TB SCIENTIFIC COMMITTEE UPDATE

18 June 2015
Anneke C. Hesseling
Burden of TB in Children: 2012

- At least 500,000 children with TB
- True burden under-estimated
- Over 70,000 TB deaths (excluding HIV/TB deaths)
- TB one of top 10 causes of child mortality in developing countries
- Under-detection and under-reporting: diagnostic challenges, incomplete registration

WHO Global report, 2013
FIGURE 2.5
Estimated TB incidence rates, 2012
Multi-Drug Resistant TB

- 500,000 new cases of MDR-TB in 2011:
  - IMPAACT sites in epicenter of epidemic
- More adult cases means more child contacts
  - Globally: >1,000,000 children potentially exposed to MDR-TB each year
  - Poor pediatric estimates
- Data and formulations appropriate for treatment of MDR and XDR TB in children are lacking
- No evidence based for preventive therapy in contacts

WHO Global TB report, 2013
Tuberculosis Scientific Agenda

- Evaluate novel TB treatment therapies
  - Safety and PK in children with MDR TB
  - Drug-drug interactions
  - Treatment shortening (drug-susceptible TB)
  - Prevention in pregnant women (DS, DR-TB)
  - MDR-TB prevention (children, adolescents, pregnant women)

- Evaluate novel tools for the diagnosis of TB in HIV-infected and un-infected infants and children

- Evaluate novel vaccines against TB: continue to work with partners
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<tr>
<th>Preventive Therapy Trials</th>
<th>Status</th>
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<tr>
<td>• IPT in HIV-infected pregnant women</td>
<td>P1078; opened 2014</td>
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<tr>
<td>• RFPT /INH in HIV-infected and uninfected pregnant women</td>
<td>P2001; in development</td>
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<td>• Ultra short Rifapentine-based regimen in adults and adolescents</td>
<td>ACTG 5279: co-endorsed; enrolled Phoenix</td>
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<tr>
<td>• Preventive therapy for MDR TB in child, adolescent and adult household contacts (pregnant women)</td>
<td>(ACTG 5300/IMPAACT P2003)</td>
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<thead>
<tr>
<th>Treatment Trials</th>
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<tr>
<td>• Shorter regimens for drug sensitive TB</td>
<td>SHINE (BMRC funded)</td>
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<tr>
<td>• Regimens for extrapulmonary TB</td>
<td>TB Meningitis (NICHD RO1)</td>
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<td>• Regimens for MDR TB with/without HIV</td>
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<td>• Bedaquiline</td>
<td>P1108</td>
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<td>• CRUSH study</td>
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<td>• Delamanid</td>
<td>P2005</td>
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<td>• DDI for TB/HIV in pregnancy</td>
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<td>• PK characteristics of cART and TB therapy in LBW infants</td>
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MDR-TB TREATMENT
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 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)
P1108: “A Phase I/II, Open-label, Single Arm Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Bedaquiline (BDQ) in Combination with Optimized Individualized Multidrug-Resistant Tuberculosis (MDR-TB) Therapy in HIV-infected and uninfected Infants, Children and Adolescents with MDR-TB disease”

Chair: Anneke C. Hesseling
Vice-chair: Simon Schaaf
In HIV-infected and uninfected infants, children and adolescents receiving BDQ plus OBR for MDR-TB, to:

• Determine the BDQ doses that achieve similar exposure of BDQ compared to adults taking BDQ at the standard recommended dose

• Evaluate the safety and tolerability of BDQ over 24 weeks from the initiation of study treatment
SECONDARY OBJECTIVES

• Evaluate the PK of BDQ over 24-weeks, by HIV status
• Describe the long-term safety and tolerability of BDQ over a 120-week (30 months) total follow-up period, by HIV status
• Describe BDQ concentrations following BDQ treatment discontinuation at 24 weeks, from study Weeks 24 to 120
• Describe the MDR-TB treatment response up to 120 weeks from the initiation of the study, by HIV status
P1108 features

