IMPAACT TB SCIENTIFIC COMMITTEE UPDATE: 2019

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AMITA GUPTA
11 JUNE 2019

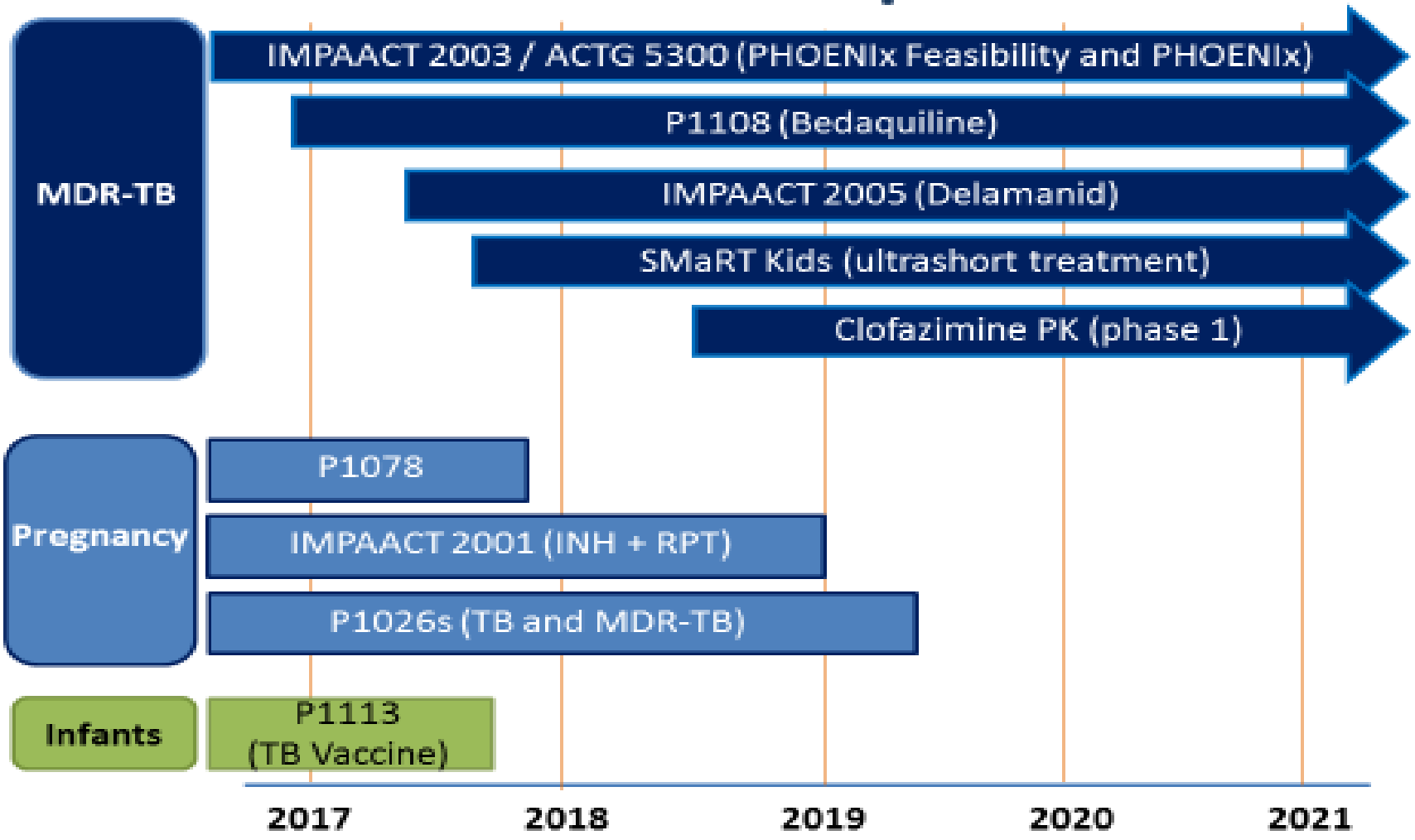
IMPAACT
International Maternal Pediatric
Adolescent AIDS Clinical Trials Network

Table 1. Estimated global burden of TB disease, mortality and infection in HIV-infected and uninfected children	
Estimated total TB cases in children <15 years	1 010 000 (uncertainty interval: 888 000 – 1 120 000
Child TB cases notified	Only 55% (451 980 cases) of the total estimated case load notified
TB deaths HIV, HIV-, Case fatality rate	Children accounted for 15% of total deaths 10% of total TB deaths in HIV positive people 233 000 death (80% in children <5, 39 000 among children living with HIV)
TB infected children	7.5 million
Preventive TB treatment given	Only 292 182 children accessed TB preventive therapy in 2017 (only 23% of the estimated 1.3 million eligible <5 year household TB contacts)
MDR TB estimates	30,000 -50 000
MDR TB infection	500 000

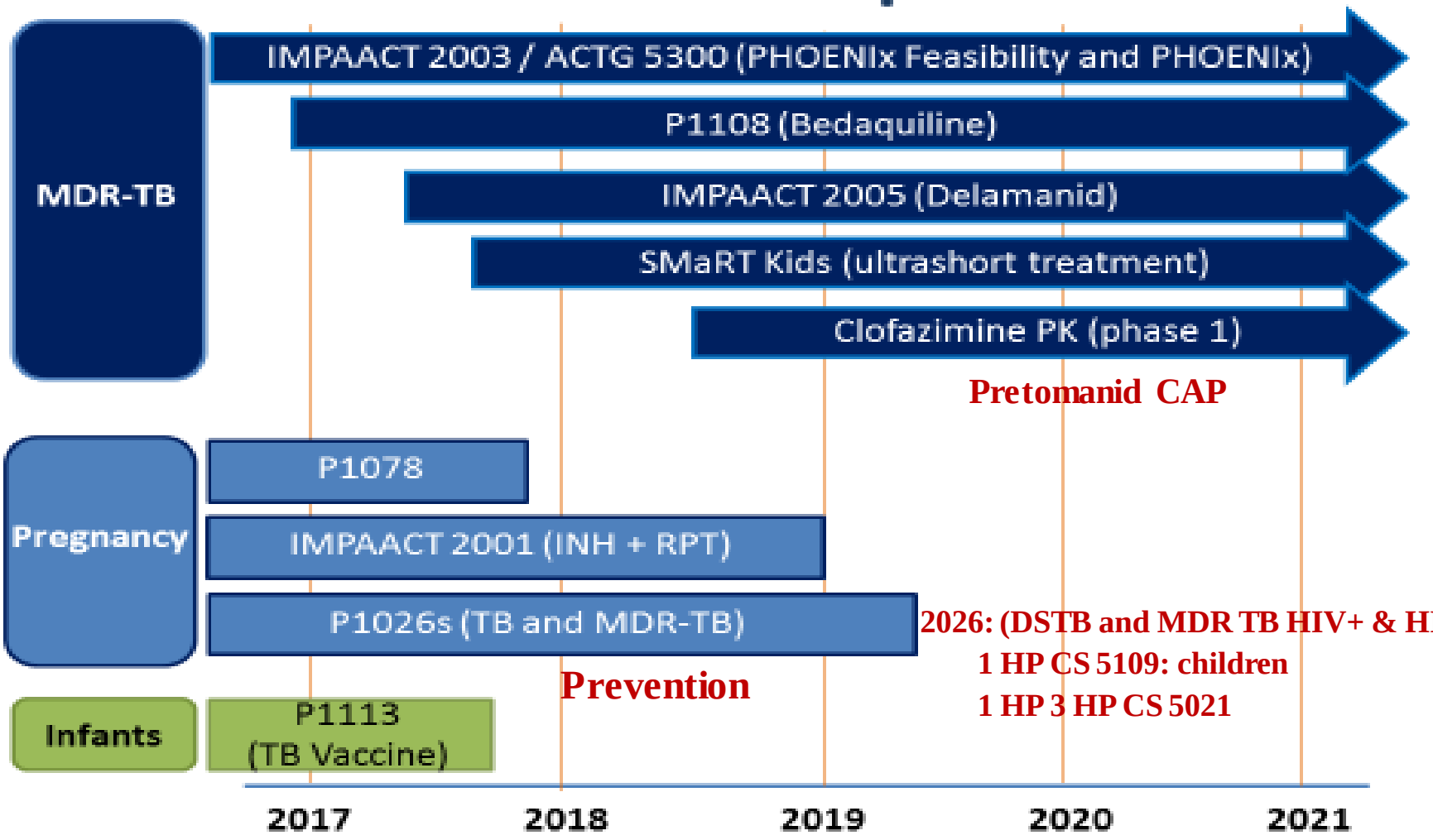
Updated Overall Goals for TB

Evaluate novel approaches for TB prevention, diagnosis and treatment in HIV-infected and uninfected infants, children, adolescents, and pregnant and lactating women that will lead to optimal dosing and regimens, licensing and improved care.

