
</table>
MDR-TB: Burden, impact on children

- WHO estimated 480,000 new cases in 2014
- Xpert MTB/RIF rollout: increased number of adult MDR-TB cases diagnosed and increasing numbers of child contacts identified
- Globally, at least a million children potentially exposed to MDR-TB each year
- Young and HIV-infected children: high risk of TB disease progression once infected
- HIV-infected children have poorer MDR-TB treatment outcome
- Current regimens cure >75% of children with MDR-TB but are long, toxic and not practical
- Limited evidence base for MDR-TB preventive regimens
- PHOENIX and other preventive trials will identify more paediatric MDR-TB cases in future

MDR TB and children

Daily intramuscular injections

Pill burden for MDR-TB and ARV co-treatment (single day’s treatment)
No paediatric formulations
## Adverse events in children treated for MDR-TB (n = 137)

<table>
<thead>
<tr>
<th>Grade of AE</th>
<th>Gr 0</th>
<th>Gr 1</th>
<th>Gr 2</th>
<th>Gr 3-4</th>
<th>Any AE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint, muscle or bone pain</td>
<td>122</td>
<td>11</td>
<td>2</td>
<td>2 (1.5)</td>
<td>15 (10.9)</td>
</tr>
<tr>
<td>Skin rashes</td>
<td>104</td>
<td>30</td>
<td>2</td>
<td>1 (0.7)</td>
<td>33 (24.1)</td>
</tr>
<tr>
<td>Itchy skin</td>
<td>110</td>
<td>24</td>
<td>2</td>
<td>1 (0.7)</td>
<td>27 (19.7)</td>
</tr>
<tr>
<td>Headache</td>
<td>120</td>
<td>16</td>
<td>1</td>
<td>0</td>
<td>17 (12.4)</td>
</tr>
<tr>
<td>Sleep/mood problem</td>
<td>124</td>
<td>9</td>
<td>3</td>
<td>1 (0.7)</td>
<td>13 (9.5)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>118</td>
<td>17</td>
<td>1</td>
<td>1 (0.7)</td>
<td>19 (13.9)</td>
</tr>
<tr>
<td>Visual problem</td>
<td>132</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>5 (3.6)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>113</td>
<td>20</td>
<td>3</td>
<td>1 (0.7)</td>
<td>24 (17.5)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>125</td>
<td>10</td>
<td>1</td>
<td>1 (0.7)</td>
<td>12 (8.8)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>133</td>
<td>1</td>
<td>2</td>
<td>1 (0.7)</td>
<td>4 (2.9)</td>
</tr>
<tr>
<td>↓Appetite/nausea</td>
<td>118</td>
<td>14</td>
<td>3</td>
<td>1 (0.7)</td>
<td>18 (13.1)</td>
</tr>
<tr>
<td>Hearing loss (n=142)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25 (17.6)</td>
</tr>
<tr>
<td>Thyroxine supplementation (n=142; ↑TSH &amp; ↓fT4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>32 (22.5)</td>
</tr>
</tbody>
</table>

*Seddon, Clin Infect Dis 2013*
**BEDAQUILINE**
Licensed in adults based on phase IIb data: accelerated pathway

**Table 2. Adverse Events during 120 Weeks in the Intention-to-Treat Population.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bedaquiline (N = 79)</th>
<th>Placebo (N = 81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of overall treatment phase (range) — wk</td>
<td>91.7 (2.0–120.0)</td>
<td>94.1 (2.0–137.3)</td>
</tr>
<tr>
<td>Adverse event — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>78 (99)</td>
<td>79 (98)</td>
</tr>
<tr>
<td>Related to treatment</td>
<td>55 (70)</td>
<td>56 (69)</td>
</tr>
<tr>
<td>Grade 3 or 4†</td>
<td>34 (43)</td>
<td>29 (36)</td>
</tr>
<tr>
<td>Leading to discontinuation of treatment</td>
<td>4 (5)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Serious adverse events — no. (%)‡</td>
<td>18 (23)</td>
<td>15 (19)</td>
</tr>
<tr>
<td>Adverse event occurring in ≥20% of patients — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>32 (41)</td>
<td>30 (37)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>29 (37)</td>
<td>22 (27)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>23 (29)</td>
<td>22 (27)</td>
</tr>
<tr>
<td>Headache</td>
<td>23 (29)</td>
<td>18 (22)</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>20 (25)</td>
<td>27 (33)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>16 (20)</td>
<td>14 (17)</td>
</tr>
</tbody>
</table>
HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SIRTURO™ safely and effectively. See full prescribing information for SIRTURO.