- N=54 participants, 3 age cohorts, modified age-descalation
- Inclusion of min 18 HIV-infected children: DDI
- Long half life, tissue bound
- Risk/benefit: long-term safety concern – long-term follow-up, mitochondrial toxicity monitoring
- Confirmed and probable MDR-TB included
- Adaptive design, real-time PK assaying and modeling, dose adjustments
- Lack of paediatric formulation: will use crushed adult 100 mg tablets (formal bio-equivalence study planned: “CRUSH study”): n=24 healthy adult volunteers
P1108 Milestones

• MPRG resubmission: May 2015
• CSRC: June/July 2015
• MCC/other regulatory: Q3/4 2015
• CRUSH BE protocol to SLG: June 2015
• SIP to sites: June 2015 (N=5)
• Projected opening: Q1/2 2016
• South Africa (N=3), Haiti, Pune
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 J. Geiter, Ph.D., and Charles D. Wells, M.D.

EMA APPROVED 2014
Delaminid (Otsuka 232/2333)
Study Population: HIV negative children and adolescents

Current Tablet Formulation

• Group 1: Adolescents 12 to 17 years
  – (100 mg BID; n=6)

• Group 2: Children 6 to 11 years
  – (50 mg BID; n=6)

Pediatric formulation

• Group 3: Children 3 to 5 years
  – (25 mg BID; n=6) and (50 mg BID; n=6)

• Group 4: Newborns and infants 0 to 2 years
  – (5 mg BID; n=6) and (25 mg BID; n=6)

Cohorts 1, 2 enrolled; cohort 3 opening Q3 2015
IMPAAACT P2005 Objectives

In HIV-infected infants, children, and adolescents aged 0-17 years treated for MDR-TB with WHO-recommended OBR:

Primary Objectives:
1. To describe the population PK of delamanid over 24 weeks
2. To determine the appropriate delamanid doses to achieve exposures that are similar to those achieved in adults with a 100 mg twice daily dose
3. To evaluate the safety of delamanid over 24 weeks

Secondary Objectives:
1. To evaluate the tolerability of delamanid over 24 weeks
2. To assess the long-term safety of delamanid over 48 weeks
3. To characterize the TB and HIV treatment outcomes by 18 months after study treatment initiation
IMPAACT P2005: features

- Opening of HIV-infected cohorts (n=4) dependent on 232/233 results
- N=28-36 children
- Drug-drug interactions with ARVs
- In collaboration with Otsuka
- Uppsala PK group: data sharing completed with Otsuka
- Novel paediatric formulation
- Protocol development approved: May 2015
- Investigators: Dooley, Garcia-Prats, Weld, Hesseling
IMPAACT P1078
A Phase IV Randomized Double-Blind Placebo-controlled trial to evaluate the safety of immediate (antepartum-initiated) versus deferred (PostPartum-Initiated) isoniazid preventive therapy among HIV-infected women in high TB incidence settings “TB Apprise”

Primary Objective

• To compare overall safety and toxicity of immediate versus deferred INH preventive therapy in HIV-infected pregnant women enrolled at ≥ 14 through ≤ 34 weeks gestation (34 weeks, 6 days) and by HAART strata.
• **Design**: Phase IV, randomized, double-blind, placebo-controlled study

• **Sample Size and Population**: 950 mother-infants pairs (enrolling HIV-infected pregnant women \( \geq 14 \) weeks through \( \leq 34 \) weeks gestation)

• Randomized to one of two arms

![Diagram](image-url)
As of 1 June, 337 mother-infant pairs were enrolled across 11 sites in 7 countries.

