TB Trials in Adults and Opportunities for Children and Pregnant Women for MDR-TB and Drug-Sensitive TB

IMPAACT Annual Meeting

Tuberculosis Scientific Committee Meeting

13 June 2015

Arlington, VA, USA

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CENTER FOR AIDS RESEARCH
JOHNS HOPKINS UNIVERSITY

DIVISION OF CLINICAL PHARMACOLOGY

THE CENTER FOR TB RESEARCH
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Research Priorities for TB, in general

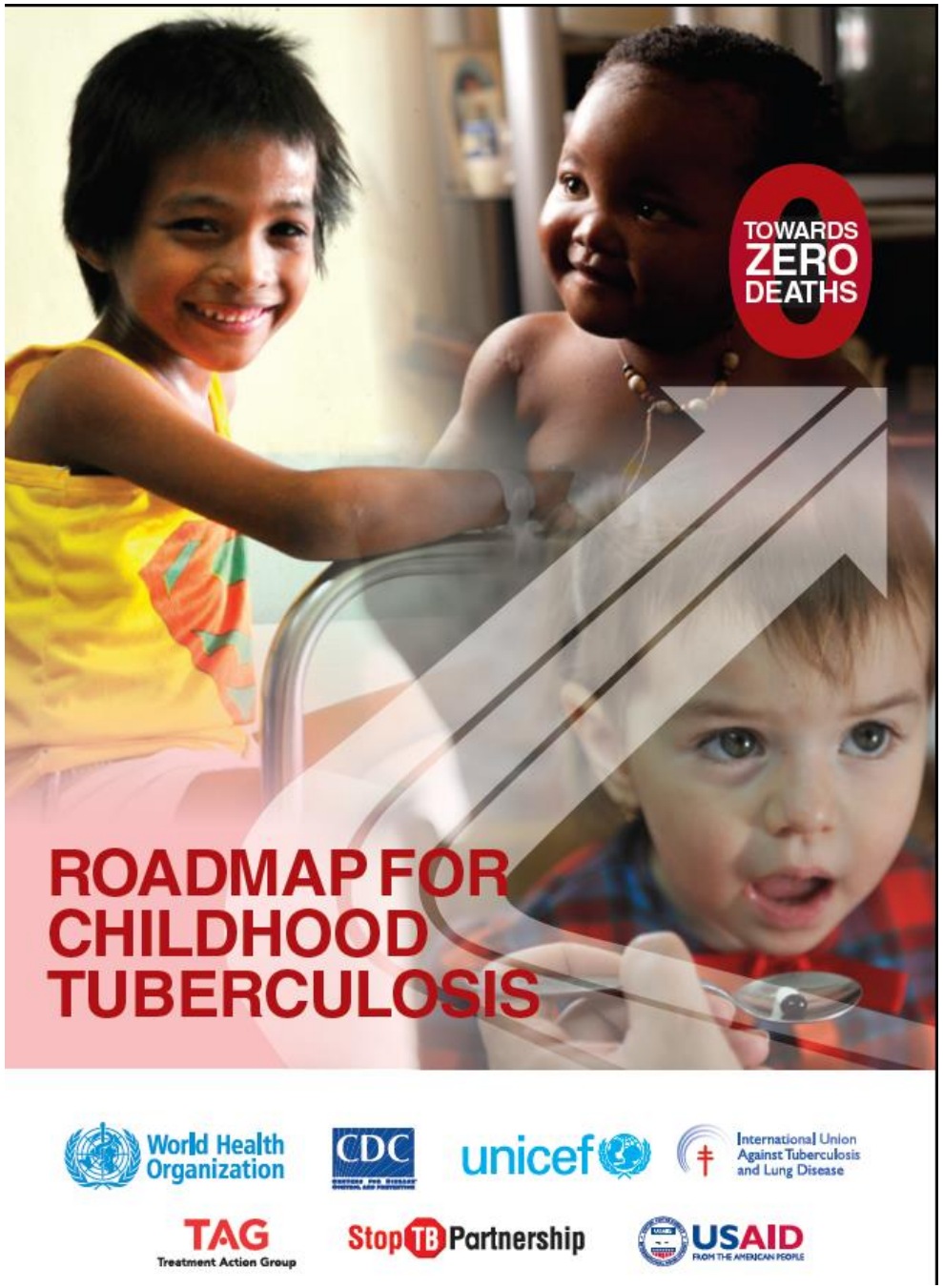
- Shortened treatment duration for **drug-sensitive TB**
- Shorter, more potent and tolerable regimens for **drug-resistant TB**
- Development of safe and effective regimens for **co-treatment of TB and HIV**
- Simple, short, safe treatment for **Latent TB Infection (LTBI)**
- Optimized dosing of new and existing drugs for **special populations including children and pregnant women**

Childhood TB:
Towards Zero Deaths

- **"Childhood TB needs to be lifted out of the shadows"**
  - **Historical neglect**