SIRTURO™ (bedaquiline) Tablets

Initial U.S. Approval – 2012

WARNINGS:

See Full Prescribing Information for complete boxed warning.

- An increased risk of death was seen in the SIRTURO treatment group (9/79, 11.4%) compared to the placebo treatment group (2/81, 2.5%) in one placebo-controlled trial. Only use SIRTURO when an effective treatment regimen cannot otherwise be provided.

- QT prolongation can occur with SIRTURO. Use with drugs that prolong the QT interval may cause additive QT prolongation.

-------------------------------INDICATIONS AND USAGE-------------------------------

SIRTURO is a diarylquinoline antitubercular drug indicated as part of combination therapy in adults (≥ 18 years) with pulmonary multi-drug resistant tuberculosis (MDR-TB). Reserve SIRTURO for use when an effective treatment regimen cannot otherwise be provided. SIRTURO is not indicated for the treatment of latent, extra-pulmonary or drug-sensitive tuberculosis. (1)
HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SIRTURO™ safely and effectively. See full prescribing information for SIRTURO.

SIRTURO™ (bedaquiline) Tablets
Initial U.S. Approval – 2012

• FDA approved 2012
• EMA approved 2014
• MCC approved 2015
• Approved in India 2015
• Part of rollout routine programs in adults

WARNINGS

See Full Prescribing Information for

• An increased risk of death was seen in the treatment group (9/79, 11.4%) compared to the control treatment group (2/81, 2.5%) in clinical trials.

Only use SIRTURO when an effective treatment regimen cannot otherwise be provided.

• QT prolongation can occur with SIRTURO. Use with drugs that prolong the QT interval may cause additive QT prolongation.

-----------------------------------INDICATIONS AND USAGE-----------------------------------

SIRTURO is a diarylquinoline antimycobacterial drug indicated as part of combination therapy in adults (≥ 18 years) with pulmonary multi-drug resistant tuberculosis (MDR-TB). Reserve SIRTURO for use when an effective treatment regimen cannot otherwise be provided. SIRTURO is not indicated for the treatment of latent, extra-pulmonary or drug-sensitive tuberculosis. (1)
IMPAACT P1108

- Phase I/II dose finding trial of PK and long-term safety of bedaquiline in HIV+ and - children with MDR-TB on OBR
- N=60 (up to 72 children)
- Minimum 18 HIV-infected children
- Adaptive design, real time PK analyses and modeling
- Modified age de-escalation to enroll younger children rapidly
- PK: University Cape Town
- Modeling: Uppsala University
- Complementing planned Janssen registration study (not open)
- P1108 sites: India, Haiti, South Africa (n=5)
PRIMARY OBJECTIVES

In HIV-infected and HIV-uninfected infants, children and adolescents receiving BDQ plus optimized background regimens (OBR) for MDR-TB:

- To determine the BDQ doses that achieve similar weekly exposure (area under the curve; AUC) of BDQ compared to adults taking BDQ at the standard recommended dose.
- To evaluate the safety and tolerability of BDQ over 24 weeks from the initiation of study treatment.
SECONDARY OBJECTIVES