Chair: Jyoti Mathad; Co-chairs Kelly Dooley, Sandesh Patil
P2001 Objectives and Status

**Primary Objective:**
- Population PK (CL/F, absorption, Vd) of RPT and desRPT in pregnant women in 2nd and 3rd trimester
- Population PK in postpartum women
- Safety, tolerability in women and infants*
- Assess adequacy of standard RPT dose in pregnancy
- RPT and desRPT levels in infants at delivery
- RPT and desRPT concentrations in breast milk

**Secondary Objectives:**

**Exploratory Objective:**

**Status**
- **Sites:** Haiti, Kenya, Malawi, South Africa, Thailand, United States, Zimbabwe.
- **IMPAACT PK lab:** Cape Town, South Africa
- **CSRC review last week. Version 1.0 by Q4 of 2015**
Unanswered Questions on Optimal Preventive Therapy

- IMPAACT studies: pre-exposure INH does not prevent TB infection or disease in HIV-infected or exposed infants <2 years of age (P1041)

- No data and no WHO recommendation on what to use for preventive therapy for MDR TB exposure
Protecting Households On Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis Patients (PHOENIx MDR TB)

Protocol Chairs
GJ Churchyard: ACTG
A Gupta: IMPAACT
S Swindells: ACTG
A Hesseling: IMPAACT
PHOENIx Study
Hypothesis and Objectives

Hypothesis
• Treating child, adolescent, and adult household contacts of MDR TB patients who are at high risk of developing TB with LVF will substantially reduce the risk of developing TB compared to INH

Primary Objectives
Among child, adolescent, and adult HH contacts of MDR TB patients at high risk of developing TB, to compare:
• The **efficacy** of LVF vs. INH for preventing confirmed or probable active TB
• The **safety** of LVF vs. INH for the treatment of presumed LTBI with MDR TB
PHOENIx Secondary Objectives

• To compare the efficacy and safety of LVF versus INH for preventing TB in each of the three high-risk groups to be enrolled

• To compare the efficacy of LVF vs. INH in reducing all-cause mortality

• To compare the efficacy of LVF versus INH for reducing the composite outcome of TB and all-cause mortality

• To compare the incidence of Grades 3 and 4 AEs among participants receiving LVF vs. INH

• To compare the DST of the index MDR TB patient to that of incident TB cases among HH contacts

• To evaluate factors, including adherence and PK measures, associated with risk of confirmed or probable TB

• To describe the PK and safety of LVF administered as
  - 15-20 mg/kg once daily in children 6 months to 2 years of age
  - 750mg once daily in pregnant women ≥ 28 weeks of gestation
PHOENIX Study Design

- **Phase III, open label, multi-center trial, cluster-randomized, superiority design** comparing 26 weeks of LVF to 26 weeks of INH for preventing TB among high-risk HH contacts of MDR TB

**High risk contact**
- Children >6 months and ≤5 years old regardless of TST/IGRA or HIV status
- HIV-infected adults and children > 5 years of age, regardless of TST/IGRA status
- Adults and children >5 years of age who are TST positive (≥5mm) and/or IGRA positive and whose HIV status is negative or unknown

**NOTE:** pregnant women will be included from 2nd trimester onwards

**Sample size & duration**
- **3,452 high-risk HH contacts** (from 1,726 HH)
- 96 weeks for each participating HH contact
- **Study duration:** 304 weeks (4 years accrual, 2 year follow-up)
A5300/I2003/PHOENIX Site Preparedness Study

Operational feasibility study of MDR TB cases and their household contacts to inform PHOENIX trial design

Jointly developed by ACTG and IMPAACT Networks
Chairs: Gavin Churchyard, Susan Swindells, Anneke Hesseling, Amita Gupta
Protocol members:
Sarita Shah, Michael Hughes, Seyeon Kim, Mark Harrington, Richard Chaisson, Lynne Jones, Dan Johnson, Betsy Smith, Kim Scarsi, Linda Naini and others
Methods

• **DESIGN:** Cross-sectional study of adult MDR TB index cases and their household contacts.
• **SAMPLE SIZE:** 250 adult MDR index cases up to 600 household contacts
• **POPULATION**
• **Index Case:** An adult (18 years or older) with
  – Xpert RIF positive pulmonary TB -OR-
  – Confirmed pulmonary MDR TB, by phenotypic or genotypic testing, who started appropriate treatment within the past six months or died within the previous 3 months.
# Diagnostics: working with ITBSL