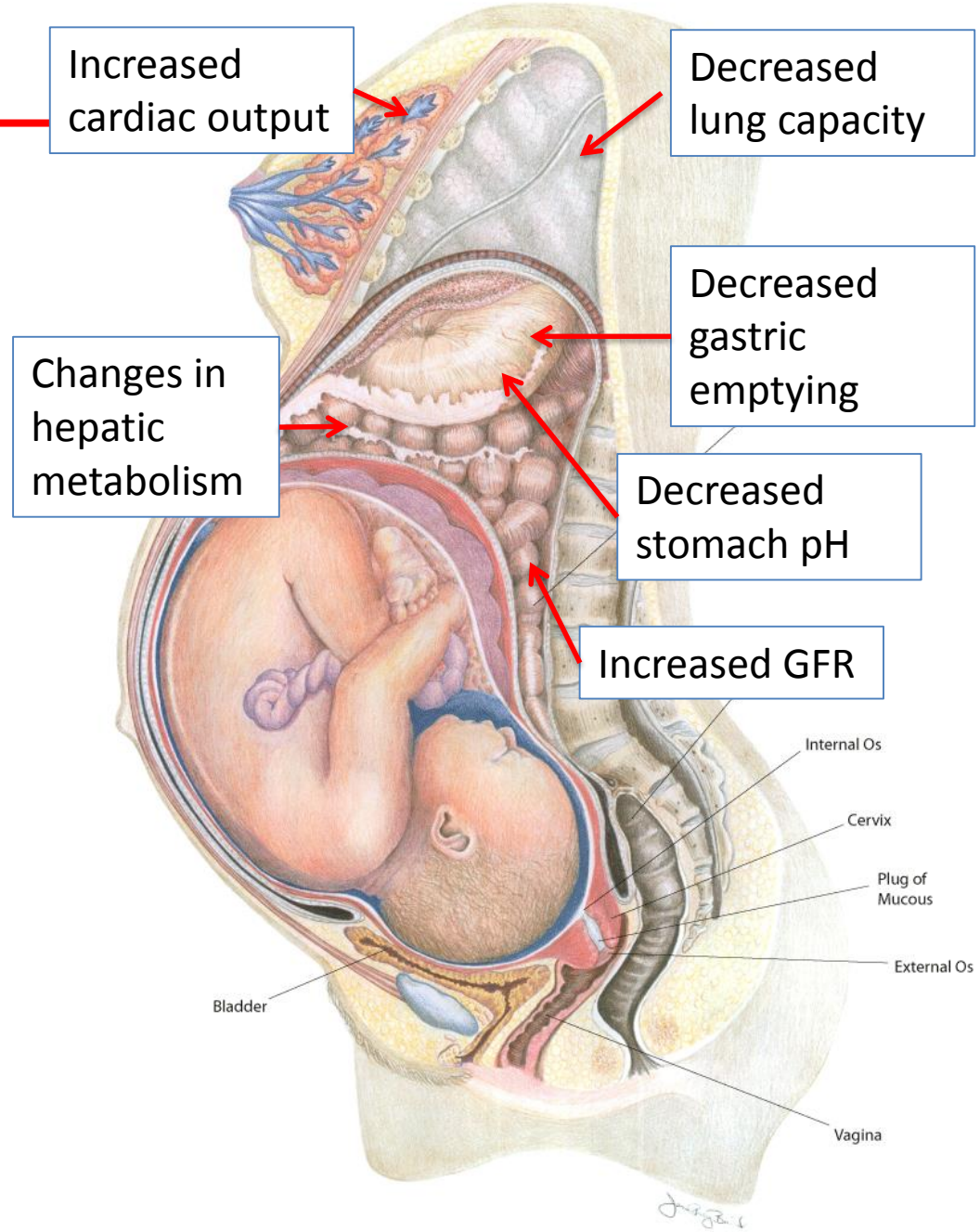
- 1,000,000 cases in 2014

- >136,000 deaths from TB yearly (55K in children with HIV)



Drugs in pregnancy

- "Pregnant women get sick, and sick women get pregnant"– the Second Wave Initiative



- Ethical imperative to include pregnant women in research of drug treatments: *Rationale:* need for effective treatment during pregnancy, fetal safety, harm from reticence to prescribe potentially beneficial medicines, justice and access to benefits of research participation Lyerly Int J Fem App Bioeth 2008

Recent/enrolling/planned trials in **adults** (DS-TB)?

TB Research Area	Key studies in Adults	Phase	Status (*children)
Drug-sensitive TB *Treatment shortening*	• TBTC 29X: **Dose-finding Rifapentine**, 8 weeks	• II	• Complete
	• RIFATOX: **Higher-dose rifampicin** (max 20 mg/kg)	• II	• Complete
	• HIGHRIF2**: Higher-dose rifampicin** (max 20 mg/kg)	• II	• In f/u
	• HIRIF: **Higher-dose rifampicin** (max 1200)	• II	• Planning
	• RIFASHORT: **Higher-dose rifampicin (to 1800), 4 months**	• III	• Planning
	• TBTC 31/A5349: **High-dose rifapentine** +/- moxifloxacin	• III	• Enrolling (*12)
	• MAMS-TB-01: **High-dose rifampicin** +/- moxifloxacin	• III	• Complete
	• RIFAQUIN: **Once-weekly RPT+MOX** in continuation phase	• II	• Complete
	• REMox: **MOX for H or E** for 4 months	• III	• Complete
	• STAND: **Pretomanid+MOX+PZA**	• III	• On hold
	• APT: **pretomanid** instead of ethambutol, 12 weeks	• II	• On hold
	• NC-005: **BDQ+Pretomanid+Z**, 8 weeks	• II	• Enrolling
	• TRUNCATE-TB: multiple **2 month regimens**	• III	• Planning(*12)
	• ACTG A5289: **Sutezolid** with RIF or RBT+HZ, 2 stage	• II	• Planning
	• ACTG PR698: **Clofazimine** + RHZE, 12 weeks	• II	• Planning
	• NUH Singapore: EBA of **faropenem+amox/clav**	• II	• Planning

Opportunities: higher-dose rifampicin; rifapentine; bedaquiline, clofazimine

Recent/enrolling/planned trials in **adults** (DR-TB)?