- To evaluate the PK of BDQ over the 24-week dosing period, by HIV status.
- To describe the long-term safety and tolerability of BDQ over a 120-week (30-month) total follow-up period, by HIV status.
- To describe BDQ concentrations following BDQ treatment discontinuation at 24 weeks, from study Weeks 24 to 120, by HIV status.
- To describe the MDR-TB treatment response up to 120 weeks from the initiation of the study, by HIV status.
- Exploratory biomarker objectives (urine, serum: Husson, Graviss group)
Need for work on secondline-line TB and new drug formulations earlier:
P1108 will use adult 100 mg tablet
BDQ CRUSH BE study will inform use (Q3 2016)
BDQ (in crushed adult formulation), given in combination with individualized OBR MDR-TB medications, for 24 weeks. For HIV-infected participants, BDQ will be given in combination with an acceptable ARV therapy regimen initiated at least 2 weeks prior to enrollment.
Enrollment of (HIV- and HIV +) participants commences with subjects combined across both weight bands. Enrollment into cohort paused once group (N= 6 participants) completes Week 2 evaluation and up to 3 additional participants are accrued.

Week 2 batched PK analysis and population PK modelling of the group (N=6) and cumulative safety data of all participants are evaluated.

Safety is unacceptable (i.e., triggers SMC review) or PK criteria not met: dose may be adjusted. Complete enrollment of next group (N=6).

Safety is acceptable and PK criteria are met: resume enrolling.

All available PK (including Week 1, Week 2, Week 8 or later sparse PK) of the group and cumulative safety data on all participants are evaluated

Safety is acceptable and PK criteria are met: complete enrollment into the cohort.

Safety is unacceptable (i.e., triggers SMC review) or PK criteria not met: dose may be adjusted. Complete enrollment of next group (N=6). All available PK (including Week 1, Week 2, Week 8 or later sparse PK) of the group and cumulative safety data on all participants are evaluated.

Safety is unacceptable and PK criteria are met or exposure is high: consider enrolling new group (N=6) in consultation with the SMC, using an adjusted dose.

Safety is acceptable in all participants and PK criteria are met in at least 8 individual participants.

Once 6 participants (and up to 3 additional participants) in addition to the 6 previously evaluated have completed Week 2 PK sampling, all available PK (including Week 1, Week 2, Week 8 or later sparse PK) of the total of 12 subjects and cumulative safety data on all participants are evaluated. Enrollment is paused; up to 3 additional participants are accrued.

Open Cohorts 2 and 3 in parallel using groups of N=6 per cohort.
P1108 status update

- Version 1.0 released to sites March 2016
- MCC submission completed April 2016
- Site IRB submissions ongoing
- Expected to open in October 2016
- Will open with adult 100 mg formulation
- Discussion ongoing with Janssen re access to paediatric formulation later on, data sharing to enable accelerated registrations
- Real time PK assays and modeling to inform dose adjustments set up
- BDQ model developed: to be updated
Delamanid for Multidrug-Resistant Pulmonary Tuberculosis

Maria Tarcela Gler, M.D., Vija Skripconoka, M.D., Epifanio Sanchez-Garavito, M.D., Heping Xiao, M.D., Jose L. Cabrera-Rivero, M.D., Dante E. Vargas-Vasquez, M.D., Mengqiu Gao, M.D., Ph.D., Mohamed Awad, M.B., B.Ch., M.D., Seung-Kyu Park, M.D., Ph.D., Tae Sun Shim, M.D., Ph.D., Gee Young Suh, M.D., Manfred Danilovits, M.D., Hideo Ogata, M.D., Anu Kurve, M.D., Joon Chang, M.D., Ph.D., Katsuhiro Suzuki, M.D., Thelma Tunasi, M.D., Won-Jung Koh, M.D., Barbara Seaworth, M.D., Lawrence I. Geiter, Ph.D., and Charles D. Wells, M.D.

