TB SCIENTIFIC COMMITTEE ACTIVITY UPDATE

ANNEKE C. HESSELING
AMITA GUPTA

13 JUNE 2016
TBSC MEETING

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Group

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

IMPAACT

International Maternal Pediatric Adolescent AIDS Clinical Trials Group

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

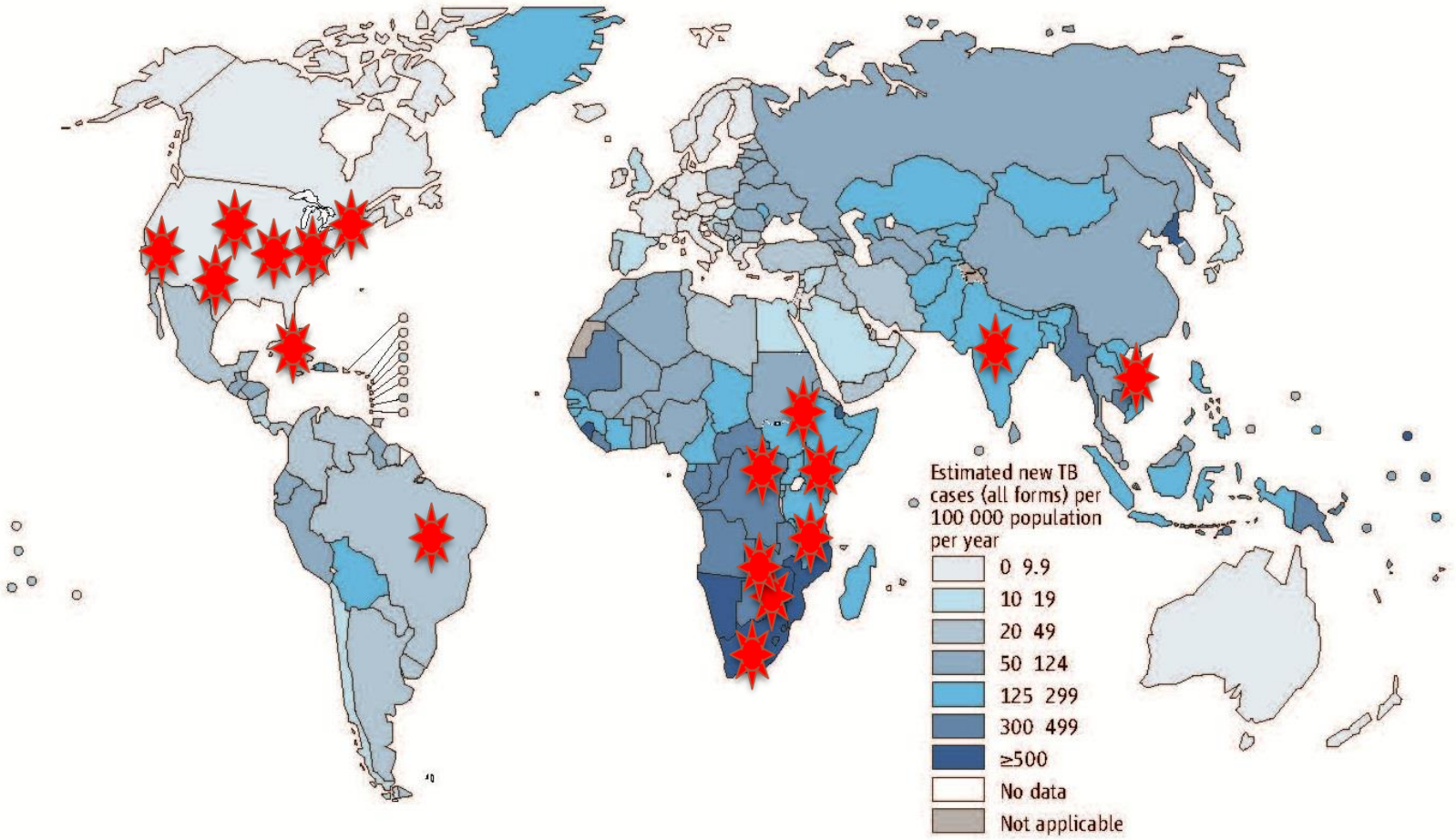
3 new concepts developed by mentored investigators in 2016: 2005, 2001, TB pregnancy registry

- 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



Estimated total cases in children	**1 000 000 (10% global burden)**
Childhood cases notified	360 000
TB deaths	136 000 (81 000 HIV-) 13.6% case fatality rate
TB infections	6.6 million