TB Research Area	Key studies in Adults	Phase	Status (*children)
Drug-resistant TB *Safer, shorter, more efficacious treatment*	• A5312: **INH dose-finding** EBA	• II	• Enrolling
	• LIN-CL001: **Linezolid** EBA/safety, dose-finding (DS-TB)	• II	• Enrolling
	• OptiQ: **Levofloxacin** dose-finding	• II	• Enrolling
	• CLAM320B2202: **Clofazimine** (50 or 100) + OBR	• II/III	• Planning
	• Trial 213: **Delamanid** + OBR vs. placebo + OBR x 6 months	• III	• In f/u
	• STREAM Stage 1: **4MCEZHKPro/5MCZE** (9 months) vs. SOC	• III	• In f/u
	• STREAM Stage 2: SOC vs. MCEZHKPro (9 mo) vs. BLCEZHPro (**9 months, all-oral**) v. BLCZHK (**6 months, includes injectable**)	• III	• Enrolling
	• STAND: **Pa-M-Z** x 6 months	• III	• On hold
	• NC-005: **B-Pa-M-Z**	• II	• In f/u
	• NIX-TB: **B-Pa-LZD** x 6 months (XDR-TB)	• III	• Enrolling (*14)
	• A5343: **bedaquiline + delamanid** added to OBR x 6 months	• II	• Planning
	• A5356: D+Lz (300, 600, 1200) + OBR vs OBR	• II	• Planning
	• NExT-5001: **LzBLvZ(H or Eth or Ter)** vs. SOC	• II/III	• Enrolling
	• MDR-END: **D+Lvf+Lzd+Z** vs. SOC	• II	• Enrolling
	• TB-PRACTECAL: **BPaMLz v BPaLzC v BPaLz** vs. SOC	• II/III	• Enrolling
	• endTB: **9BLzMZ v 9BLzCLvZ v 9BLzDLvZ v 9DCMZ** v SOC	• III	• Planning (*15)

Opportunities: shortened MDR-TB regimen (existing drugs); injectable-sparing regimens; short/inj-sparing with new drugs

Key: Lz=linezolid; Lf=levofloxacin; D=delamanid; B=bedaquiline; Pa=PA824, or pretomanid; C=clofazimine; Z=pyrazinamide

WHO treatment guidelines for DR-TB: 2016 Update
"Conventional treatment"– 18-24 months

Table 6. Medicines recommended for the treatment of rifampicin-resistant and multidrug-resistant TB[1]

A. Fluoroquinolones[2]		Levofloxacin Moxifloxacin Gatifloxacin	Lfx Mfx Gfx
B. Second-line injectable agents		Amikacin Capreomycin Kanamycin (Streptomycin)[3]	Am Cm Km (S)
C. Other core second-line agents[2]		Ethionamide / Prothionamide Cycloserine / Terizidone Linezolid Clofazimine	Eto / Pto Cs / Trd Lzd Cfz
D. Add-on agents (not part of the core MDR-TB regimen)	**D1**	Pyrazinamide Ethambutol High-dose isoniazid	Z E H[h]
	D2	Bedaquiline Delamanid	Bdq Dlm
	D3	*p*-aminosalicylic acid Imipenem-cilastatin[4] Meropenem[4] Amoxicillin-clavulanate[4] (Thioacetazone)[5]	PAS Ipm Mpm Amx-Clv (T)

Standard treatment (5 "effective" drugs):

- One drug from Group A
- One drug from group B
- Two drugs from Group C
- Add Pyrazinamide

- Add group D2 or D3 if you don't have 5
- Consider strengthening with D1 (EMB, hi-INH)

WHO treatment guidelines for DR-TB: 2016 Update; *"Shorter MDR-TB regimen" – 9-12 months*

4-6 month intensive phase	Gatifloxacin (or MOX) Kanamycin Prothionamide/Eth* Clofazimine High-dose INH* Pyrazinamide* Ethambutol*
5 month continuation phase	Gatifloxacin Clofazimine Ethambutol* Pyrazinamide*

For these patients:

- **Not previously treated for DR-TB**
- **Infected with strain that does not have or is not expected to have FQ or injectable resistance**

Individual patient data analysis (N=1,205)

Resistance pattern	*Shorter MDR-TB regimen*	
	N	% (95% CI)
All cases regardless of pyrazinamide and fluoroquinolone susceptibility	1008/1116	*90.3% (87.8%- 92.4%)*
Pyrazinamide resistant; fluoroquinolone resistant	19/28	67.9% (47.6%-84.1%)
Pyrazinamide resistant; fluoroquinolone susceptible	90/100	88.8% (47.3%-98.6%)
Pyrazinamide susceptible; fluoroquinolone resistant	12/15	80.0% (50.0%-94.1%)
Pyrazinamide susceptible; fluoroquinolone susceptible	121/125	96.8% (77.3%-99.6%)

*resistance among MDR-TB strains not uncommon

Recent/enrolling/planned trials in adults ?