EMA APPROVED 2014
DELAMANID

- **Trial 232: Phase 1 PK Age De-escalation study**
  - Define dose of delamanid in children resulting in AUC comparable to the effective AUC observed in adult MDR-TB trials

- **Trial 233: Phase 2 Safety Study**
  - Investigate the safety, tolerability, and PK of delamanid administered for six months in a pediatric population receiving concomitant OBR
  - Enrolling: Philippines, South Africa; age de-escalation, HIV-
    - Groups 1, 2 fully accrued (6-17 years)
    - Good PK and safety profile
    - Group 3 (3-5 years): 7 enrolled; interim analysis planned July
    - Group 4 to open 2017 data by Q3 2017
    - Paediatric formulation available and already used
IMPAACT 2005: A Phase I/II Open-label, Single-Arm Study to Evaluate the PK, Safety, and Tolerability of Delamanid in Combination with Optimized Multidrug Background Regimen (OBR) for Multidrug-Resistant Tuberculosis (MDR-TB) in Children with MDR-TB with and without HIV

KELLY DOOLEY
ANTHONY GARCIA-PRATS
ETHEL WELD
Objectives

In HIV-infected and HIV-uninfected children treated for MDR-TB with currently recommended OBR

**Primary Objectives**
- Determine the delamanid doses most likely to achieve adult-equivalent exposures, using a model-based approach.
- Safety and tolerability of delamanid over treatment period (24 weeks)

**Secondary Objectives**
- Effects of HIV co-infection and/or co-treatment, dose, age contributions on PK variability
- Acceptability
- Long-term safety (48 weeks)
- TB treatment outcomes

**Exploratory Objectives**
- HIV treatment outcomes; safety and tolerability of injectable-sparing, delamanid-containing regimens in the treatment of MDR-TB; PK-QT relationships
## Design

**Design:** Phase I/II open label, single-arm study with modified age de-escalation approach

- **Cohort 1:** ages 12 to <18 years: adult formulation
- **Cohort 2:** ages 6 to <12 years: adult formulation
- **Cohort 3:** ages 3 to <6 years: pediatric formulation
- **Cohort 4:** ages 0 to <3 years: pediatric formulation

**Regimen:**
- **Cohorts 1 & 2:** 100 mg BID for 15-35 kg; 50 mg BID for < 35 kg
- **Cohorts 3 & 4:** model-based dosing

**Duration:** 24 weeks on study treatment, follow-up through 96 weeks

**Population:** Children with confirmed or probable MDR-TB (including XDR), with or without HIV co-infection

**PK sampling:** 14 samples per child, over 28 weeks; 504 total observations (semi-intensive & sparse)

*participants will also receive optimized background treatment, ART as appropriate

**Status:** CSG completed, MPRG review completed, version 1 expected Q4 2016
• Otsuka to provide study drug; pediatric formulation now available. Otsuka provided raw PK data & PK model to Uppsala
• DLM registered in Europe and several other countries; ?NDA submission date
• DLM & DM-6705 metabolite assays developed at UCT
• Pharmacometrics Collaborators: Mats Karlsson & Elin Svensson (Uppsala University)
• Strong industry collaboration: Otuska
• Version 1 to sites: Q4 2016

**IMPAAACT Sites with Capacity, Expertise & Interest:**

• Stellenbosch University Desmond Tutu TB Center: Cape Town, South Africa
• Gabarone & Molepolole: Botswana
• Soweto: JHB, South Africa
• BJ Medical College Pune, India
• Kilimanjaro Christian Medical Center: Moshi, Tanzania

**Additional DAIDS-supported, non-IMPAAACT sites with Capacity, Expertise & Interest needed**

• Sizwe Tropical Diseases Hospital: JHB, South Africa
• Klerksdorpp
• Peru
MDR TB in Household Contacts

- Child and HIV+ contacts of MDR TB patients have a high risk of progressing to active TB and possibly death
- Vast majority of MDR TB in young children arises from HH transmission (including MDR-TB)
- No evidence base to guide MDR-TB prevention
A5300B/I2003B Study Hypothesis

- Treating HIV-infected and other child, adolescent and adult household contacts of MDR TB patients who are at high risk of developing TB with DLM will substantially reduce the risk of developing TB, compared to INH

- Joint protocol development and implementation: IMPAACT and ACTG
Primary Objectives

Among HIV-infected and other child, adolescent, and adult HH contacts of MDR TB patients at high risk of developing TB, to compare:

- The efficacy of DLM vs. INH for preventing confirmed or probable active TB
- The safety of DLM vs. INH for the treatment of presumed LTBI with MDR TB
Secondary Objectives