TB Roadmap


MDR-TB
IMPAACT 2003 / ACTG 5300 (PHOENIx Feasibility and PHOENIx)
P1108 (Bedaquiline)
IMPAACT 2005 (Delamanid)
SMaRT Kids (ultrashort treatment)
Clofazimine PK (phase 1)
Pregnancy
P1078
IMPAACT 2001 (INH + RPT)
P1026s (TB and MDR-TB)
Infants
P1113
(TB Vaccine)
2017
2018
2019
2020
2021

TB Roadmap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Pretomanid CAP
Pregnancy
P1078
IMPAACT 2001 (INH + RPT)
P1026s (TB and MDR-TB)
2026: (DSTB and MDR TB HIV+ & HIV
1 HP CS 5109: children
1 HP 3 HP CS 5021
Prevention
Infants
P1113
(TB Vaccine)
2017
2018
2019
2020
2021

Strategy

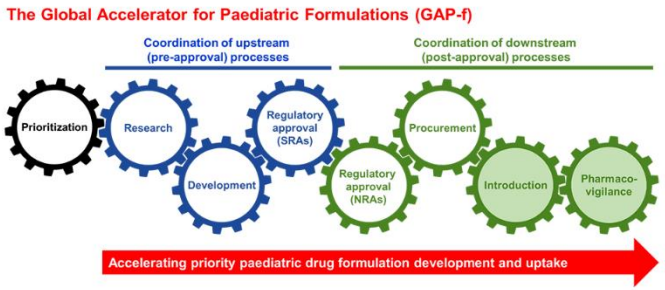
- Studies designed with rapid uptake of findings into policy and practice
- Phase I/II trials where efficient
- Phase III as required
- Earlier inclusion of adolescents
- Inclusion of pregnant and lactating women
- Collaboration with industry
- Cross-network collaboration (HVTN, ACTG, TBTC,PADO, GAP-f, other)
- Address additional science through nested RFPs/other grants (diagnostics, biomarkers, AMR)

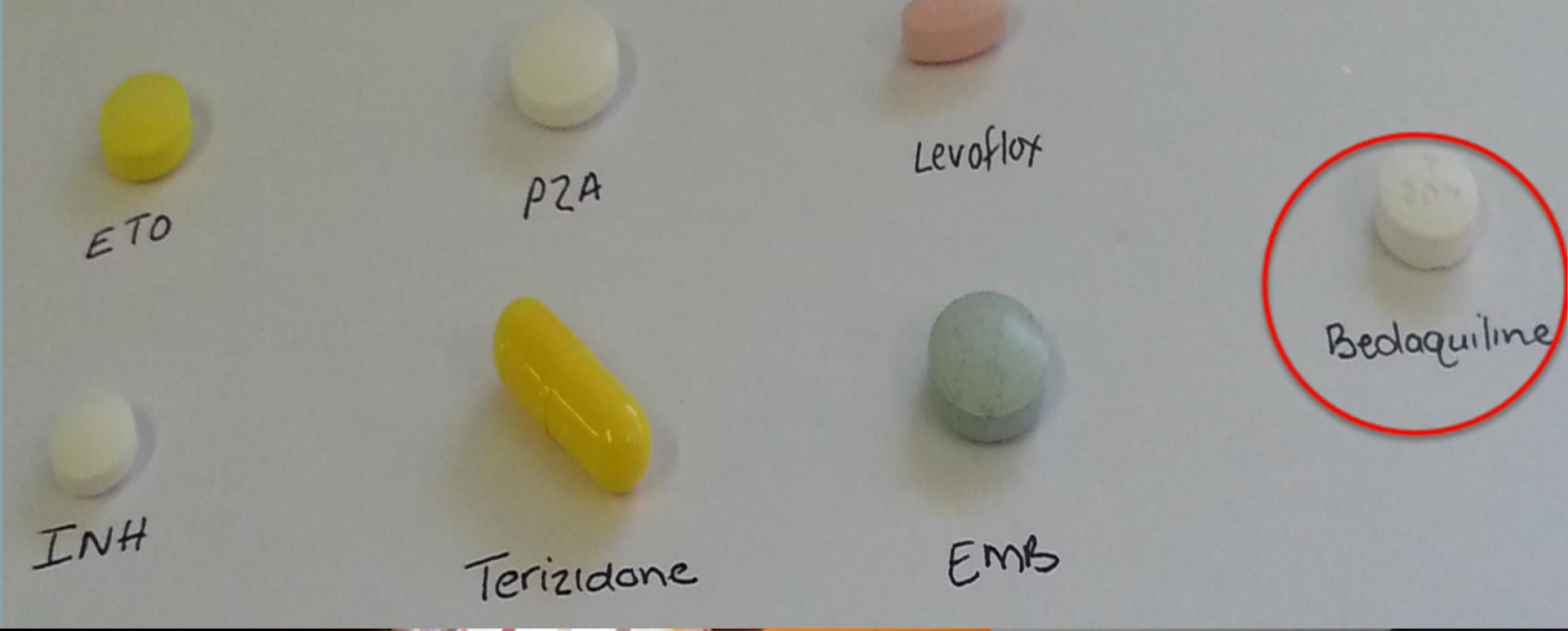
Additional critical cross cutting methods/sciences

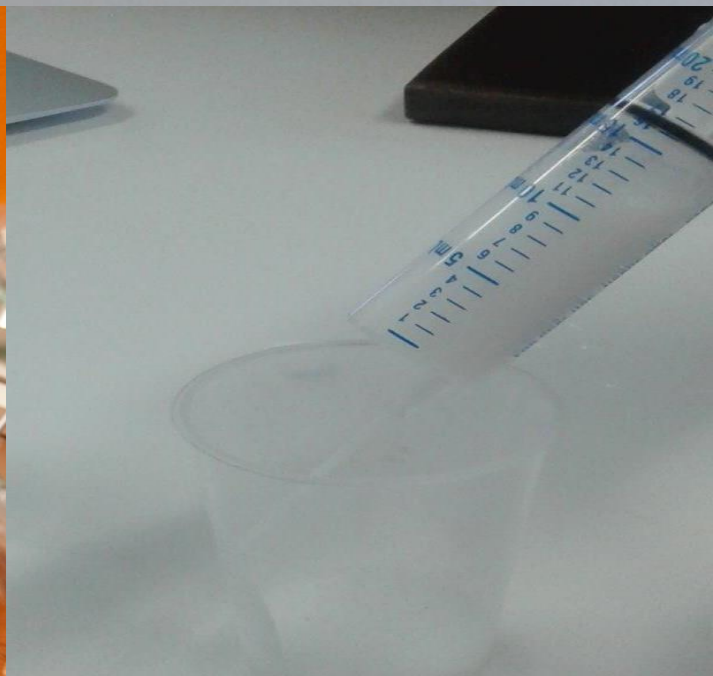
- Socio-behavioural work core capacity: acceptability, preferences of treatment strategies, measurement of outcomes (e.g. DOOR), adherence
- Community engagement
- Adolescents and young people
- State of the art pharmacometrics to design and analyze PK studies; innovative trial design
- TB microbiology expertise
- Improved imaging: PTB EPTB
- TB vaccines and ACTG/HVTN: immunology, design
- Platform opportunities PK for long acting ARVs and DDI protocols: HPTN, ACTG

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
- Formulations needed to support appropriate dosing




ETO
PZA
Levoflox
Bedaquiline
INH
Terizidone
EMB



2018 Global New TB Drug Pipeline [1]

Small Pharma | Non Profits

Preclinical Development | Clinical Development

Early Stage

- Caprazene nucleoside CPZEN-45*
- Spectinamide 1810*
- Gyrase inhibitor SPR720*
- Pyrazolopyridine carboxamide TB-47*

GMP/ GLP Tox.

- TBAJ-587
- TBAJ-876
- GSK-286*
- TBI-223
- Sanfetrinem
- S-004992*

Phase 1

- BTZ-043*
- TBI-166
- Macozinone* (PBTZ-169)
- GSK-656* (070)
- TBA-7371*
- Contezolid (MRX-4/MRX-1)

Phase 2

- OPC-167832*
- Telacebec (Q203*)
- Delpazolid (LCB01-0371)
- Sutezolid (PNU100480)
- SQ-109*
- Macozinone*

Phase 3

- Bedaquiline*
- Delamanid*
- Pretomanid*

Global Market

Underline = new to Phase since March 2018

New chemical class* Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

[1] New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

Ongoing projects without a lead compound series identified: http://www.newtbdrugs.org/pipeline/discovery

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: October 2018

Selected new and existing re-purposed TB drugs for consideration in future IMPAACT trials			
Drug class	Producer	Target	Status
Rifamycins **Rifapentine*** **Rifampin***	Sanofi-Aventis	Latent TB Infection TB disease	1 HP planned (CS 5019) 1 HP vs. 3 HP pregnancy study planned (CS 5021) Treatment shortening of DS-TB: SHINE PLUS
Diaryquinolone **Bedaquiline***	Jansen	MDR TB only	P1108 open; 2020
Nitroimidazole **Delamanid*** **Pretomanid***	Otsuka TB Alliance	MDR TB only DS/DR TB	PHOENIX (A5300/I2003) for MDR prevention Pediatric phase I/II planned
Oxazolidinones **Sutezolid *** **Tedizolid *** **Linezolid phosphate***	TB Alliance Sequellla Prius/Pfizer	MDR TB MDR/DS TB MDR/DS TB/TBM	Pediatric Phase I/II planned (pending adult date) Pediatric Phase I /II planned (pending adult data) Pediatric PK completed
Fluoroquinolones **Moxifloxacin** **Levofloxacin***	Bayer Macleods	DS/DR TB DR prevention	Pediatric PK completed (levofloxacin and moxifloxacin) Phase IIb planned (2020) TB CHAMP
B-lactams **Sanfetrinem.**	GSK	DR TB	Pediatric phase I planned based on adult EDCTP data
Clofazimine*	Novartis	DR-TB	Pediatric phase I/II trial planned