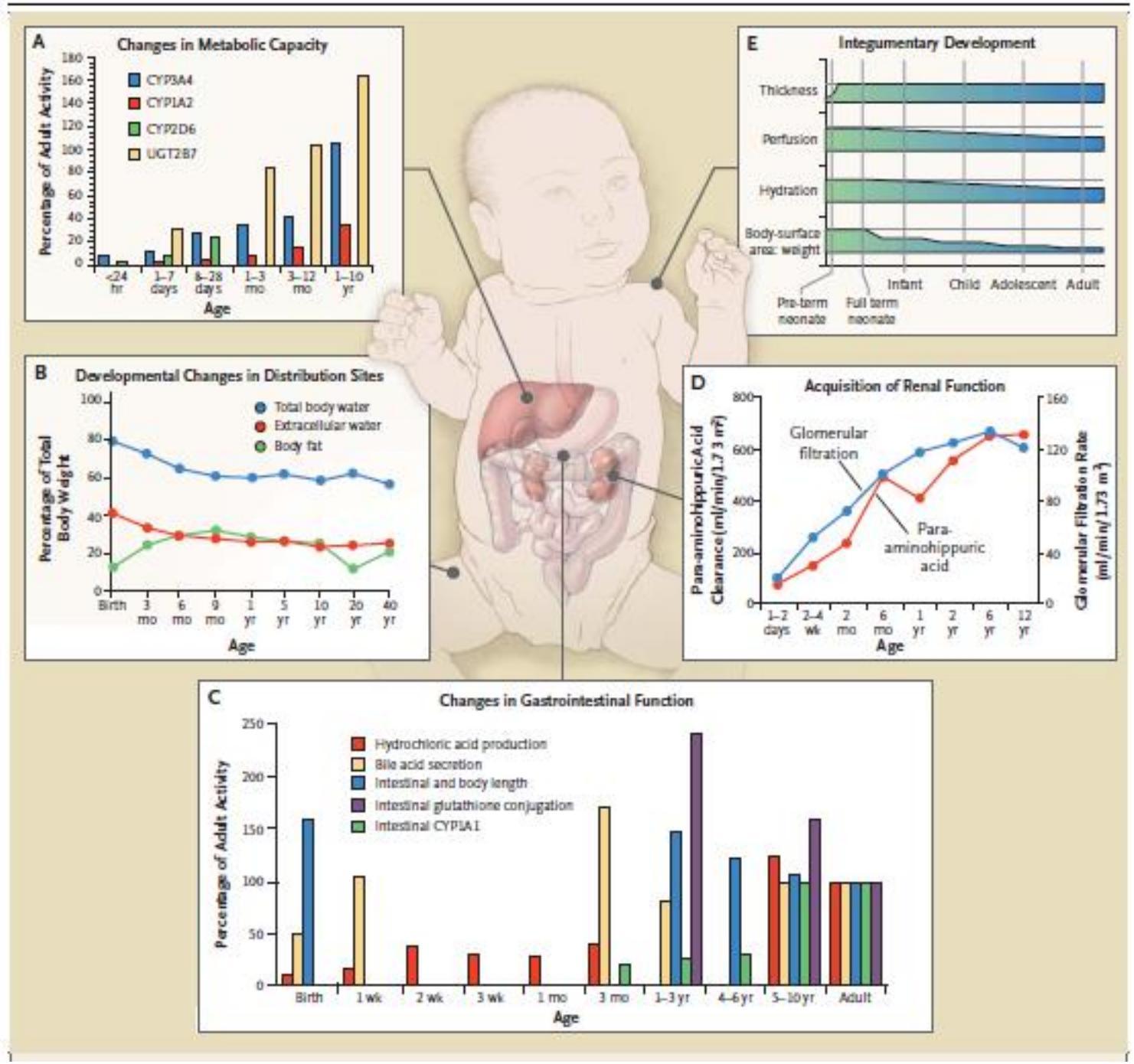
TB Research Area	Key studies in Adults	Phase	Status (*children)
Co-treatment TB/HIV *Effective, safe combinations, taking into account DDI*	• Rifavirenz: **EFV with higher-dose rifampicin** • REFLATE-TB: **RAL 400 BID vs. RAL 800 BID vs. EFV** w TB Rx • INSPIRING: **Dolutegravir** with standard TB treatment • A5290: H**Rb**ZE**+LPV/r +/- RAL vs.** HRZE**+high dose LPV/r** • EARNEST: **Rifabutin thrice-weekly vs. daily** with LPV/r	• II • II • II • II • II	• Enrolling • Complete • Enrolling • In f/u • Enrolling*
Treatment LTBI *Shorter, very safe regimens*	• TBTC Study 26, subsets: **once-weekly rifapentine+INH** • **TBTC Study 37: RPT qd for 6 wks vs. RIF qd 4 mo vs. RPT+INH qwk** • A5279, **daily RPT+INH x 30 days** • A5300 PHOENIX: **MDR** prophylaxis with **DLM** (vs. standard INH) • V-QUIN: MDR prophylaxis with Levo (vs. placebo)	• III • III • III • III • II	• Complete* • Planning • In f/u* • Planning* • Planning*
Severe disease *Regimens that reduce mortality*	• TBM-IT: Enhanced Rx with **levofloxacin 20 mg/kg + RIF 15 mg/kg** • TBM trial in Indonesia: high-dose IV rifampicin +/- MOX	• III • II	• Complete • Enrolling*

Rb=rifabutin; R or RIF =rifampicin; Z=pyrazinamide; E=ethambutol; LPV/r=boosted lopinavir; RAL=raltegravir; MOX=moxifloxacin

Developmental pharmacology:

A Moving Target,

role of ontogeny



Kearns et al NEJM 2003 349: 1157.

PK/safety

Revised WHO dosing for children-

Are we achieving target concentrations?

Drug	Revised dose	2-hour target	Mean concentration	% achieving target
Isoniazid	10-15 mg/kg	3 mcg/mL	4.5 mcg/mL	65%
Rifampicin	10-15 mg/kg	8 mcg/mL	2.9 mcg/mL	6%
Pyrazinamide	30-40 mg/kg	20 mcg/mL	23 mcg/mL	55%
Ethambutol	15-25 mg/kg	2 mcg/mL	1.1 mcg/mL	15%

PHATISA Study (n=23, Durban, SA): Hiruy et al JAC doi:10.1093/jac/dku478

See also results from Indian children: Ramachandran *et al.* AAC doi:10.1128/AAC.04338-14

TB drug concentrations *matter* in children, and are influenced by HIV infection

TABLE 2. Peak Concentration and Exposure in HIV-infected and HIV-uninfected Children with TB

Dose Factors	HIV and TB (77) Median (Interquartile Range)	TB (84) Median (Interquartile Range)	P*
Peak concentration (C_{max})			
RMP	2.6 (1.3–4.5)	5.1 (3.4–6.9)	<0.001
INH	4.7 (2.8–7.2)	6.1 (4.0–8.4)	0.008
PZA	41.2 (31.7–48.0)	39.2 (30.5–44.9)	0.132
Exposure (AUC_{0-8})			
RMP	10.4 (6.1–18.2)	23.4 (15.1–33.2)	< 0.001
INH	19.9 (10.7–30.8)	22.0 (15.0–33.1)	0.056
PZA	219.1 (172.6–273.9)	218.2 (175.9–255.8)	0.452

*Mann-Whitney U test was used at 5% level of significance.