To compare DLM vs INH with respect to:

1. Efficacy and safety in each high-risk group
2. All-cause mortality
3. Grades 3 and 4 AEs
4. Drug-susceptibility pattern of the index patient vs. incident TB cases
5. Factors, including adherence and PK measures, associated with risk of TB
Phoenix Feasibility update:

- 16 sites enrolled in a 5 month period Oct2015-April 2016
- 308 MDR TB index cases
- 1018 adult and pediatric household contacts
2012
- >500 million latent TB infections (LTBI)
- Peak TB disease incidence 15-45 years of age
- 2.9 million with active TB (38% of global burden)
- 410,000 died
- 50% of HIV-related TB deaths
- 68% of cases Africa and SE Asia
- More than 50% of cases went undetected
- 216,000 TB cases occur in pregnancy
- Up to 50% of HIV+ pregnant women have LTBI in high burden settings

http://www.who.int/tb/publications/tb_women_factsheet_251013.pdf?ua=1
Sugarman Lancet Global Health 2014
TB APPRISE: Phase IV Randomized Double-blind Placebo-controlled Trial to Evaluate the Safety of Immediate (Antepartum-initiated) vs. Deferred (Postpartum-initiated) Isoniazid Preventive Therapy among HIV-infected Women in High TB Incidence Settings

IMPAACT P1078
CHAIR: AMITA GUPTA
VICE CHAIRS: ADRIANA WEINBERG, TIMOTHY STERLING (TBTC), GERARD THERON
STATISTICIANS: GRACE MONTEPIEDRA AND LISA AARON
SPONSORS: NIAID, NICHD, TBTC
TBSC CHAIR: ANNEKE HESSELING
HIV-infected pregnant woman, ≥14 through ≤34 weeks gestation

TB Screening, rule out active TB

Active TB Suspected OR Documented

Woman meets other eligibility criteria

YES

Refer to local TB program for evaluation and TB treatment; not eligible for study

ARM A: Immediate INH
INH x 28 weeks, then
Placebo x 12 weeks

ARM B: Deferred INH
Placebo until week 12
postpartum, then INH x
28 weeks

Study drugs (INH/Placebo), open label Pyridoxine (vitamin B₆) and open label prenatal multivitamin terminated at 40 weeks postpartum

End of follow-up: 48 weeks postpartum
P1078 sites

13 sites (8 countries) fully accrued 956 HIV+ pregnant women between 19 Aug 2014 and April 4, 2016
<table>
<thead>
<tr>
<th>Maternal Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median)</td>
<td>29 yrs.</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>Black African or African origin</td>
<td>90%</td>
</tr>
<tr>
<td>Indian</td>
<td>3%</td>
</tr>
<tr>
<td>Thai</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Enrollment</strong></td>
<td></td>
</tr>
<tr>
<td>14 - &lt;24 weeks gestation</td>
<td>34%</td>
</tr>
<tr>
<td>24 - 34 weeks gestation</td>
<td>66%</td>
</tr>
<tr>
<td><strong>HIV Viral Load &lt;200 copies/mL</strong></td>
<td>81%</td>
</tr>
<tr>
<td>CD4 count (median absolute)</td>
<td>493 cells/mm³</td>
</tr>
<tr>
<td><strong>WHO Clinical Stage 1</strong></td>
<td>89%</td>
</tr>
<tr>
<td><strong>ARV Regimen</strong></td>
<td></td>
</tr>
<tr>
<td>Triple ARV</td>
<td>99%</td>
</tr>
<tr>
<td>TDF + 3TC(or FTC) + EFV</td>
<td>83%</td>
</tr>
<tr>
<td>TDF(or AZT)+ 3TC(or FTC)+ NVP</td>
<td>13%</td>
</tr>
</tbody>
</table>
P1078 status update

- Fully accrued and results expected Q4 2017
- Hepatotoxicity being carefully monitored especially with efavirenz and INH
- DSMB meeting every 6 months (next Sept 2016)
IMPAACT 2001
A Phase I/II Trial of the Pharmacokinetics, Tolerability, and Safety of Once-Weekly Rifapentine and Isoniazid in HIV-1-infected and HIV-1-uninfected Pregnant and Postpartum Women with Latent Tuberculosis Infection