PK STUDIES	ONGOING/COMPLETED PAEDIATRIC STUDIES
PK/safety studies *Standard first- and second-line drugs-Establishing doses that achieve adult-equivalent exposures*	• **DATiC:** PK/safety first-line TB drugs: NICHD R01: McCilleron • **STEP-TB:** New pediatric dispersible formulations of first-line drugs (TBA, Unitaid): 1 FDC • **Infant PK study:** low Rif exposures (TBA/Unitaid): Hesseling/Bekker • **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 • **MDR PK 2**: Optimizing Levofloxacin, moxifloxacin, linezolid (NICHD R01): Garcia-Prats • **Rifabutin** in children, NIRT (terminated; NICHD): Moultrie • **OptiRIF Kids**: high-dose rifampicin PK safety: accrued (TB Alliance/Unitaid): Hesseling: • **Clofazimine PK**
PK/safety studies *New drugs* *Establishing doses that achieve adult-equivalent exposures*	• **Study 35**- Rifapentine/isoniazid in HIV+/-children < 12 years of age: TBTC: opens Q3 2019 • **P1108 and** Jansen C211: Bedaquiline in children–BDQ in HIV-uninfected children (Janssen) • **232/233-** Delamanid in children- Otsuka (Otsuka) • **2005** -injectable-sparing DLM-based regimen in children with and without HIV infection: 2017 (Dooley) • **2001**: safety and PK of rifapentine in HIV-infected pregnant women • **P1026S/2026:** including new TB drug arms • **Pretomanid CAP**: in development: BDQ and Linezolid (EMA PIP)
HIV/TB DDI studies	• **DNDi:** Ritonavir boosting of LPV/r in TB/HIV: completed • **NICHD PK**: first-line TB drugs with ART: completed • **P1101:** RAL-based ART with standard TB drugs: ongoing

IMPAACT P1108
Design: phase I/II multicenter trial

Sparse PK

Wk 2 intensive PK

Wk 1 sparse PK

Enrollment

Cohort	Age and Weight	BDQ Dosing
Cohort 1 up to 24 participants to achieve 18 evaluable (nine in each weight band)	≥ 6 to < 18 years ≥30 kg	400 mg once per day for two weeks then 200 mg three times per week for 22 weeks
	≥ 6 to < 18 years ≥15 to <30 kg	200 mg once per day for two weeks then 100 mg three times per week for 22 weeks
Cohort 2 up to 24 participants to achieve 18 evaluable	≥ 2 to < 6 years ≥7 kg	Calculated using model-based dose selection
Cohort 3 up to 24 participants to achieve 18 evaluable	≥ 0 to < 2 years ≥3 kg	Calculated using model-based dose selection

Study status

- Minimum evaluable: n=54
- N=15 enrolled (ages 6-17 years); 3 HIV+
- Formal PK criteria met for PK and safety (SMC December 2018)
- LOA for dosing submitted to SAHPRA cohorts 1 and 2 (in parallel); new proposed dosing
- CTA signed with Janssen
- Study on pause: unrelated death, 14 year HIV+ adolescent with advanced AIDS and wasting; weight 24.5 kg; SMC review ongoing

Weight range	Loading dose per day	Maintenance dose per week (M/W/F)
3 to 7 kg	100 mg	150 mg (50/50/50)
>7 to 15 kg	200 mg	300 mg (100/100/100)
>15 to 30 kg	200 mg	300 mg (100/100/100)

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

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Objectives

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

Primary Objectives

- Evaluate the PK of **Delamanid** (DLM), at doses most likely to achieve exposures similar to those achieved in adults with 100mg twice-daily
- Safety of DLM over treatment period (24 weeks)

Secondary Objectives

- Effects of HIV co-infection and/or co-treatment, dose, age contributions on PK variability
- Acceptability/ tolerability of DLM
- Long-term safety (72 weeks following treatment initiation)
- TB treatment outcomes

Exploratory Objectives

- HIV treatment outcomes ; TB treatment outcomes, safety and tolerability of injectable-sparing, delamanid-containing regimens in the treatment of MDR-TB; PK-QT relationships; longitudinal biomarkers of TB treatment responses in children

N= 36

Progress

Cohort	Age in Years	DLM Dose
1	12 to < 18	≥ 40 kg: 100 mg twice daily (adult formulation)
2	6 to < 12	30 to < 40 kg: 50 mg twice daily (adult formulation)
3	3 to < 6	15 to < 30 kg: 25 mg twice daily (peds formulation)
4	0 to < 3	< 15 kg: 15 mg twice daily (peds formulation)

Open to Enrollment at 6 sites!

Accrual

- **Two** participants enrolled (BJMC) into Cohort One
  - One switched off of a regimen involving an injectable
- One potential XDR-TB patient to be screened mid-June

Barriers

- Difficulty finding children with MDR-TB who weigh > 40 kg
  - With prior OBR MDR-TB regimen duration 2-8 weeks
- Cannot open to younger children until protocol amendment containing revised dosing approved (submitted May 16)

Encouraging headway

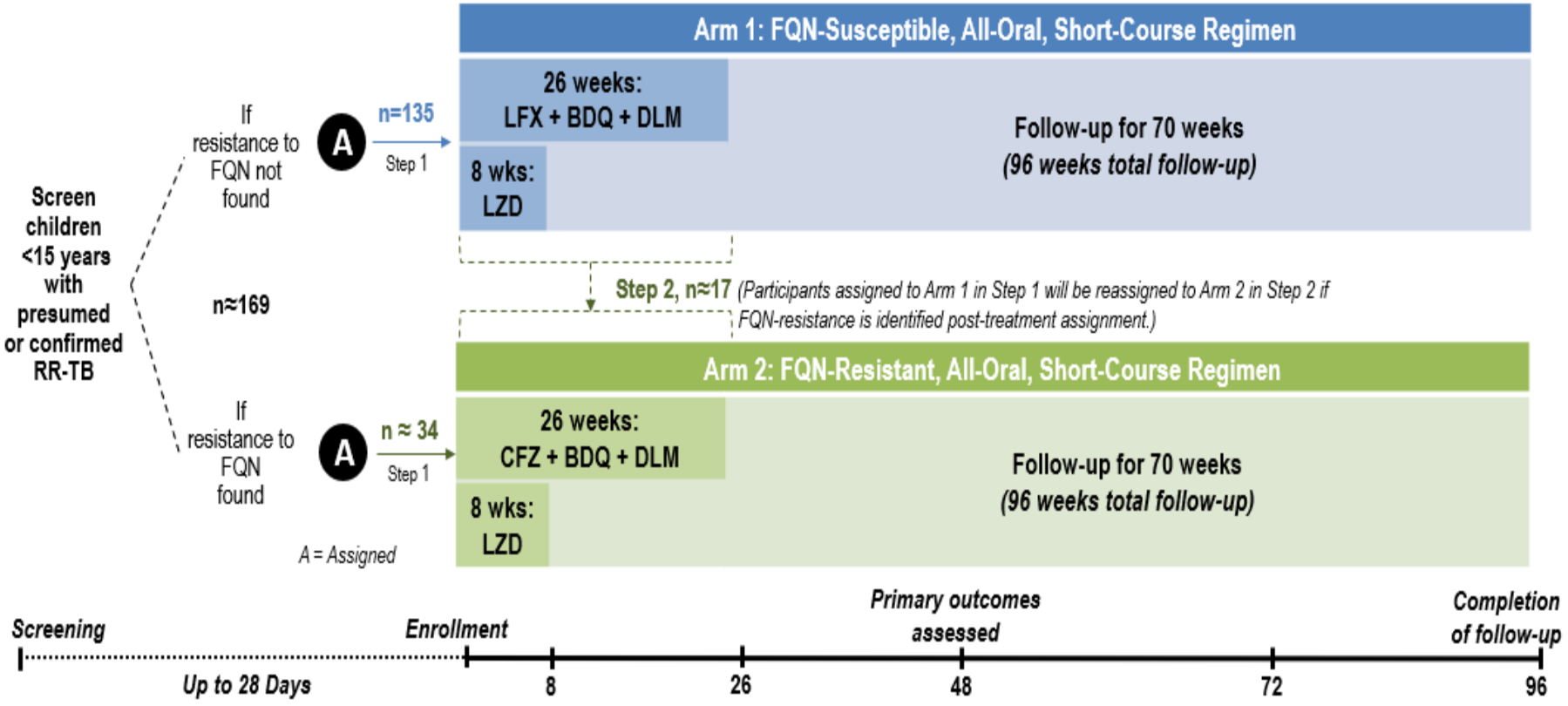
- First Round DAIDS regulatory review complete; making ICF revision
- **Goal of getting revised protocol out to sites by July 2019**