TABLE 4. Logistic Regression Showing Factors Influencing TB Treatment Outcome

Factor	Unadjusted Odds Ratio (95% CI)	P	Adjusted Odds Ratio (95% CI)	P
Age	1.002 (0.891–1.125)	0.979		
HIV infection	0.818 (0.375–1.787)	0.615		
HAZ	1.033 (0.832–1.281)	0.771		
WAZ	1.171 (0.828–1.656)	0.373		
WHZ	1.043 (0.741–1.469)	0.809		
C_{max}, µg/mL				
RMP	1.396 (1.148–1.698)	0.001	1.437 (1.157–1.784)	0.001
INH	1.094 (0.951–1.259)	0.210		
PZA	1.041 (1.007–1.076)	0.018	1.041 (1.005–1.079)	0.027

Age, HIV Infection, HAZ, WAZ, WHZ and C_{max}, µg/mL (RMP, INH and PZA) were taken in univariate analysis. Among those, C_{max} of RMP and PZA were significant at <0.1 level. These variables were considered by stepwise method at <0.05 level.

Among HIV-coinfected children, C_{max} of RMP (1.0 vs. 2.7 mcg/mL; p=0.003) and PZA (31.9 vs. 44.4 mcg/mL; p=0.012) were significantly lower in unfavorable than favorable responders

Ramachandran *et al* PIDJ 2016 35: 530

PHARMACOKINETICS OF AMIKACIN (20 mg/kg) (N=28)

	C_{max} (µg/ml)			T_{max} (h)			AUC_{0-8} (µg·h/ml)		
	N	Median (IQR)	p-value	N	Mean (SD)	p-value	N	Median (IQR)	p-value
Age group									
0-2 years	6	43.65 (42.20 - 49.20)		6	1.00 (0.00)		6	103.85 (96.80 - 119.10)	
2-5 years	7	49.10 (40.70 - 59.20)		7	1.14 (0.38)		7	124.15 (97.75 - 162.05)	
6-15 years	15	49.60 (40.30 - 56.40)	0,845	15	1.13 (0.35)	0,593	14	159.25 (124.20 - 179.48	0,016
HIV status									
HIV-infected	10	47.05 (42.20 - 54.40)		10	1.10 (0.31)		9	151.00 (109.40 - 162.05)	
HIV-uninfected	18	46.85 (40.70 - 53.00)	0,719	18	1.11 (0.32)	0,931	18	128.65 (112.50 - 174.95)	0,918

Adult target values:
C_{max}: 35-45 ug/ml

Slide from A. Hesseling,
See more second-line drug data later today

Hesseling, IUATLD 2014

Why HIV/TB Co-Treatment is harder in children than adults: *Limited ART Options*

ART	Pediatric challenges
Nevirapine and efavirenz	Less efficacious in children < 1 year of age
Efavirenz	Dose not established for children < 3 years
Ritonavir-boosted protease inhibitors	Double dosing insufficient Rifabutin can't be substituted for rifampicin
Triple nucleoside regimens	May have higher risk failure in children because of high baseline viral loads
Integrase inhibitors	No drug interaction studies with raltegravir or dolutegravir with anti-TB Treatment in children

But children may have rapidly progressive HIV disease and they are at higher risk of severe TB….

Rifabutin dosing for children with TB/HIV co-infection taking PI-based ART- an example of *when toxicities in adults and children appear to differ*

J Antimicrob Chemother
doi:10.1093/jac/dku382

Pharmacokinetics and safety of rifabutin in young HIV-infected children receiving rifabutin and lopinavir/ritonavir

Harry Moultrie[1]*, Helen McIlleron[2], Shobna Sawry[1], Tracy Kellermann[2], Lubbe Wiesner[2], Gurpreet Kindra[1], Hermien Gous[1] and Annelies Van Rie[3]

RBT 5 mg/kg three times a week in children < 5 years of age taking LPV/r
Study stopped after 6 participants by IRB because of **severe, transient neutropenia**