WHO 2015 Global TB report www.who.int

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

WHO Global TB Report 2015; Jenkins HE et al. Lancet 2014; Dodd PJ et al. Lancet Global Health 2014

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)

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

Seddon, Clin Infect Dis 2013

BEDAQUILINE

Licensed in adults based on phase IIb data: accelerated pathway

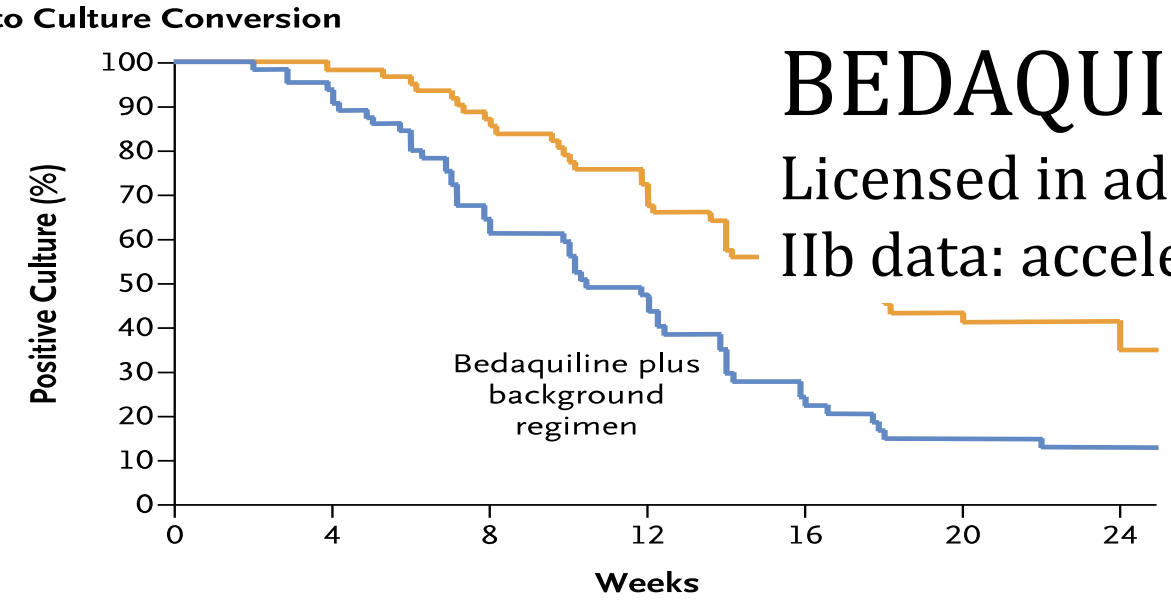


Table 2. Adverse Events during 120 Weeks in the Intention-to-Treat Population.*

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

Diacon, NEJM, 2015

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)

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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

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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)