CHAIR: JYOTHI MATHAD,
CO-CHAIR: KELLY DOOLEY
VICE-CHAIR: SANDESH PATIL
**IMPAAACT P2001 Study Design**

**Design:** Prospective, open-label, multi-center study

**Population:** HIV-1-infected and -uninfected pregnant women with latent TB and their infants

- Cohort 1: Enrolled in 2\textsuperscript{nd} trimester
- Cohort 2: Enrolled in 3\textsuperscript{rd} trimester (with participation continuing into postpartum period)

**Sample Size:** 25 evaluable women per cohort. At least 10 evaluable HIV-1-infected women per cohort.

**Treatment:** 12 directly observed once-weekly doses of RPT (900mg) and INH (900mg) taken with pyridoxine

**Duration:** follow-up until 24 weeks postpartum

**Goal:** Characterize effects of pregnancy on PK of RPT with intent of extending use of this new regimen to pregnant women, a group with high risk of progression from latent to active TB

- Establish that the regimen is tolerable with no unexpected serious safety events
P2001 status update

- Protocol to sites
- Assays established, MTA Sanofi/UCT
- First enrolment expected Q3 2016: delay safety issue?
- Strong partnership with Sanofi
- Sites:
  - Haiti
  - Kenya
  - Malawi
  - Thailand
  - United States
  - Zimbabwe
Maternal TB registry

- Moving forward through TBTC, TAG; no DAIDS support
- Collect key data re TB in pregnancy: HIV+/-
- Maternal and infants outcomes
- Prodivde template for future standard data collection
- Leadership: Adrie Bekker, Lyndsay McKenna, Lisa Cranmer, Jyothi Mathad, Kathryn Snow, Anneke Hesseling, Amita Gupta
Co-endorsed treatment protocols

- **P1106**: “Pharmacokinetic characteristics of antiretrovirals and associated medications in low birth weight infants”
- **P1026S**: “Pharmacokinetic Properties of Antiretroviral Therapy during Pregnancy” – MDR-TB arm added
- **P1101**: Treatment Scientific Committee: status: TB component open, enrolling
- **A5279**: “Phase III Clinical Trial of Short-Course Rifapentine/Isoniazid for the Prevention of Active Tuberculosis in HIV-Infected Adults with Latent Tuberculosis Infection” ACTG: status: open, also IMPAACT sites: >1800/3000 enrolled
TB vaccine trials: P1113: Phase I safety and immunogenicity of a recombinant protein TB vaccine in BCG-primed infants

Chairs: Avy Violari, Sharon Nachman

Partners: Sanofi, Aeras, DAIDS, HVTN
• Vaccine: HyVac 4/AERAS-404,+IC3
  ○ Dose escalation study, given after BCG vaccine novel antigen and novel adjuvant
  ○ HIV unexposed infants

• Primary objective:
  ○ Evaluation of safety of vaccine when given as part of primary EPI schedule

• Secondary objective:
  ○ Evaluation of immunogenicity of study vaccine

• Exploratory objective:
  ○ Immunogenicity interactions with EPI vaccines
  ○ Status: enrolment completed in 2016
# Accrual status (June 2016)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Actual</th>
<th>(Target)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled</td>
<td>(Target)</td>
<td></td>
</tr>
<tr>
<td>Cohort 1</td>
<td>14 (14)</td>
<td></td>
</tr>
<tr>
<td>Cohort 2</td>
<td>14 (14)</td>
<td></td>
</tr>
<tr>
<td>Cohort 3</td>
<td>14 (14)</td>
<td></td>
</tr>
<tr>
<td>Cohort 3</td>
<td>46 (45)</td>
<td></td>
</tr>
<tr>
<td>Cohort 4</td>
<td>38 (36)</td>
<td></td>
</tr>
<tr>
<td>Cohort 5</td>
<td>40 (36)</td>
<td></td>
</tr>
<tr>
<td>Cohort 6</td>
<td>58 (70)</td>
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</tr>
<tr>
<td>Total</td>
<td>224</td>
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Projected accrual completion Q3 2016
# Diagnostics and biomarkers work