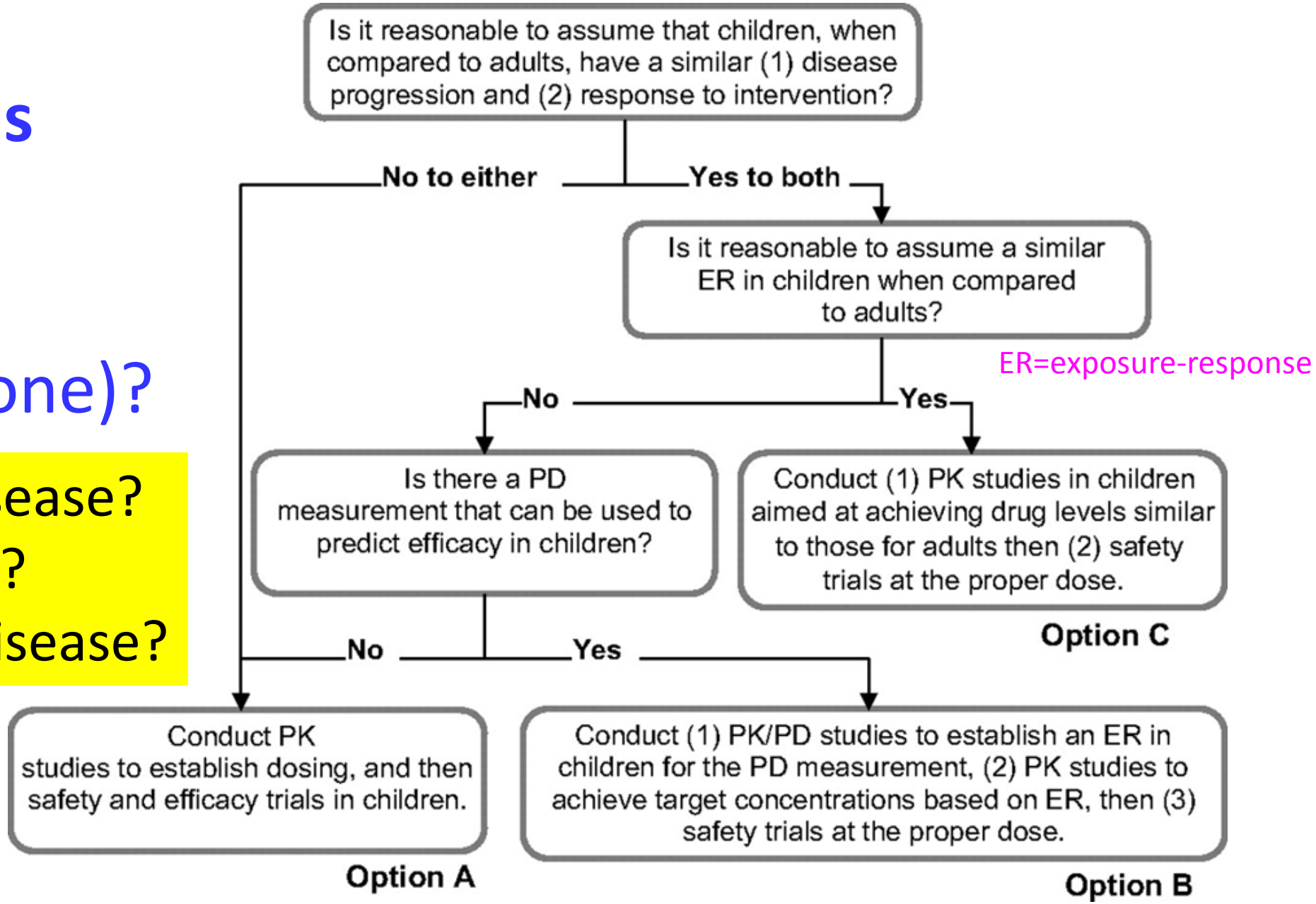
Safe rifabutin dose has not been established in children. Furthermore, there is no pediatric formulation

Moultrie *et al* JAC (2015) 70: 543.

Efficacy

When are **efficacy trials** required for children (vs. PK/safety alone)?

Non-severe disease?
Severe disease?
LTBI-> active disease?



Slide, modified, from FDA

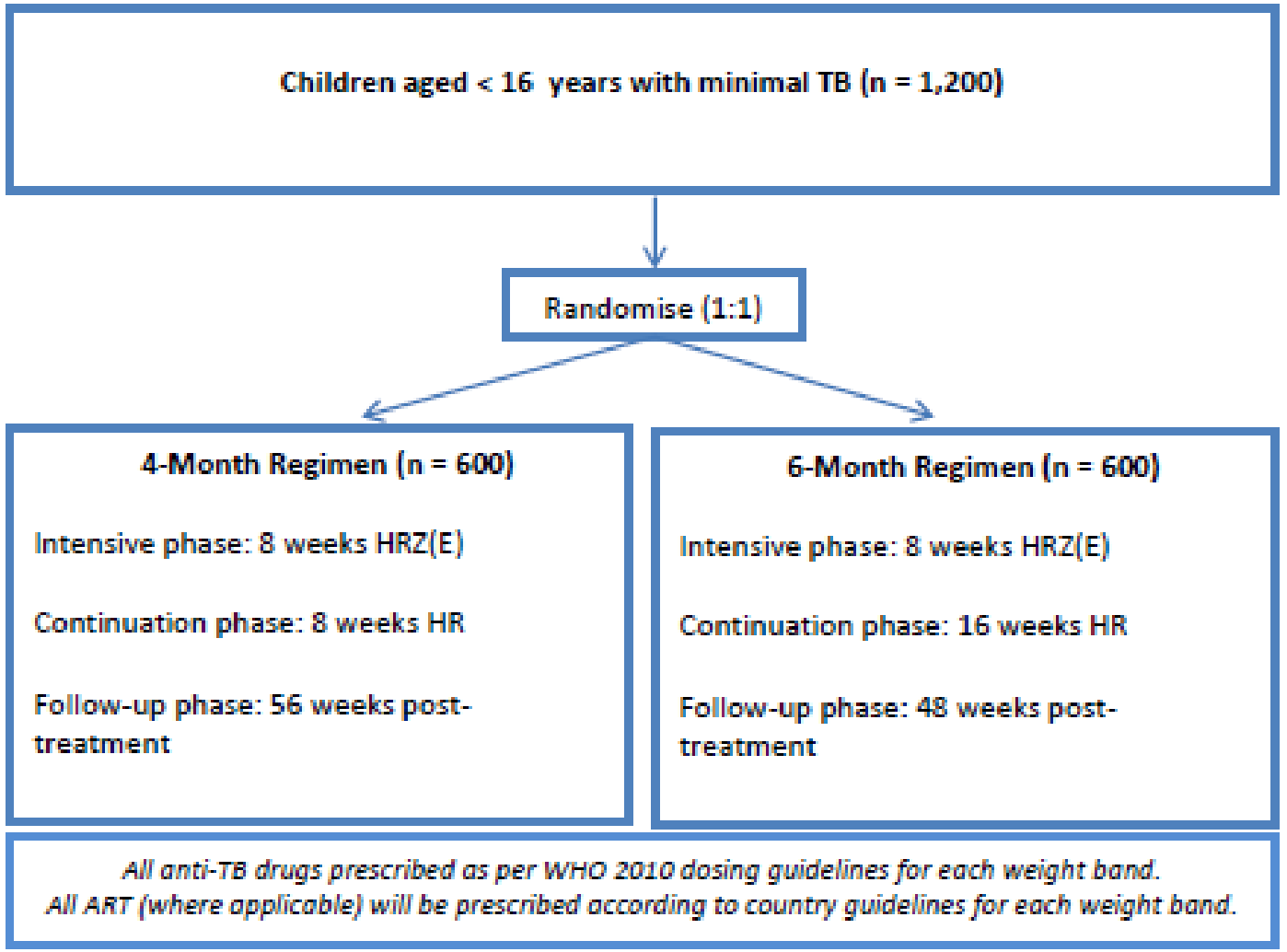
Shortening TB treatment for children with minimal disease