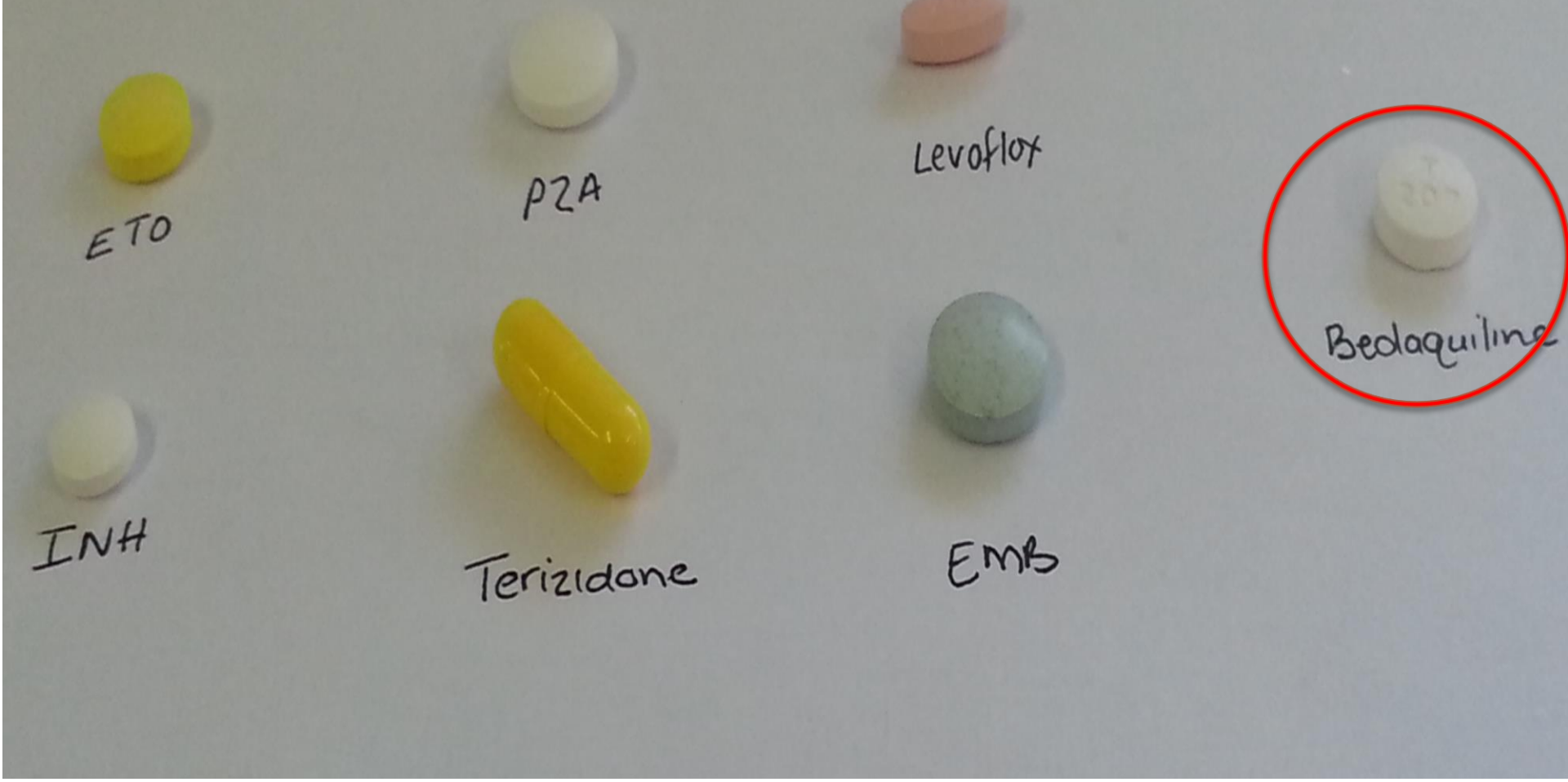
PRIMARY OBJECTIVES

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)



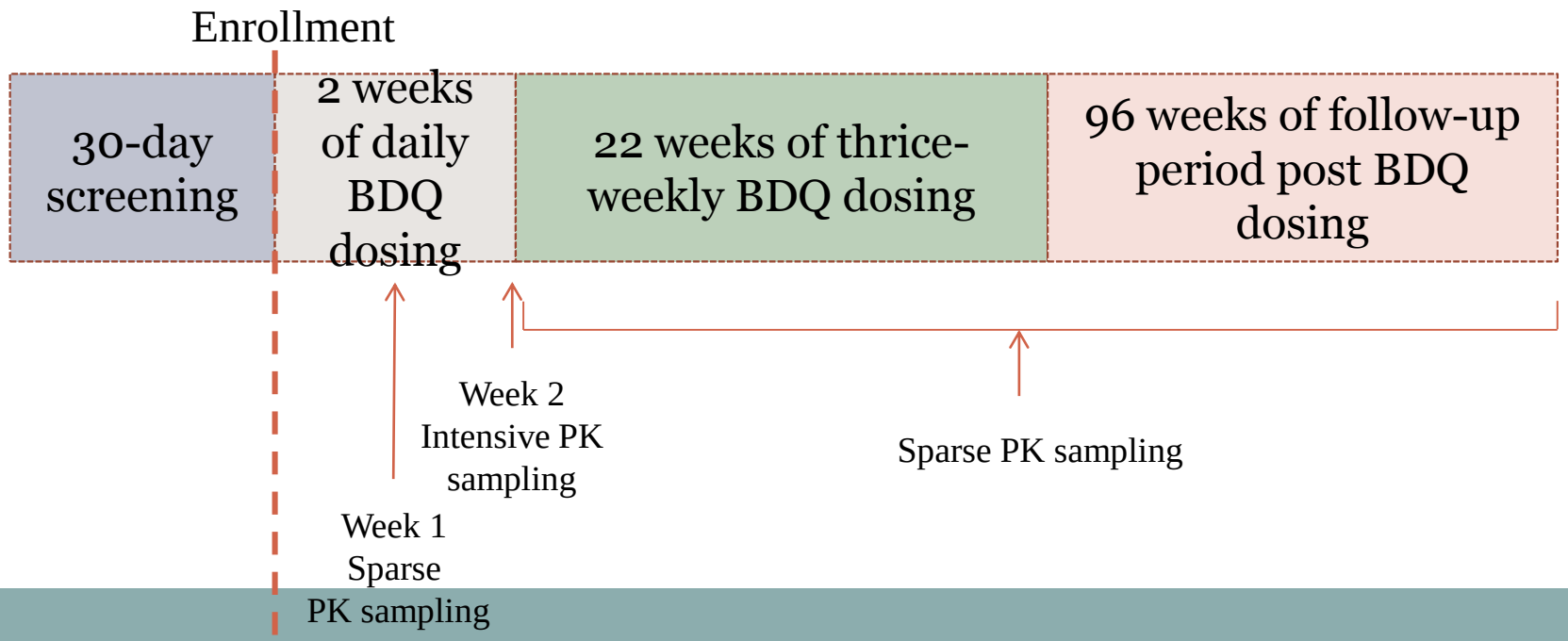
Need for work on secondline-line TB and new drug formulations earlier:

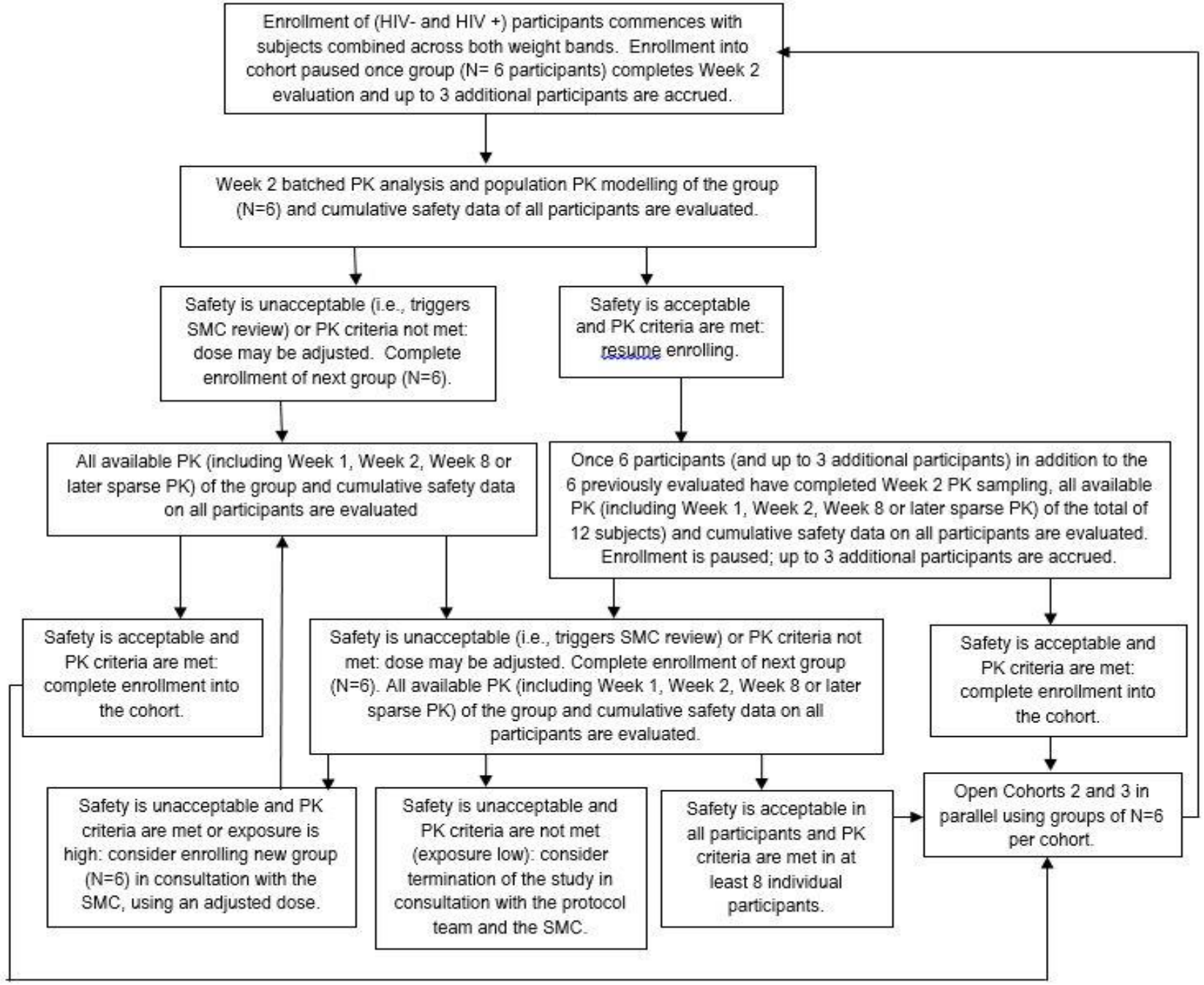
P1108 will use adult 100 mg tablet

BDQ CRUSH BE study will inform use (Q3 2016)

Design

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
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.
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 acceptable and PK criteria are met: complete enrollment into the cohort.
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 unacceptable and PK criteria are not met (exposure low): consider termination of the study in consultation with the protocol team and the SMC.
Safety is acceptable in all participants and PK criteria are met in at least 8 individual participants.
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

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 7, 2012 VOL. 366 NO. 23

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 Tupasi, 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

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: Phillipines, South Africa; age de-escalation, HIV-
  - Groups1, 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

IMPAACT 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-IMPAACT sites with Capacity, Expertise & Interest needed

- Sizwe Tropical Diseases Hospital: JHB, South Africa
- Klerksdorrp
- 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