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<td>Lymphocyte/monocyte ratio</td>
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<td>IGRA vs. TST to detect TB infection</td>
<td>1041</td>
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<td>DACS 658</td>
<td>Application of NIH consensus definitions</td>
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<td>NWCS 127</td>
<td>LDL as novel biomarker for TB in children</td>
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<td>PROMISE</td>
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<tr>
<td>Phoenix</td>
<td>Biomarkers of infection and disease</td>
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Bacteriological yield can be optimized

Children with a clinical TB diagnosis, n=172
Bacteriologically confirmed = 81 (47%)
P1113: Phase I safety and immunogenicity of a recombinant protein TB vaccine in BCG-primed infants

• Vaccine: HyVac 4/AERAS-404,+IC3
  – Dose escalation study, given after BCG; novel antigen and novel adjuvant
  – HIV unexposed
• Primary objective:
  – Evaluation of safety of vaccine when given as part of primary EPI schedule
• Secondary objective:
  – Evaluation of immunogenicity of study vaccine
• 239 screened; 127 enrolled.
• Once completed, the study will pause, safety and immunogenicity a dose selected; final cohort enrolled 2016

Areas, DAIDS, HVTN
TB - 1 Year Goals

Pregnant Women with Active TB

- Obtain PK/safety data for 1st line TB drugs
  - work with P1026s PK/safety of 1st line TB drugs in pregnancy

- Identify need and feasibility of opportunistic PK/safety studies
  - HIV protease inhibitors + rifabutin
  - Goal: Conduct feasibility and site survey

- Develop a maternal TB registry
  - Similar to ARV registry
  - Include women who become pregnant in TB trials and pregnant women who develop TB disease
  - Goal: Develop and review capsule in Q3 2015
1 Year Goals

PREGNANT WOMEN with LATENT TB INFECTION
• Finalize P2001: INH + rifapentine weekly PK/safety for treatment of latent TB infection in HIV-infected and uninfected
  — Goal: protocol Q3 2015

PREGNANT WOMEN and CHILDREN CONTACT PROPHYLAXIS
• Finalize PHOENIX: Levofloxacin versus isoniazid preventive therapy for MDR TB household contacts
  — collaboration with ACTG
  — Initial site feasibility/preparation study fast tracked Q3 2015 V1.0 (non-intervention)
  — Goal: Protocol Q3 2015 & obtain green light from NIH strategic working group in Jan 2016
CHILDREN
• Complete P1113 enrolment
• Complete P1108 Bedaquiline PK/safety
• Complete P2005 Delamanid PK/safety
• Design clofazamine PK/safety study
• Implement P1106, P1101
• Plan rifampicin dose optimization study

PREGNANT WOMEN
• Complete P1078 INH + ART in pregnancy trial
• Complete P2001 INH + rifapentine weekly PK/safety
• Initiate dolutegravir-rifampin study in pregnant women with HIV/TB
• Initiate an opportunistic PK/safety study for MDR-TB, PI/rifabutin,
TBSC mentored investigators

- Liz Walters (diagnostics): South Africa
- Ethel Weld (P2005): JHU
- Louvina van der Laan (MDR PK – OBR, HIV DDI): South Africa
- Sylvia La Course (maternal infant TB, P1078): UWash
- Jyoti Mathad (P2001, P1078): Cornell
- Vanessa Rouzier (Maternal TB registry): Haiti
- Tony Garcia-Prats (P2005, P1108): South Africa
- Vidya Mave (P2001, P1078): India
- Adrie Bekker (P1106, P2001, Maternal TB registry): South Africa
- Christy Beneri (CS4108, DACS 658): Stonybrook
- Cathy Cluver (P2001): South Africa
- Sandesh Patil (P2001): India
- Lisa Cranmer (P1041, maternal TB registry): Emory