SHINE

Shorter treatment for minimal TB in children

A randomised trial of therapy shortening for minimal tuberculosis with new WHO-recommended doses/ fixed-dose-combination drugs in African and Indian HIV+ and HIV- children

- Parallel group, non-inferiority trial
- 4 vs. 6 months, open label
- Children aged 0-16 years
- Non-severe TB
- WHO-recommended doses first-line drugs
- N=1200 children
- New FDC; 75, 50, 150



PI=Di Gibb

Multinational trial

Pediatric TB meningitis: are outcomes different in adults and children?

- **Can improved treatment change outcomes in children?**
  - Mortality lower in children than adults
  - Plasticity of developing brain– neurologic outcomes may differ

- **How does TBM & its treatment affect neurocognitive development?**
  - Data are sparse
  - Cognitive impairment
  - Behavioral difficulties
  - Emotional problems

What is going on in children already?

TB Research Area	Key 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 to be completed 2016) • STEP-TB: New pediatric **dispersible formulations** of first-line drugs • Infant PK study (completed, disseminated, low Rif exposures; TBA) • PK/safety of **second-line drugs** in children with and without HIV: MDR PK 1 (levo, moxi, oflox, amik, HD INH, ethio, PAS, cycloserine) MDR PK 2: Optimizing Levofloxacin, moxifloxacin, linezolid (NICHD) • **Rifabutin** in children, NIRT • OptiRIF Kids: **high-dose rifampicin** PK safety (TB Alliance)
PK/safety studies *New/investigational drugs* *Establishing doses that achieve adult-equivalent exposures*	• TBTC Study 35- **Rifapentine/isoniazid** in HIV+/-children < 12 years of age • **Bedaquiline** in children– Janssen study in HIV-uninfected children; IMPAACT P1108 in children with and without HIV infection • 232/233- **Delamanid** in children- Otsuka study; IMPAACT P2005 -injectable-sparing DLM-based regimen in children with and without HIV infection
HIV/TB DDI studies	• DNDi: **Ritonavir boosting** of LPV/r in TB/HIV • NICHD: first-line TB drugs with ART (Awewura) • P1101: **RAL-based ART** with standard TB drugs