World Health Organization

TUBERCULOSIS IN WOMEN

- 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

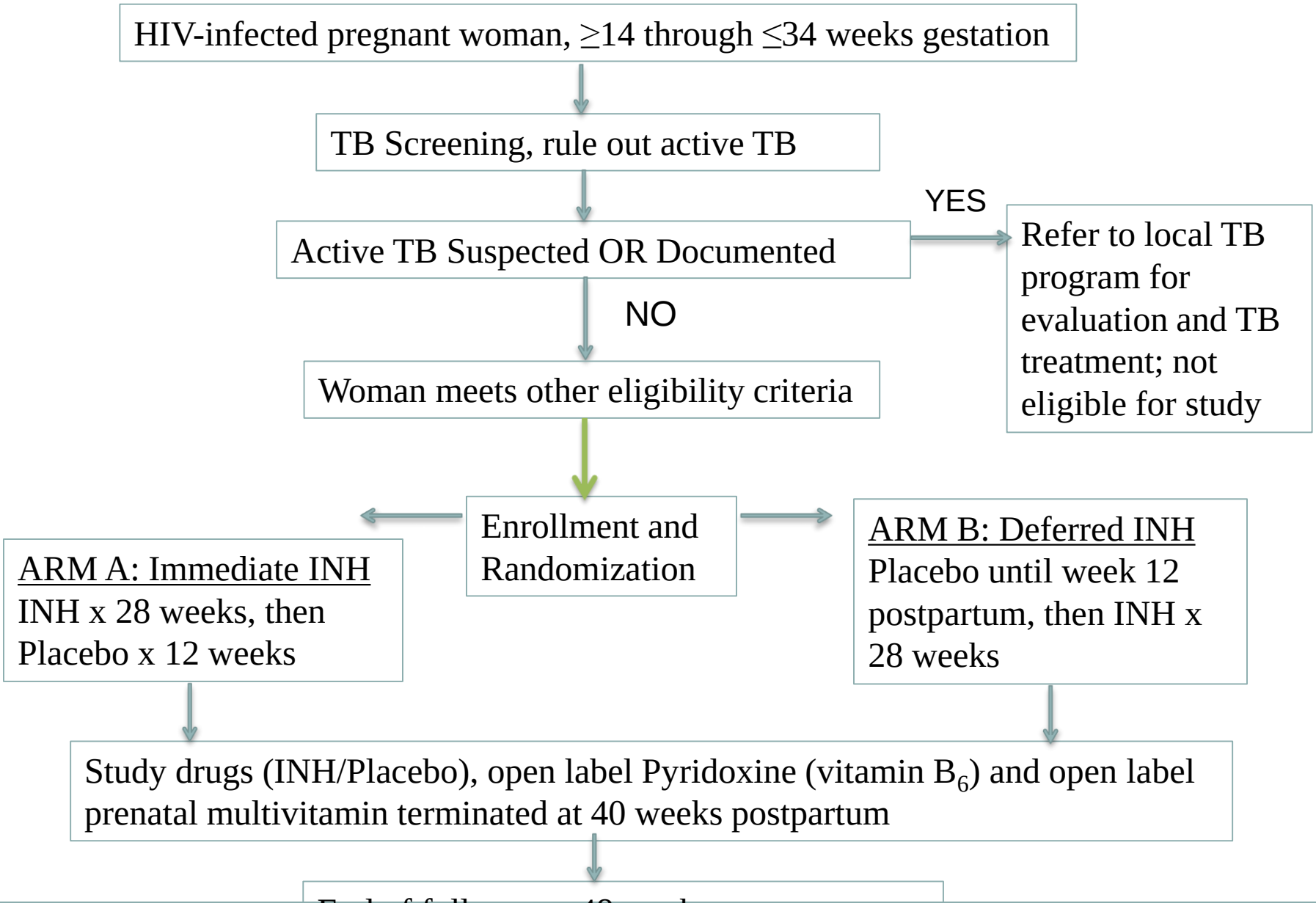
STATISTICIANS: GRACE MONTEPIEDRA AND LISA AARON

SPONSORS: NIAID, NICHD, TBTC

TBSC CHAIR: ANNEKE HESSELING

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

P1078 Study Schema



P1078 sites

13 sites (8 countries) fully accrued 956 HIV+ pregnant women between 19 Aug 2014 and April 4, 2016

Botswana (2)
Haiti
India
Kenya*
Malawi*
South Africa (3*)
Tanzania
Thailand
Uganda
Zimbabwe (3)

Baseline P1078 Maternal Characteristics

Maternal Characteristic	Value
Age (median)	29 yrs.
Ethnicity	
Black African or African origin	90%
Indian	3%
Thai	3%
Enrollment	
14 - <24 weeks gestation	34%
24 - 34 weeks gestation	66%
HIV Viral Load <200 copies/mL	81%
CD4 count (median absolute)	493 cells/mm^3
WHO Clinical Stage 1	89%
ARV Regimen	
Triple ARV	99%
TDF + 3TC(or FTC) + EFV	83%
TDF(or AZT)+ 3TC(orFTC)+ NVP	13%

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

IMPAACT 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 2nd trimester
- Cohort 2: Enrolled in 3rd 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)

Cohort	Actual
Enrolled	(Target)
Cohort 1	14 (14)
Cohort 2	14 (14)
Cohort 3	14 (14)
Cohort 3	46 (45)
Cohort 4	38 (36)
Cohort 5	40 (36)
Cohort 6	58 (70)
Total	224

Proječted accrual completion Q3 2016

Diagnostics and biomarkers work

Ongoing/completed		
DACS 6571	Lymphocyte/monocyte ratio	1041 (published)