EFFICACY STUDIES	ONGOING TRIALS
TB prevention *Prevention of TB in children (high risk of TB progression)*	• **A5300 PHOENIX: delamanid vs. SD INH for MDR-TB prevention: 2019** • TB-CHAMP: Levo vs placebo for MDR-TB prevention: open • VQUIN: levo vs. placebo for MDR-TB prevention: open • ACTG5279: one month of rifapentine+isoniazid daily for DS-TB prevention • P4v9 Trial: 4 months RIF vs 9 months INH for DS-TB prevention: ongoing • TBTC 37: RPT 6 weeks vs. local SOC (RIF 4 mo or RPT/INH q week x 3 mo): planned • **P1078: IPT in HIV-infected pregnant women** • **1 HP in HIV+/- kids CS 5019** • **1 HP vs/ 3 HP in pregnant women: CS 5021**
DS-TB disease *Reduce mortality, improve neurocognitive dysfunction*	• TBM-KIDS: High-dose RIF +/- Levo for children with TBM (NICHD Ro1 - Dooley • SURE Kids: Gibb
Non-severe DS-TB *Reduce treatment duration for children with non-severe disease*	• SHINE: 4 vs. 6 months standard TB Rx (new FDCs, nested PK): open label (MRC CTU; Gibb) N=1200 (accrual completed) • IMPAACT priority
MDR-TB disease	• **SMART-KIDS: 2020 (phase 2)**

IMPAACT 2020 (SMaRT Kids)

- Design: Phase 2 multi-centre trial
- Eligibility
  - Children 0 to <15 years of age;
  - Probable or confirmed pulmonary or extrapulmonary MDR/RMR-TB/Rif-R, and MDR-TB with FQN-res
  - HIV-infected and uninfected
- Assignment to 1 of 2 arms based on FQN-susc
  - Arm 1 – FQN-Susc – 26 weeks BDQ-DLM-Levo, 8 weeks Lzd
  - Arm 2 – FQN-Res – 26 weeks BDQ-DLM-CFZ, 8 weeks Lzd
- Objectives – 1^{0} - Safety; 2^{0} - outcomes, PK, others
- N=163

IMPAACT 2020: Study schema



Primary Objectives

Among infants, children, and adolescents with confirmed or probable RR-TB without resistance to FQNs, to:

- Characterize the safety and tolerability of an all-oral, short-course regimen through Week 48

Secondary Objectives

Among infants, children, and adolescents with confirmed or probable RR-TB without resistance to FQNs, to:

- Characterize treatment outcomes of an all-oral, short-course regimen through:
  - Week 48 and Week 72

Among all infants, children, and adolescents who received applicable drugs, to:

- Characterize the pharmacokinetics of CFZ, LFX, LZD, BDQ, and DLM through Week 8
- Characterize the pharmacokinetics of antiretrovirals among HIV-infected participants through Week 8

Among all infants, children, and adolescents, to:

- Characterize the cardiac safety of co-treatment with BDQ and DLM through Week 26

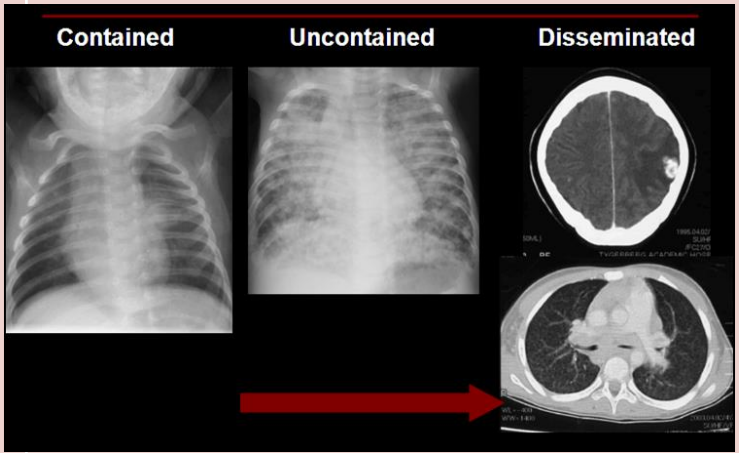
Among infants, children, and adolescents with confirmed or probable RR-TB with resistance to FQNs, to:

- Characterize the safety and tolerability of an all-oral, short-course regimen through Week 48
- Characterize treatment outcomes of an all-oral, short-course regimen through:
  - Week 48 and Week 72

DS-TB	Gaps for children	Priority studies
	• Optimal treatment for TB meningitis (levofloxacin, high dose rifampin)	• PK and outcome (TBM Kids; NICHD; Dooley) : opened Q2 2017 ; SURE KIDS
	• Rifampicin and rifapentine dose optimization (severe disease not addressed in SHINE, treatment shortening): OptiRif Kids	• Priority: building on SHINE, rifampin dose optimization. Daily RFPT (CS 5019)

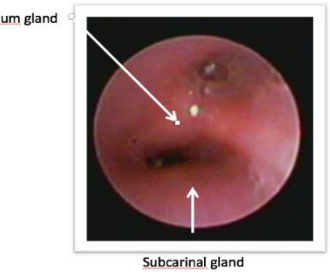
	• Treatment shortening: non-severe and severe disease
	  • Build on adult phase IIb/III trials (TBTC Study 31, TB Alliance)
	  • Innovative design and outcome assessment
	  • Informed by drug optimization studies and site of disease PK
		• SHINE+: Priority – complementing SHINE and Optirif Kids

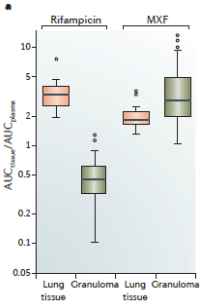
	Moving to treatment of pan susceptible disease in future	



Summary Information Type	Summary Details
Short Name Title of Trial	**SHINE** (Shorter treatment for minimal TB in children)
Long Title of Trial	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
Version	1.0
Date	24-Mar-2014
ISRCTN #	ISRCTNXXXXXXXX
Study Design	Parallel group, randomised, non-inferiority, open label, 2 arm phase III clinical endpoint trial
Type of Participants to be Studied	Children < 16 years with suspected minimal (limited) TB disease, with or without HIV infection, will be screened
Setting	South Africa (Cape Town); Zambia (Lusaka); Uganda (Kampala) and India (Chennai and Pune)
Interventions to be Compared	**4-MONTH REGIMEN** 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** 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.

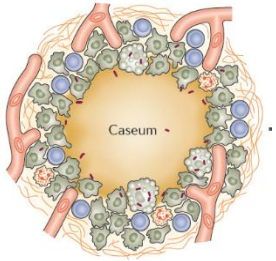
Knowledge needed re site of disease PK
Role of additional imaging



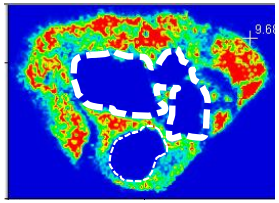


Homogenize
Extract

LC/MS/MS
Quantify



MALDI MS imaging



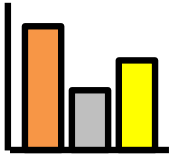
PK

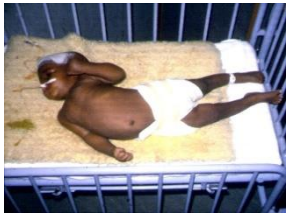
PD

Drug activity in caseum

Laser capture microdissection

LC/MS/MS
Quantify





Courtesy. V Dartois

Treatment of persons exposed to MDR TB: data limited

Author	Country	Population	Regimen	HIV	Rx vs No Rx
Bamrah	Micronesia	108 Adults and Children	FQ alone FQ +EMB FQ+ETH	None	0/93 vs 3/15 0% vs 20% RR 0.02
Denholm	Australia	49 Contacts	FQ alone FQ+EMB PZA+EMB INH or RIF	None	0/11 vs 2/38 0% vs 5% RR 0.83
Schaaf	South Africa	78 Children <5yrs	INH/PZA/EMB or ETH	None	2/14 vs 13/64 5% vs 20% RR 0.20
Trieu	USA	199 Adults	FQ	70%	0/30 vs 0/166
Adler-Shohet	USA	31 Children	FQ+PZA	Unknown	0/26 vs 0/5
Williams	UK	12 Children	Various 2 drugs	None	0/8 vs 0/4
Garcia-Prats	South Africa	31 Children	FQ+EMB+INH	None	0/21 vs 0/10

Marks CID 2017; WHO, Latent TB Infection Guidelines, 2018

Protecting Households On Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis Patients (A5300B/I2003B/PHOENIx)

ACTG: GJ Churchyard, S Swindells
IMPAACT: AC Hesseling, A Gupta

27 international sites; joint IMPAACT/ACTG

ACTG AIDS CLINICAL TRIALS GROUP

IMPAACT International Maternal Pediatric Adolescent AIDS Clinical Trials Network

PHOENIx

- Design: Multi-center, cluster-randomized, superiority trial comparing 26 weeks of daily delaminid vs INH
  - Cluster = eligible high risk contacts from same HH
- Sites: 27 ACTG and/or IMPAACT sites in high MDR TB burden countries
- Population:
  - Index case: adult PTB with confirmed INH/rifampin resistance
  - High-risk household contact:
    - HIV-infected,
    - Child <5 years of age
    - LTBI+ (Quantferon Plus or TST)
- Sample Size: 2158 Index cases and 3452 high risk HHCs
- Follow-up: 96 weeks

PHOENIx Objectives

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

- Efficacy of DLM vs. INH for preventing confirmed or probable active TB
- Safety of DLM vs. INH for the treatment of presumed LTBI with MDR TB

Secondary: To compare DLM vs INH with respect to:

- Efficacy and safety by High-risk group (HIV+, children, LTBI+)
- Efficacy in preventing
  - Confirmed MDR TB
  - All-cause mortality
  - Confirmed or probable TB and all-cause mortality
- PK of DLM in children and adults
- Adherence
- Cost-effectiveness
- Biomarkers of progression to TB

