

The challenges posed by Tuberculosis in HIV-infected children

Helena Rabie



2020

THE TREATMENT TARGET



diagnosed

on treatment

virally suppressed

REACH. TREAT. CURE EVERYONE



**REACH THE
3 MILLION.**

FIND. TREAT. CURE TB.

EVERY YEAR
9 MILLION PEOPLE
GET SICK WITH TB.

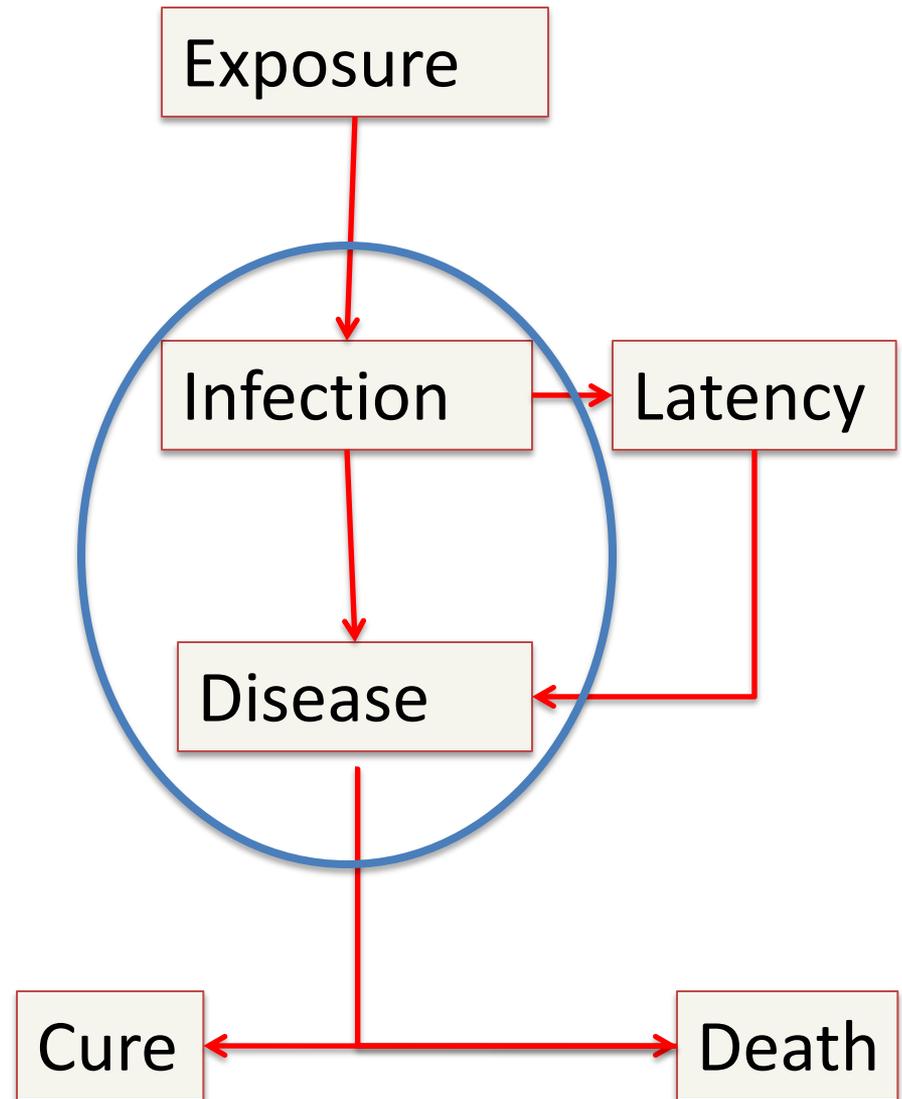
3 MILLION DON'T GET
THE CARE THEY NEED.
HELP US TO REACH THEM.

WORLD TB DAY 24 MARCH 2015

Tuberculosis in child hood

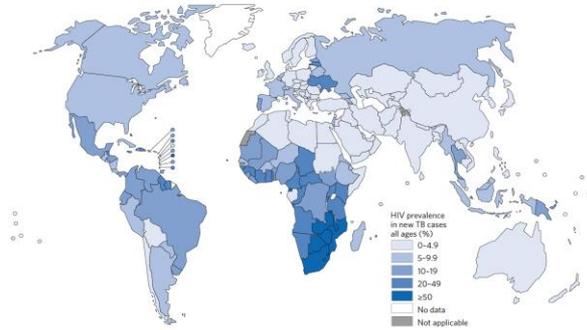
Risk of Disease progression post infection:

- Age
 - 43% of infants (children < 1year)
 - 25% of children aged 1-5
 - 15% of adolescents
- Recent infection (1-2 years)
- Malnutrition
- HIV
- Measles