<table>
<thead>
<tr>
<th>Ongoing/completed</th>
<th>Details</th>
<th>Status</th>
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<tbody>
<tr>
<td>DACS 6571</td>
<td>Lymphocyte/monocyte ratio</td>
<td>1041 (published)</td>
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<tr>
<td>IGRA studies</td>
<td>IGRA vs. TST to detect TB infection</td>
<td>1041 (submission pending)</td>
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<tr>
<td>DACS 658</td>
<td>Application of NIH consensus definitions</td>
<td>1041 (published)</td>
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<tr>
<td>NWCS 127</td>
<td>LDL as novel biomarker for TB in children</td>
<td>1041 (pending): Stonybrook, DTTC</td>
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## Planned

<table>
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<tbody>
<tr>
<td>Novel molecular tests, DST (MDR-TB)</td>
<td>Xpert Ultra, molecular DST, novel drugs</td>
<td>Phoenix, 1108, 2005</td>
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<tr>
<td>Serum biomarker dx</td>
<td>Hue, Graviss</td>
<td>Phoenix, others</td>
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<tr>
<td>Urine biomarkers</td>
<td>Husson</td>
<td>P1108, other</td>
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<tr>
<td>Immune correlates protection</td>
<td>Prevention trials</td>
<td>P1078, 1113</td>
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</table>
# IMPAACT TREATMENT AND PREVENTION PROTOCOLS

## Preventive Therapy Trials
- IPT in HIV-infected pregnant women
- RFPT /INH in HIV-infected and uninfected pregnant women
- Ultra short Rifapentine-based regimen in adults and adolescents
- Preventive therapy for MDR TB in child, adolescent and adult household contacts (pregnant women)
- TB vaccine trial

### STATUS
- P1078; enrolled
- P2001: opening 2016
- ACTG 5279: co-endorsed; enrolled
- Phoenix: feasibility completed; B opening Q4 2017
- P1113: accrued in 2016

## Treatment Trials
- Shorter regimens for drug sensitive TB
- Regimens for extrapulmonary TB
- Regimens for MDR TB with/without HIV
  - Bedaquiline
  - Delamanid
  - DLM/BDQ
  - Clofaz
  - Shorter duration all oral regimen
- DDI for TB/HIV in pregnancy
- PK characteristics of cART and TB therapy in LBW infants
- Dose finding RAL with TB

### STATUS
- SHINE (BMRC funded): open
- TB Meningitis (NICHD RO1)
- P1108 (Q4 2016)
- P2005 (Q2 2017)
- Planned
- Planned
- Planned
- P1026 S (co-endorsed)
- P1106 (co-endorsed)
- P 1101 (co-endorsed)
MDR-TB: 1 year plan

Children

- Implement Phoenix (A5300/I2003 B) prevention trial
- Implement P1108 (Bedaquiline phase I, II) HIV+/-
- Implement P2005 (Delamanid Phase I, II) HIV+/-
- Develop clofazamine PK (HIV+/-) : CAP
- Develop BDQ/DLM DDI safety DDI (HIV+/-): CAP
- Develop MDR-TB treatment shortening trial protocol
- Develop white paper: MDR-TB priorities, gaps (RESIST TB IMPAACT Landscape meeting June 17th)
- Plan nested diagnostic, DR-TB testing
MDR-TB: 1 year plan

Pregnant women

- Implement P1026 S (DS-TB and MDR-TB arm)
- Support implementation of TB pregnancy registry: TBTC, TAG, others
- Plan Phoenix sub study
MDR-TB: 5 year plan

Children

- Implement Phoenix MDR prevention trial
- Implement phase 3 MDR-TB shortened treatment trial
- Work on novel molecular diagnostics, DST
- Build paediatric MDR-TB trial site capacity (clinical and lab)
Thank you!