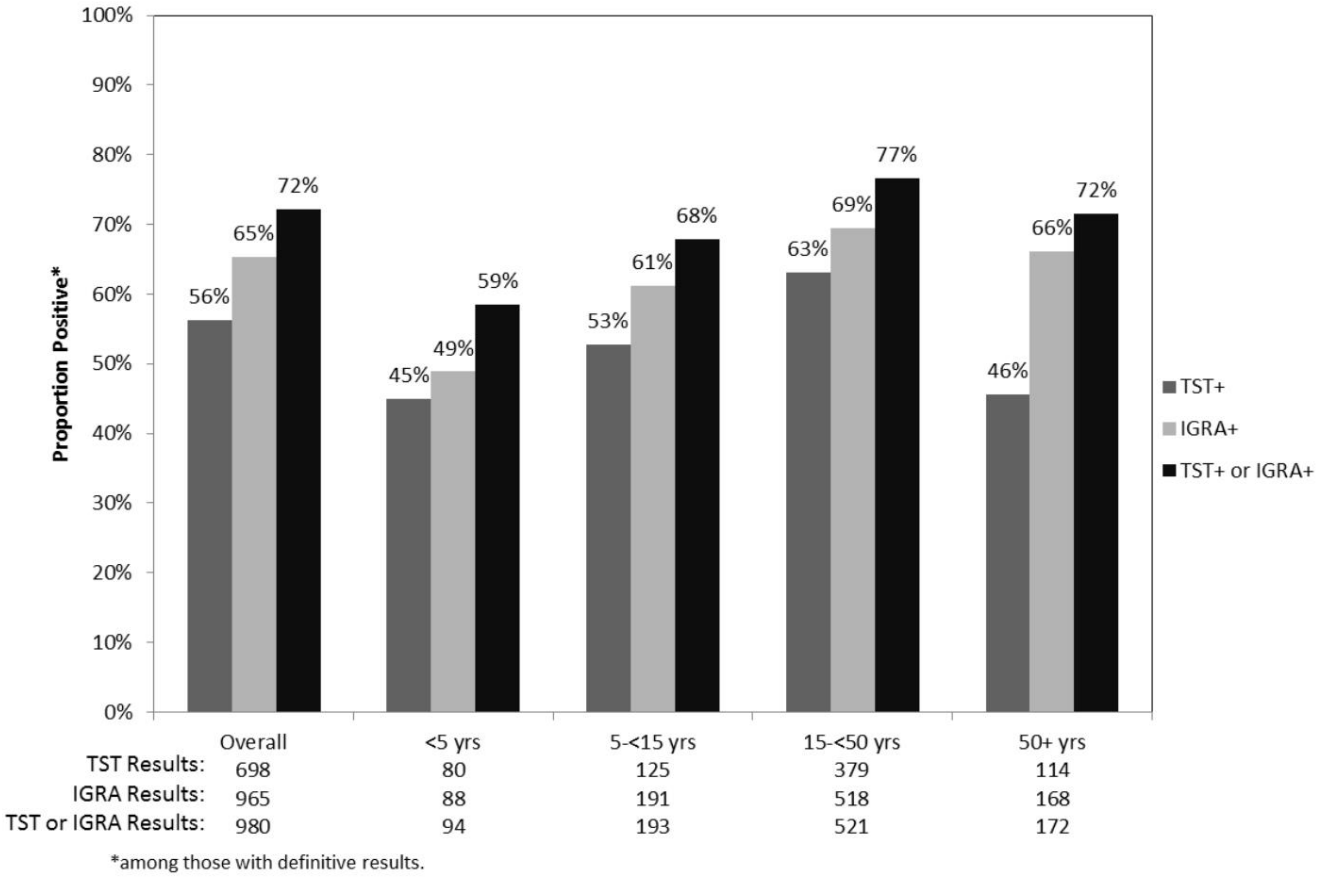
PHOENIx is rising!

- Version 2 released to sites September 25, 2018
- First site activated in Brazil June 7, 2019
- Second site activated in Botswana June 11, 2019
- Refresher trainings planned IMPAACT June 12 and ACTG June 18, 2019

PHOENIx Feasibility Study
TB infection by TST and IGRA by age groups

Figure 3. Distribution of tuberculin skin test (TST) and interferon gamma release assay (IGRA) positivity

3a. By age group

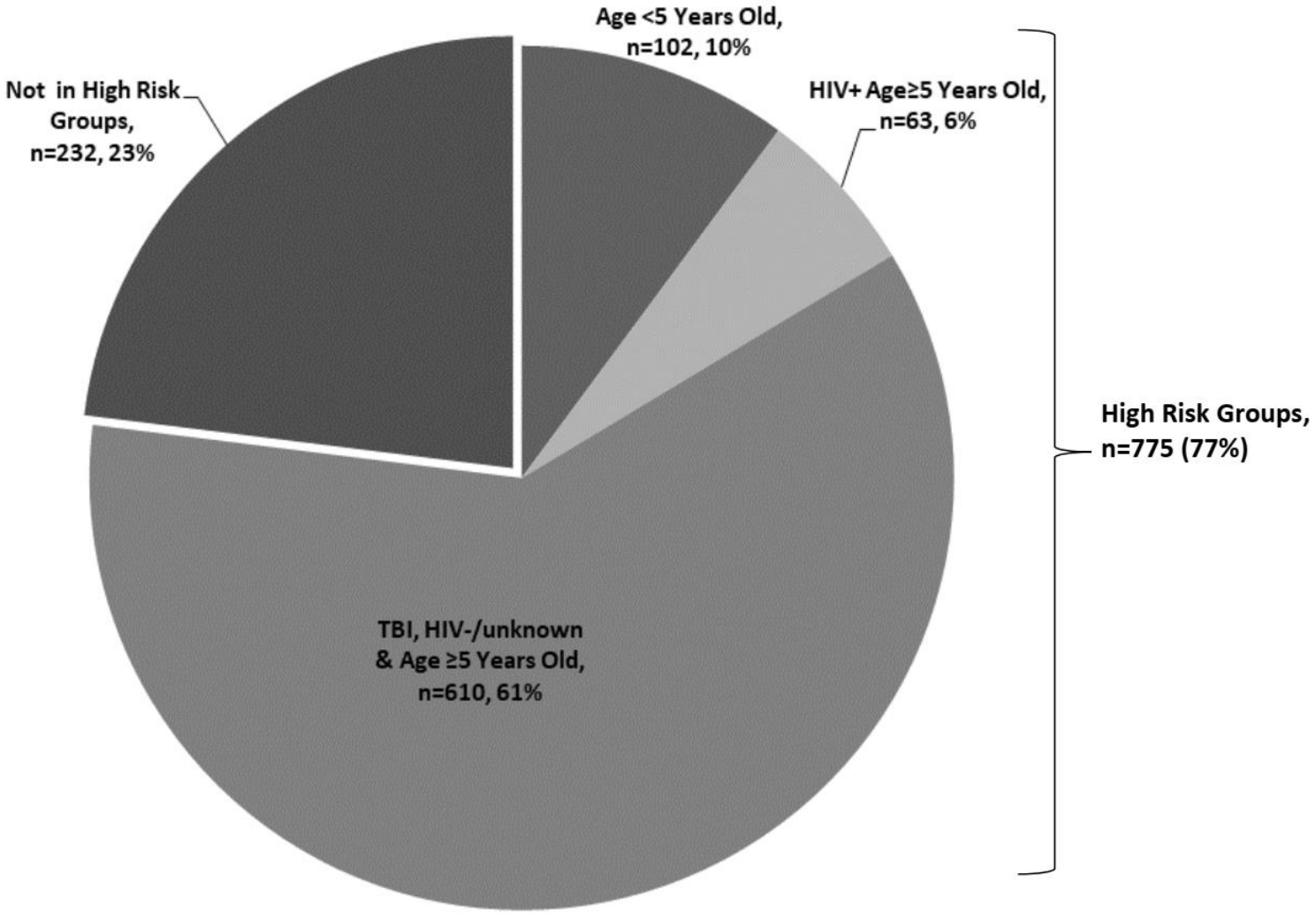


*among those with definitive results.