Efficacy trials in children

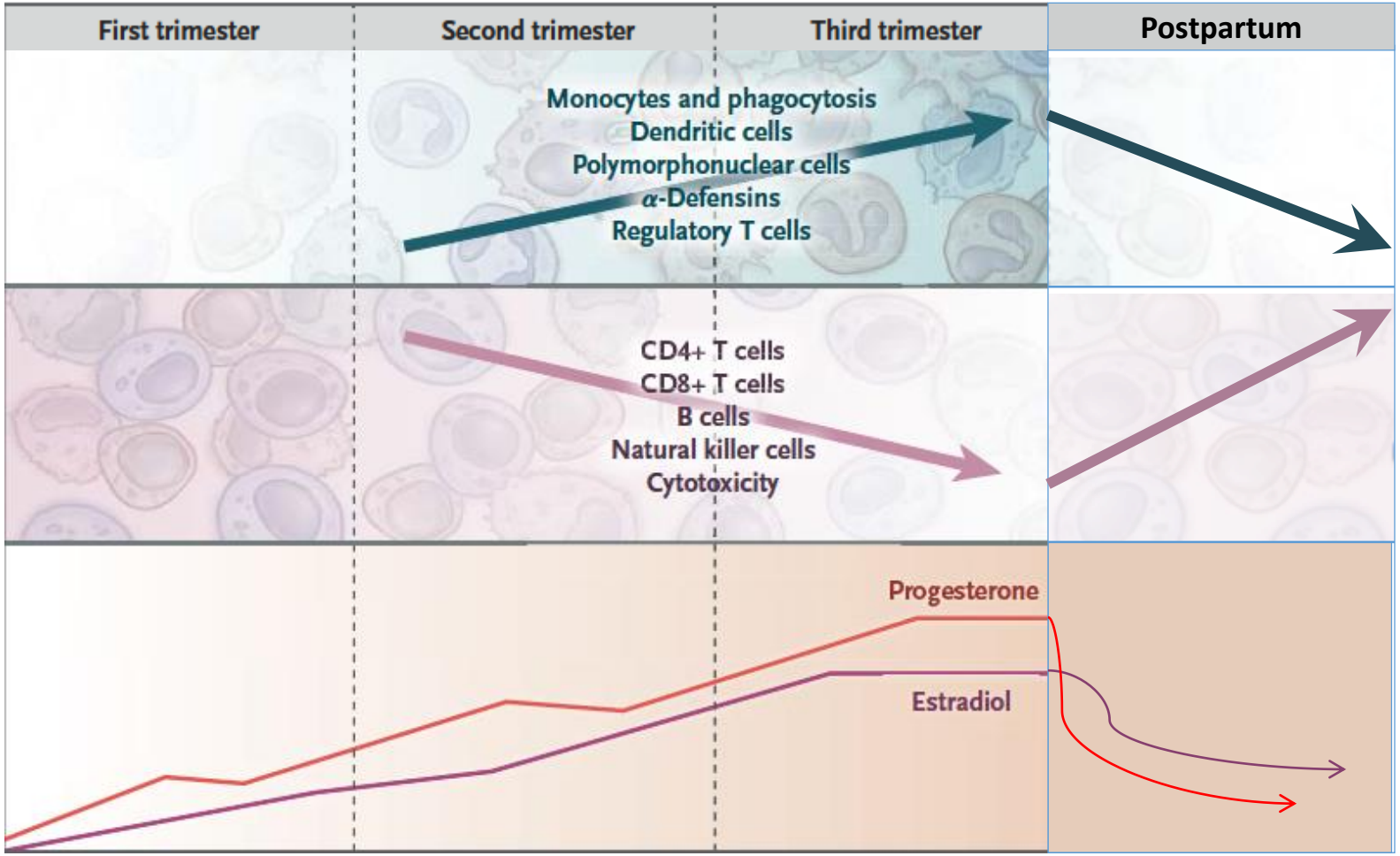
TB Research Area	Key studies
TB prevention *Prevention of TB in children (higher risk of progression than adults)*	• TB-CHAMP: Levo vs placebo for MDR-TB prevention • VQUIN: levo vs. placebo for MDR-TB prevention • A5300 PHOENIX: delamanid vs. SD INH for MDR-TB prevention • ACTG5279: one month of rifapentine+isoniazid daily for DS-TB prevention • P4v9 Trial: 4 months RIF vs 9 months INH for DS-TB prevention • TBTC 37: RPT 6 weeks vs. local SOC (RIF 4 mo or RPT/INH q week x 3 mo)
Severe disease *Reduce mortality, neurocognitive dysfunction*	• TBM-KIDS: High-dose RIF +/- Levo for children with TBM
Non-severe PTB and EPTB disease *Reduce treatment duration for children with non-sevre disease*	• SHINE: 4 vs. 6 months standard TB Rx (new FDCs, nested PK)

Specific priorities for children (TB)

TB Research Area	Priorities	Not being done/opportunities
Drug-sensitive TB	• PK/safety first-line drugs at higher doses, esp. infants • Treatment shortening for all children (not just minimal disease) • Optimal treatment for TB meningitis	• Rifampicin pediatric formulation • High-dose RIF for treatment shortening • The "Stellenbosch regimen" (TB-SURE), host-directed therapy
Drug-resistant TB	• PK/dosing second-line drugs • Shorter regimens (like "Bangladesh") • New drug PK and safety (bedaquiline, delamanid, pretomanid, sutezolid) • Injectable-sparing regimens	• Modeling existing data, testing doses predicted to achieve PK targets • Clofazimine in children, INH dose • Safety/QT for BDQ+ DLM in children • Most rely on BDQ, DLM or Pretomanid
Co-treatment TB/HIV	• Super boosting LPV/r in young children taking HRZE • EFV-based regimen in children < 3 years • INSTI-based ART with standard TB drugs (HRZE) • RBT dose with boosted PI	• EFV+HRZE in slow CYP2B6 genotype • DTG-based ART with TB drugs • RBT child-friendly formulation
Treatment LTBI	• DS-TB prevention • MDR TB prevention	• Daily RPT-based prophylaxis

TB in pregnancy

- Pregnant women at higher risk of TB than peers, especially post-partum
- Higher risk of pregnancy complications with TB
  - For mother and her fetus/infant
- Pregnancy may impact TB drug disposition and safety



Adapted from Jyoti Mathad; Kourtis NEJM 2014

Specific priorities for pregnant women (TB)

TB Research Area	Current efforts	Gaps
Drug-sensitive TB	• PK first-line drugs in pregnancy (P1026S) • Tshepiso	• Isoniazid, pyrazinamide, pyrazinamide • High-dose rifamycins
Drug-resistant TB		• PK second-line drugs • Substitution for injectables • New drug safety/PK
Co-treatment TB/HIV		• EFV free drug exposures in pregnant women with EFV fast metabolizer genotypes taking TB Rx • DTG in pregnant women with HIV/TB • LPV/r+RBT in pregnant women with HIV/TB
Treatment LTBI	• IMPAACT 2001: INH/RPT once weekly for 12 doses • P1078: INH antepartum vs. postpartum in women with HIV infection	• Risk of newly-reported severe liver injury with efavirenz- impacts of pregnancy, post-partum state, isoniazid, EFV metabolizer genotype

Summary

- Pediatric TB, the “silent epidemic”, increasingly recognized as a major global health concern, knowledge gaps about best treatments for children are substantial
- For some drugs/indications, studies to establish doses that achieve adult-equivalent exposures (PK) plus safety of those doses is sufficient
  - Knowledge of developmental pharmacology, mathematical modeling can make these studies much more efficient
- Exposure-toxicity relationships, though, may differ in adults and children
- Efficacy studies may be needed when disease presentation, progression, and/or treatment response are likely to be different in children and adults
- Pregnancy increases risk of TB but best preventive therapy not yet established
- PK of most anti-TB drugs not established in pregnancy, yet they must be used

- **Lots of work to do to improve treatment for drug-sensitive TB, drug-resistant TB, TB/HIV co-infection, LTBI in children and pregnant women**

Thank you.