IGRA studies	IGRA vs. TST to detect TB infection	1041 (submission pending)
DACS 658	Application of NIH consensus definitions	1041 (published)
NWCS 127	LDL as novel biomarker for TB in children	1041 (pending): Stonybrook, DTTC
Planned		
Novel molecular tests, DST (MDR-TB)	Xpert Ultra, molecular DST, ovel drugs	Phoenix, 1108, 2005
Serum biomarker dx	Hue, Graviss	Phoenix, others
Urine biomarkers	Husson	P1108, other
Immune correlates protection	Prevention trials	P1078, 1113

IMPAACT TREATMENT AND PREVENTION PROTOCOLS	STATUS
Preventive Therapy Trials	
• IPT in HIV-infected pregnant women	P1078; enrolled
• RFPT /INH in HIV-infected and uninfected pregnant women	P2001: opening 2016
• Ultra short Rifapentine-based regimen in adults and adolescents	ACTG 5279: co-endorsed; enrolled
• Preventive therapy for MDR TB in child, adolescent and adult household contacts (pregnant women)	Phoenix: feasibility completed; B opening Q4 2017
• TB vaccine trial	P1113: accrued in 2016
Treatment Trials	
• Shorter regimens for drug sensitive TB	SHINE (BMRC funded): open
• Regimens for extrapulmonary TB	TB Meningitis (NICHD RO1)
• Regimens for MDR TB with/without HIV	
• Bedaquiline	P1108 (Q4 2016)
• Delamanid	P2005 (Q2 2017)
• DLM/BDQ	Planned
• Clofaz	Planned
• Shorter duration all oral regimen	Planned
• DDI for TB/HIV in pregnancy	P1026 S (co-endorsed)
• PK characteristics of cART and TB therapy in LBW infants	P1106 (co-endorsed)
• Dose finding RAL with TB	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!