Gupta et al CID 2019

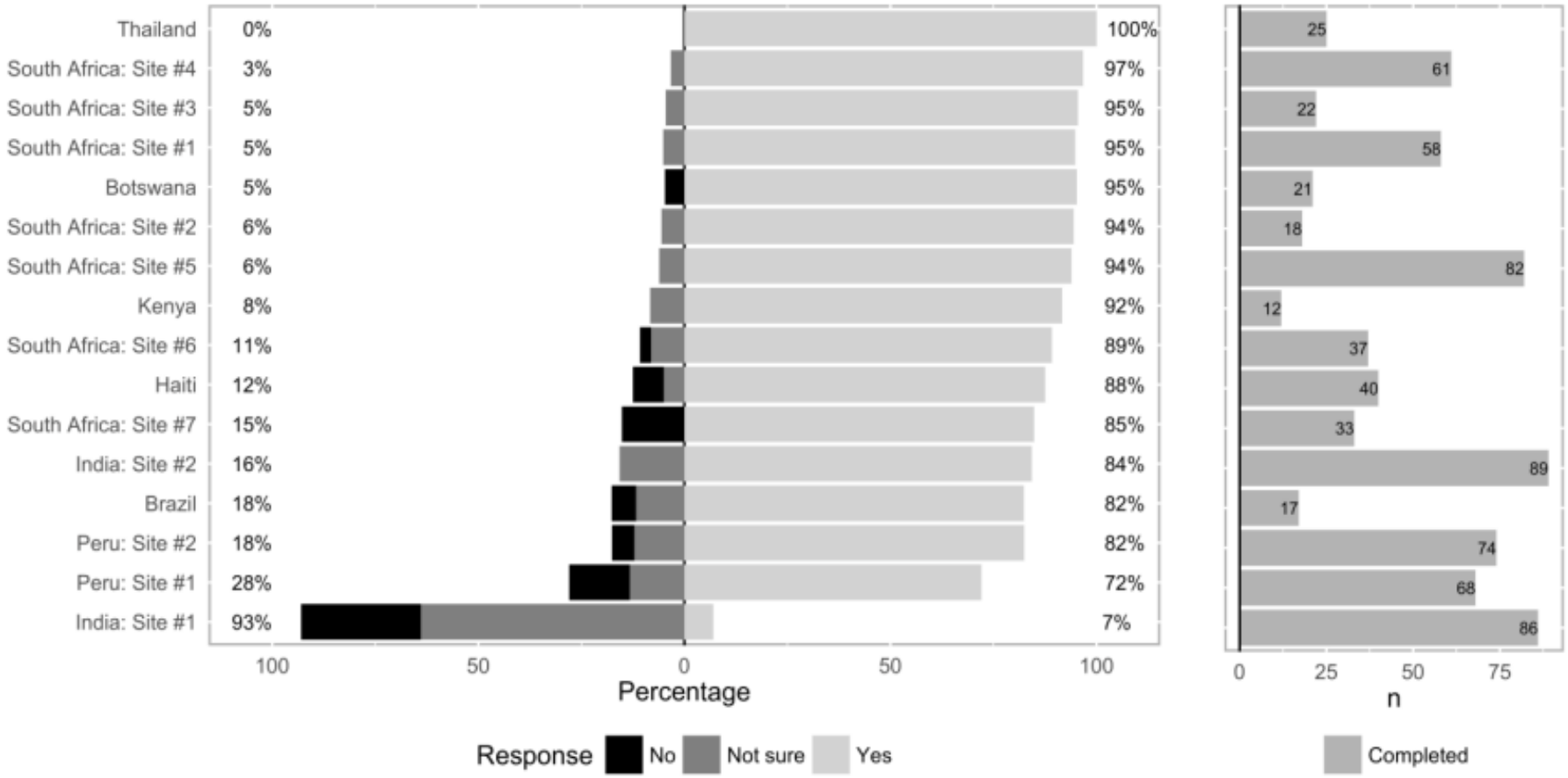
PHOENIx Feasibility Study
Proportion of HHCs that are high risk

Figure 4. Proportion of HHCs that were identified as high risk contacts*



Gupta et al CID 2019

PHOENIx Feasibility Study
Majority of household contacts report Willingness to take MDR TB preventive therapy



Suryavanshi, Murrill et al CID 2019

IMPAACT P1026s

IMPAACT P1026s
Current Maternal Accrual into Open Protocol Arms, Version 10.0
(accrual target = 25 evaluable for each arm)

	# Enrolled
Antepartum/HIV-infected Arms	
TAF 25 mg qd with COBI or ritonavir	22
ATZ/COBI	9
Antepartum/TB Arms	
EFV (first line TB/HIV-infected)*	24
LPV/r (first line TB/HIV-infected)*	2
Second Line TB (HIV-infected and not-infected)	8
TB only*	22
Postpartum Contraception Arms	
DRV/Cobi or ATZ/COBI + oral contraceptives	2
DRV/Cobi or ATZ/COBI + implant contraceptive	5

**Opened under protocol Version 9.0*

IMPAACT P1078

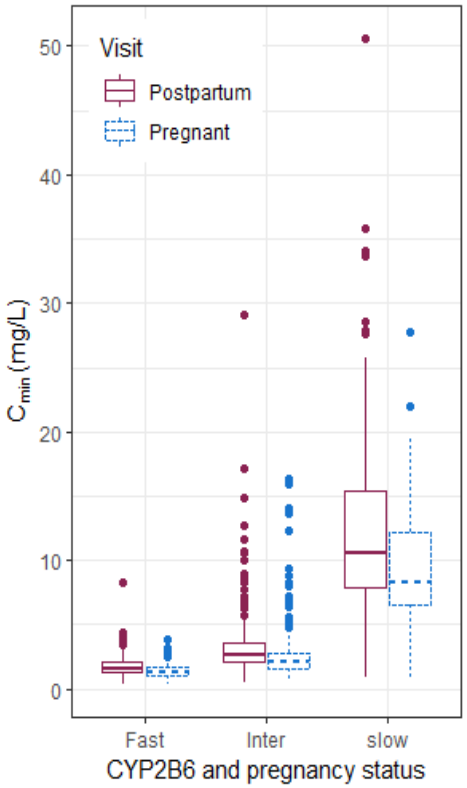
- Primary paper. "Isoniazid Preventive Therapy in HIV-Infected Pregnant and Postpartum Women" *Accepted NEJM 2019*
- Impact of maternal isoniazid preventive therapy (IPT) timing on acquisition of infant TB infection (TBI) in the IMPAACT P1078/TB APPRISE trial
  - Union 2018 Oral presentation, manuscript draft in preparation
- Pharmacokinetics of isoniazid preventive therapy among HIV-infected pregnant women in high tuberculosis incidence settings
  - Kamunkwala Gausi et al CROI March 2019 and PAGE conference July 2019 poster, Manuscript draft prepared
- Impact of isoniazid and pregnancy on efavirenz pharmacokinetics in women living with HIV
  - Kamunkwala Gausi et al IAS 2019 poster, Manuscript draft prepared
- Effects of Pregnancy and Isoniazid Preventive Therapy on *M. tuberculosis* Interferon Gamma Response Assays in Women with HIV
  - Adriana Weinberg et al, ID week abstract. Manuscript draft prepared

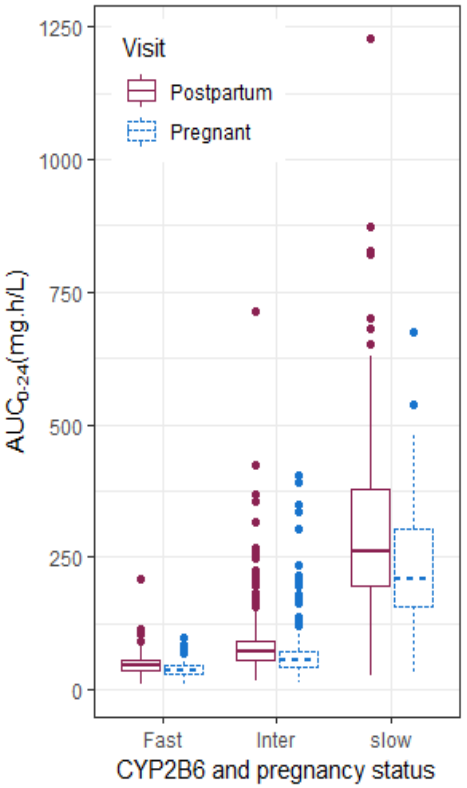
Selected additional analyses underway

- Adverse pregnancy outcomes (Gerhard Theron);
- Hepatotoxicity (A Gupta);
- Risks and benefits DOOR/RADAR (Grace Montipiedra);
- NWCS 626/RO1 awarded on maternal-infant immunology (Savita Pahwa);
- Maternal immunology and IPT responses grant submission (Adriana Weinberg)

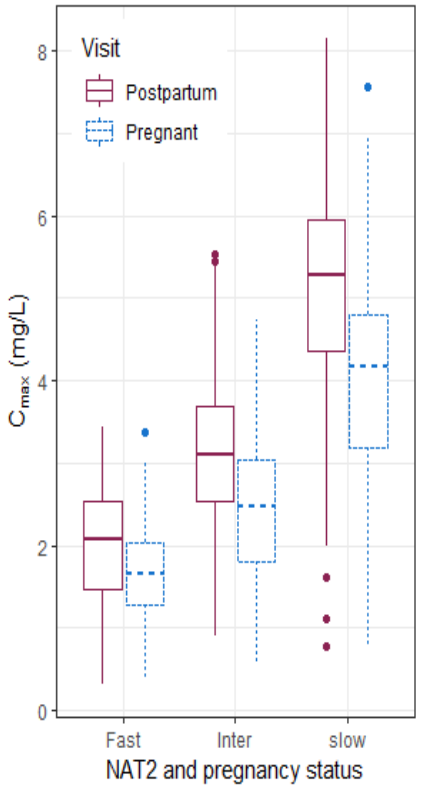
IMPAACT P1078
PK data

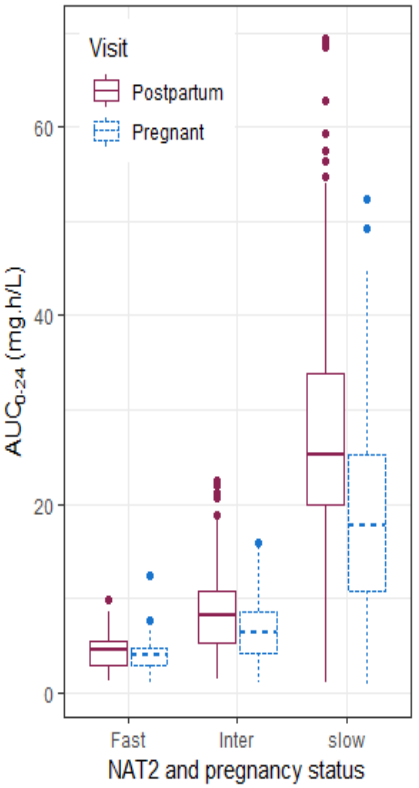
Efavirenz Cmin and AUC by NAT2 genotype and pregnancy





