TB SCIENTIFIC COMMITTEE UPDATE: 2017

ANNEKE C. HESSELING

30 MAY 2017

Aims

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

Estimated total TB 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
MDR-TB estimates	30-50 0000
MDR-TB infection	500 000

WHO 2015 Global TB report www.who.int

PK STUDIES	ONGOING 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 (enrolment completed 2016): NICHD R01 • **STEP-TB:** New pediatric dispersible formulations of first-line drugs (TBA, Unitaid) • **Infant PK study:** low Rif exposures (TBA/Unitaid) • **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) • **MDR PK 2**: Optimizing Levofloxacin, moxifloxacin, linezolid (NICHD R01) • **Rifabutin** in children, NIRT (terminated; NICHD) • **OptiRIF Kids**: high-dose rifampicin PK safety: opened 2017 (TB Alliance/Unitaid)
PK/safety studies *New drugs* *Establishing doses that achieve adult-equivalent exposures*	• **Study 35**- Rifapentine/isoniazid in HIV+/-children < 12 years of age **P1108**, Jansen: Bedaquiline in children–BDQ in HIV-uninfected children; IMPAACT P1108 in children with and without HIV infection: 2016 • **232/233-** Delamanid in children- Otsuka • **P2005** -injectable-sparing DLM-based regimen in children with and without HIV infection • **P2001**: safety and PK of rifapentine in HIV-infected pregnant women • **BDQ/DLM co-treatment (future)**
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

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: 2018** • TB-CHAMP: Levo vs placebo for MDR-TB prevention: 2016 • VQUIN: levo vs. placebo for MDR-TB prevention: open • ACTG5279: one month of rifapentine+isoniazid daily for DS-TB prevention: enrolment completed • 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**
Severe DS-TB disease *Reduce mortality, improve neurocognitive dysfunction*	• TBM-KIDS: High-dose RIF +/- Levo for children with TBM (NICHD R01
Non-severe DS- TB *Reduce treatment duration for children with non-sevre disease*	• SHINE: 4 vs. 6 months standard TB Rx (new FDCs, nested PK): open label

MDR-TB	• **SMART-KIDS**
	  • Treatment shortening trial MDR-TB
	  • All oral 6 month regimen
	  • Full Spectrum of TB disease
	  • Full spectrum of DR
	  • Key PK gaps still need to be addressed: LNZ/DLM/Clofaz

DS-TB	Gaps for children	Priority studies
	• PK/safety first-line drugs at new WHO higher doses, esp. infants, HIV+	• PK studies first-line drugs at higher doses (DaTic: NICHD): enrollment complete 2016
	• Optimal treatment for TB meningitis (levofloxacin, high dose rifampin)	• PK and outcome (TBM Kids; NICHD) : opened Q2 2017
	• Rifampicin dose optimization (severe disease not addressed in SHINE, treatment shortening): OptiRif Kids	• Priority: building on SHINE, rifampin dose optimization
	• Treatment shortening: non-severe and severe disease	• SHINE+: Priority – complementing SHINE and TBM Kids, Optirif Kids

MDR-TB: 2 year plan

Children

- Implement Phoenix (A5300/I2003) and build paediatric capacity
- Implement P1108 (Bedaquiline phase I, II) HIV+/-
- Implement P2005 (Delamanid Phase I, II) HIV+/-
- Develop MDR-TB treatment shortening trial: SMART Kids
- Develop BDQ/DLM DDI PK (HIV+/-)
- Developed white paper: MDR-TB priorities, gaps (RESIST TB IMPAACT Landscape meeting June 17th) – submitted, IJTLD, 5 papers submitted, 1 published

MDR-TB: 2 year plan

Pregnant women

- Implement P1026 S (also MDR-TB arm)
- Implement P2001

MDR-TB: 5 year plan

Children

- Implement Phoenix MDR prevention trial
- Implement phase 3 MDR-TB shortened treatment trial: SMART-Kids

DS-TB: 5 year plan

Children

- Develop phase 3 treatment shortening treatment trial (full spectrum of TB disease)

Diagnostics and biomarkers: DS-TB and DR-TB

- Support nested diagnostics, biomarker studies
- Support expansion of site and TB lab capacity: MDR-TB
- Use IMPAACT and other lab platforms
- Work with ITBSL
- Work with other investigators: serum, urine biomarkers
- Evaluate novel commercial molecular tests (Xpert Ultra), DST methods
- Ideal cohorts through planned protocols: SMART-Kids, P1108, PHOENIX, diagnostic studies: prognostic markers, treatment response and diagnostic markers

Xpert MTB/RIF on stool is useful for rapid diagnosis of TB in children with severe TB

Characteristic	All children	Confirmed TB	Unconfirmed TB	Unlikely TB
	N=379 (100%)	N=73	N=185	N=121
Age, months: median (IQR)	15.7 (9.2-29.4)	19.1 (10.9-44.0)	16.0 (9.6-28.3)	13.3 (6.2-25.7)
Male (%)	195 (51.5)	27 (37.0)	105 (56.8)	63 (52.1)
HIV-infected (%)	51 (13.5)	8 (11.0)	30 (16.2)	13 (10.7)
Treated for TB	170 (44.9)	73 (100)	69 (37.3)	28 (23.1)

- Stool Xpert SENS vs. overall bacteriological confirmation =31.9% (95% CI 21.4-44.0%)
- Stool Xpert was positive in 1 in 2 children with bacteriologically confirmed severe TB
- Stool Xpert was positive in 1 in 4 children with radiologically severe disease

Walters E et al, PIDJ, 2017

TBSC core members

- Anneke Hesseling (chair)
- Amita Gupta (vice-chair)
- Kelly Dooley
- Bob Husson
- Anne-Marie Demers
- Vanessa Rouzier
- Carol Onyango
- (Lyndsay McKenna; Advocacy)

Significant impact of mentored investigators

- Elin Svensson: PhD awarded P1108, 2005, Phoenix
- Adrie Bekker: P1106, PhD awarded, CIPHER fellowship
- Vidya Mave: Hair PK P1078, Phoenix, PROMISE TB DACS
- Ethel Weld: P2005, 2 MS
- Vanessa Rouzier: Phoenix, 1108, clofazamine
- Sylvia La Course: 4 MS maternal TB, MS (IGRA)
- Jyothi Mathad: P2001, K23 and R01
- Tony Garcia-Prats: 2005, SMART-Kids, 8 MS
- Liz Walters: 2 MS, Xpert stool, R01 (serum biomarkers)
- Yael Hirch-Moverman: K ongoing, 2 MS (IPT)
- Lisa Cranmer: submitted 1041 IGRA MS, Union symposium, maternal TB immunity