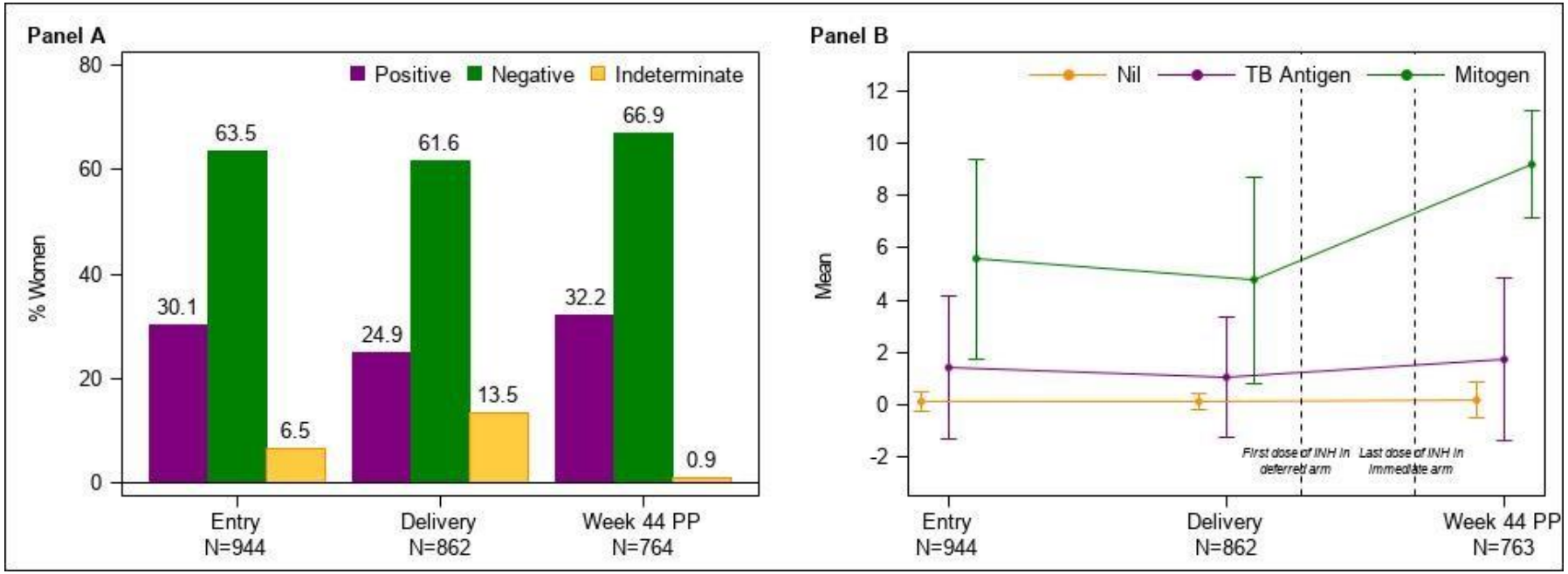
Isoniazid C_{max} and AUC by NAT2 genotype and pregnancy





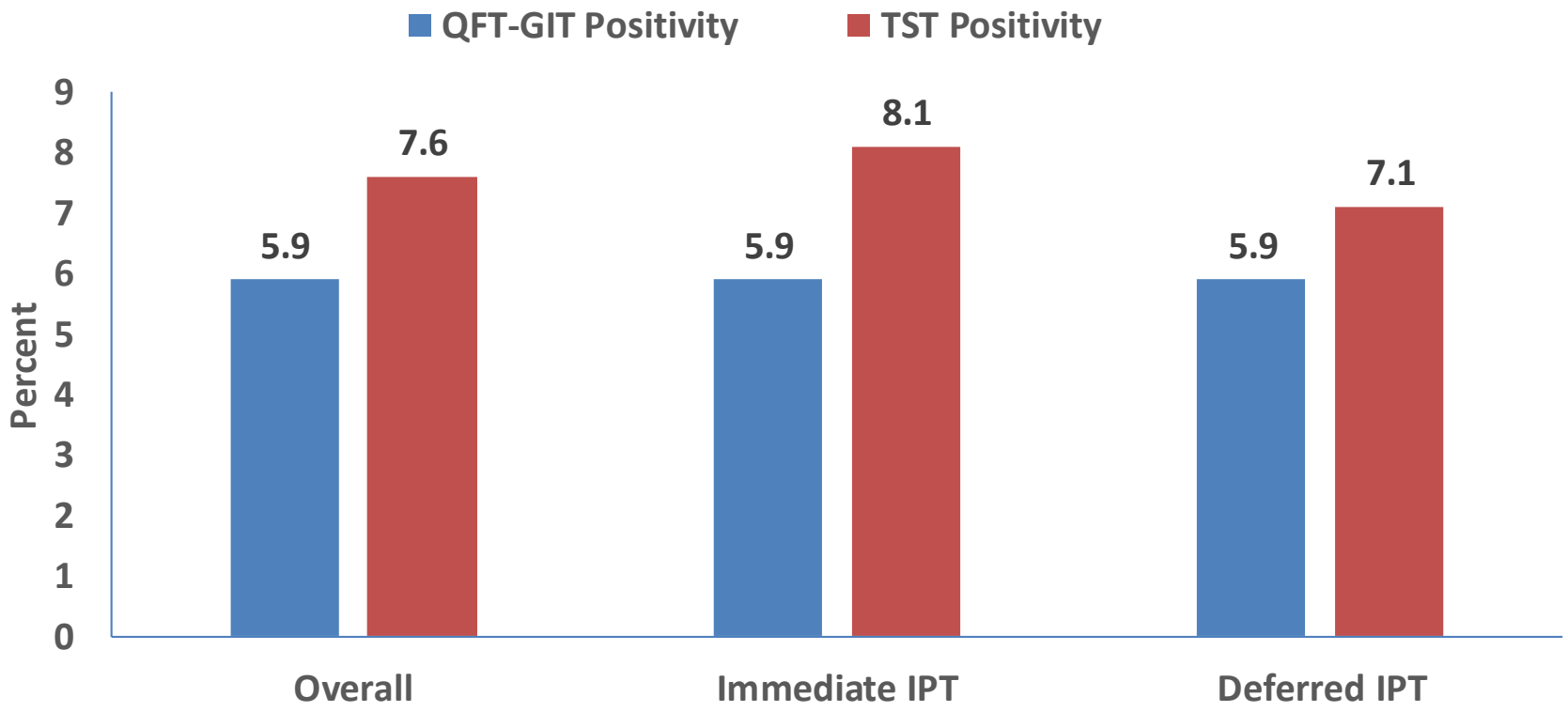
Gausi et al CROI 2019 and IAS 2019

IMPAACT P1078
IGRA by pregnancy stage



Weinberg A et al, Manuscript in preparation

IMPAACT P1078: Prevalence of Infant TB infection at Week 44 by Study Arm



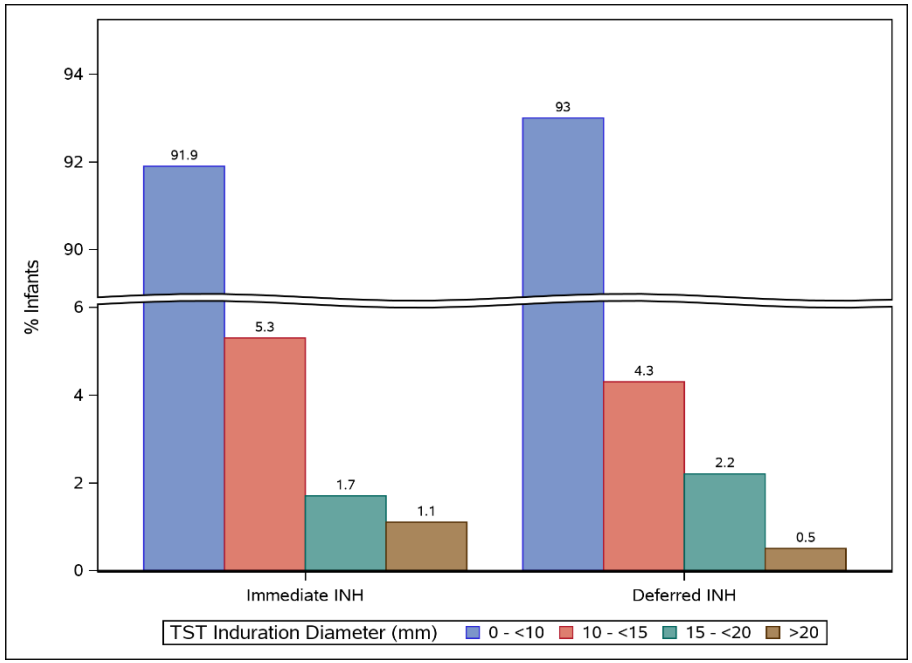
Timing of Maternal IPT did not affect infant TBI acquisition

Gupta et al Union 2018

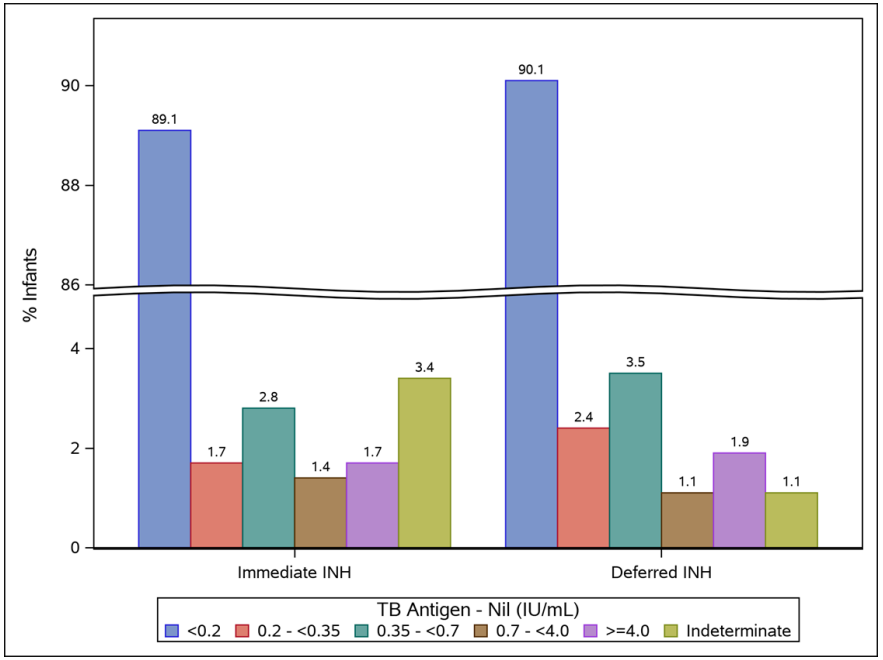
IMPAACT International Maternal Pediatric Adolescent AIDS Clinical Trials Network

P1078 Infant TB infection by maternal IPT arm

TST Quantitative Results by Maternal IPT arm



QFT-GIT Quantitative Results by Maternal IPT arm



- **Infant TBI differed across sites and by type of TBI test used**
- **Small proportion have QFT-GIT at 4.0 IU or higher**
- **Agreement between infant TST and IGRA was poor: Kappa=0.1**

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

Jyoti S. Mathad (Protocol Chair)

- Rationale:
  - Pregnant/postpartum women have a high risk of developing active TB.
  - Recently, results from P1078 raise concerns about safety of 6H in pregnancy
  - The regimen of 3 months of weekly INH + RPT (3HP) has improved completion rates and decreased hepatotoxicity in all populations, including HIV-infected and children
- **Objective:** To provide data needed to extend use of 3HP to pregnant women
  - Determine the impact of pregnancy on RPT PK
  - To estimate the incidence of serious adverse events (SAEs) in maternal-infant pairs

IMPAACT 2001 Updates

- 6 sites: US, Haiti, Kenya, Malawi, Thailand, Zimbabwe
- 50 participants enrolled
- Interim results: No dose change needed for RPT in 2nd or 3rd trimester of pregnancy*
  - Need additional analysis of full HIV+ cohort

Event	Date
Study Closure	May 15, 2019
Study Data Closure	August 7, 2019
Raw analysis of PK samples (maternal/cord)	Start: June/July 2019 End: August 2019
Raw analysis of breastmilk PK	Pending approvals
PK modeling	September 2019
Core analysis to study chair	October 2019
Draft manuscript	January 2020

Selected Novel TB Vaccine Candidates *priority		
Type	Product	Sponsor
Mucosal delivery	BCG	Gates
Recombinant live	VPM 1002	Max Planck, VPM, Serum Institute
Viral recombinant	CMV	
Recombinant protein	M72+AS01 H56:IC31 ID93+GLASE	GSK, Aeras SSI, Aeras IDRI, Wellcome Trust
Whole cell, inactivated	*DAR 901* *M. vaccae* *MIP* *RUTI*	Aeras NIH, Immodulon ICMR, India

IMPAACT P1113: with HVTN and AERAS

Chair: Avy Violari

- Vaccine: HyVac 4/AERAS-404,+IC31
  - Dose escalation study, given after BCG vaccine
    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
- Exploratory objective:
  - Immunogenicity interactions with EPI vaccines

Design

Group	Dose (H4mcg/IC3 1nmol)	# of doses	Age at vaccination	Vaccine /placebo	N
1	5/100	1	6mo	20/5	25
2	5/500	1	6mo	20/5	25
2a	5/500	2	18wk, 24 wk	40/10	50
3	5/500	3	10/14/38w	30/10	40
4	15/500	3	10/14/38w	30/10	40
5	50/500	3	10/14/38w	30/10	40
Total				170/50	220

Status: enrolled; safety data meets formal criteria, immunogenicity data pending

HVTN/ACTG/IMPAACT TB vaccine cross-network working group

- Lisa Cranmer, Jyothi Rengarajan, Cheryl Day, Amita Gupta, Anneke Hesseling (IMPAACT).
  - Discuss TB vaccine landscape and opportunities for TB vaccine collaborations in the DAIDS funded networks
  - HVTN focused on POI
  - ACTG on adult therapeutic vaccines and POD
  - IMPAACT on POD/ therapeutic
- TB vaccine concepts and ideas welcome

Diagnostics and biomarkers

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

Milestones

- P1078: completed
- 2001: completed
- P1113: completed
- Opened to accrual: P1108, 2005, PHOENIX
- IMPAACT 2020: Version 1 .0 June 2019
- IMPAACT 2026: new TB arms
- 3 new CAPs: 1 HP children (CS 5019), 1 HP vs. 3 HP pregnancy (CS 5021): Pta (in development)
- IMPAACT TB trials symposium: Union 2018, 2019
- TB PADO 1 (February 2019)
- TB vaccines Working Group (cross-network)

Mentored investigator graduates

- Adrie Bekker: P1106, 2026S
- Jyothi Mathad: 2001
- Vidya Mave: SHINE TB, PHOENIx
- Anthony Garcia-Prats: 2005, 2020
- Elin Svensson: P1108, 2005, 2020, PHOENIx

New mentored investigators

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

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Group

Recent Publications

- Swindells S. Resource utilization for multidrug-resistant tuberculosis household contact investigations (A5300/I2003). Int J Tuberc Lung Dis. 2018 Sep 1;22(9):1016-1022. doi: 10.5588/ijtld.18.0163. PubMed PMID: 30092866.
- Gupta A,: ACTG 5300/IMPAACT I2003 PHOENIx Feasibility study team. Feasibility of Identifying Household Contacts of Rifampin- and Multidrug-Resistant Tuberculosis Cases at High Risk of Progression to Tuberculosis Disease. Clin Infect Dis. 2019 Mar 28. pii: ciz235. doi: 10.1093/cid/ciz235. PubMed PMID: 30942853.
- Suryavanshi N. A5300/I2003 Study Team. Willingness to Take Multidrug-Resistant Tuberculosis (MDR-TB) Preventive Therapy among Adult and Adolescent Household Contacts of MDR-TB Index Cases: An International Multi-Site Cross-Sectional Study. Clin Infect Dis. 2019 Mar 28. pii: ciz254. doi: 10.1093/cid/ciz254. [Epub ahead of print] PubMed PMID: 30919881.
- Opollo VS. HIV testing uptake among the household contacts of multidrug-resistant tuberculosis index cases in eight countries. Int J Tuberc Lung Dis. 2018 Dec 1;22(12):1443-1449. doi: 10.5588/ijtld.18.0108. PubMed PMID: 30606316; PubMed Central PMCID: PMC6364692
- Svensson EM. Relative bioavailability of bedaquiline tablets suspended in water: Impli- cations for dosing in children. Br J Clin Pharmacol. 2018 Jun 27. doi: 10.1111/bcp.13696. [Epub ahead of print] PubMed PMID:29952141.
- Thuboy B. The determination of capreomycin in human plasma by LC-MS/MS using ion-pairing chromatography and solid-phase extraction. Biomed Chromatogr. 2018 May 3:e4269. doi:10.1002/bmc.4269. [Epub ahead of print] PubMed PMID: 29726023.
- Hoddinott G. Community engagement for paediatric MDR-TB clinical trials: principles to support ethical trial implementation. Int J Tuberc Lung Dis. 2018 May 1;22(5):40-45. doi: 10.5588/ijtld.17.0356. PubMed PMID: 29665952.
- Seddon JA, Conducting efficacy trials in children with MDR-TB: what is the rationale and how should they be done? Int J Tuberc Lung Dis. 2018 May 1;22(5):24-33. doi:10.5588/ijtld.17.0359. PubMed PMID:29665950.
- Garcia-Prats AJ, Current status of pharmacokinetic and safety studies of multidrug-resistant tuberculosis treatment in children. Int J Tuberc Lung Dis. 2018 May 1;22(5):15-23. doi: 10.5588/ijtld.17.0355. PubMed PMID:29665949.
- Gupta A, Hughes MA, Garcia-Prats T, Mcintire K, Hesseling AC. Plos Med in press: Inclusion of key populations in clinical trials of new antituberculosis treatments
- Gupta A et al. NEJM IMPAACT P1078