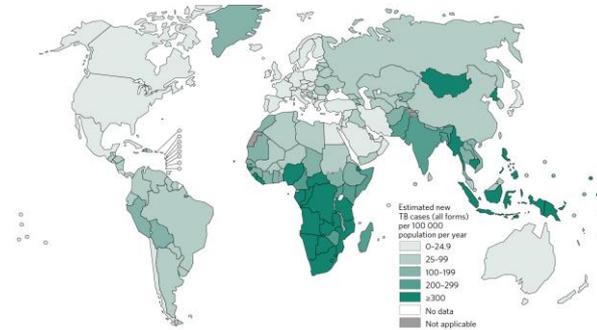


Epidemiology of TB and HIV

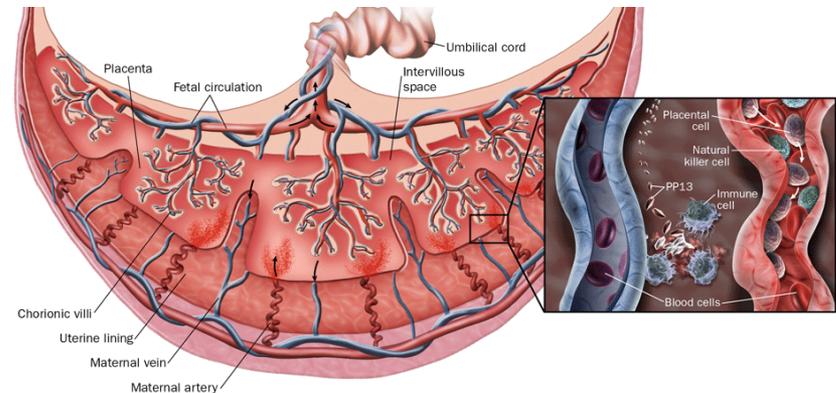
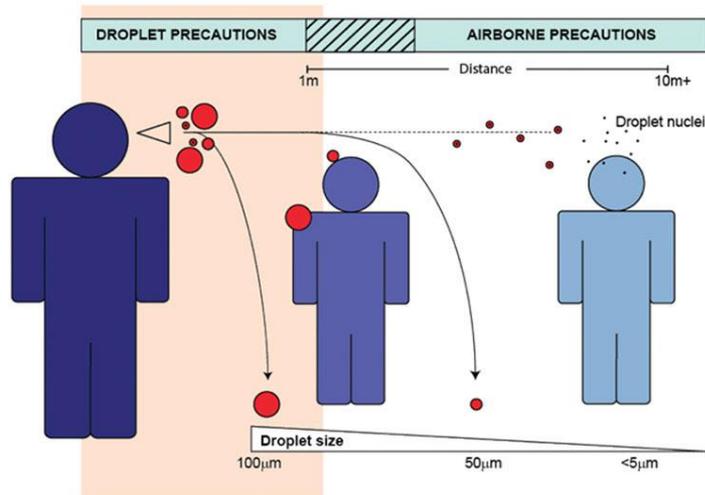
Estimated HIV prevalence in new and relapse TB cases, 2015



Estimated TB incidence rates, 2015



HIV exposed and infected children live with HIV-infected adults



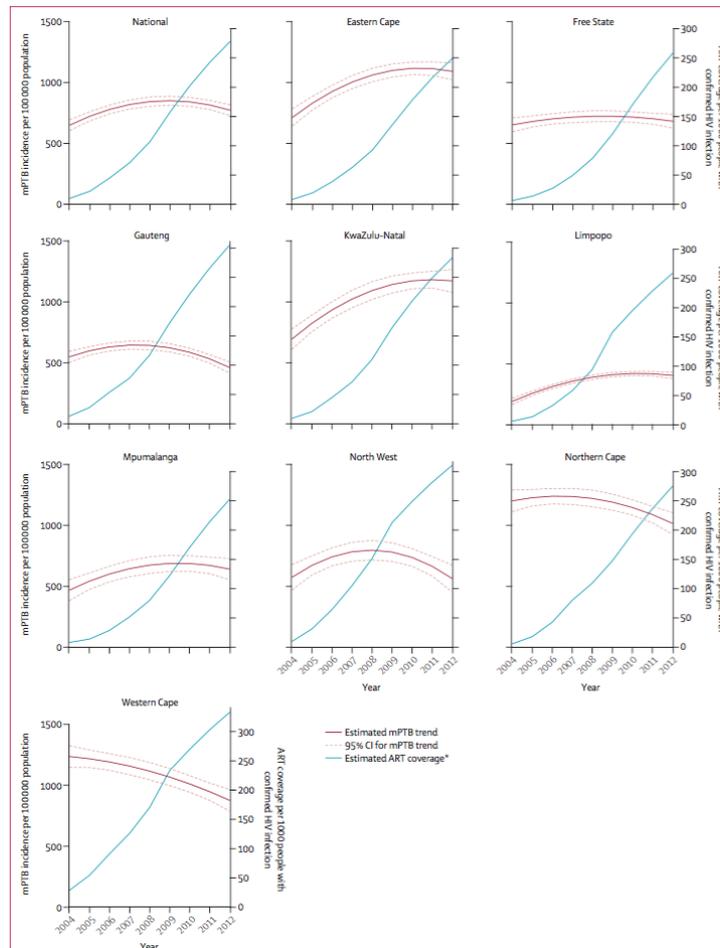
Where there is TB in pregnant HIV infected women

- 795/100 000 of pregnant women 201/100 000 if no HIV
- 27% of deaths in women who died of AIDS-related complications during pregnancy, childbirth, puerperium
- Maternal mortality in HIV infected woman
 - 12 170/100 000 Where there is TB
 - 3 850/100 000 Where there is NO TB
- Increased the risk of HIV transmission to the infant
- Risk of TB to the infants

In P1041 – TB prevention trial

- 229 contact occasions
 - 83% household
 - 53 + microbiologically assessment
 - 81% positive
- 49% of source case contact identified **at or AFTER** child diagnosed with TB
- 48% with confirmed TB
- 58% probable
- 43% possible
- 8% deaths

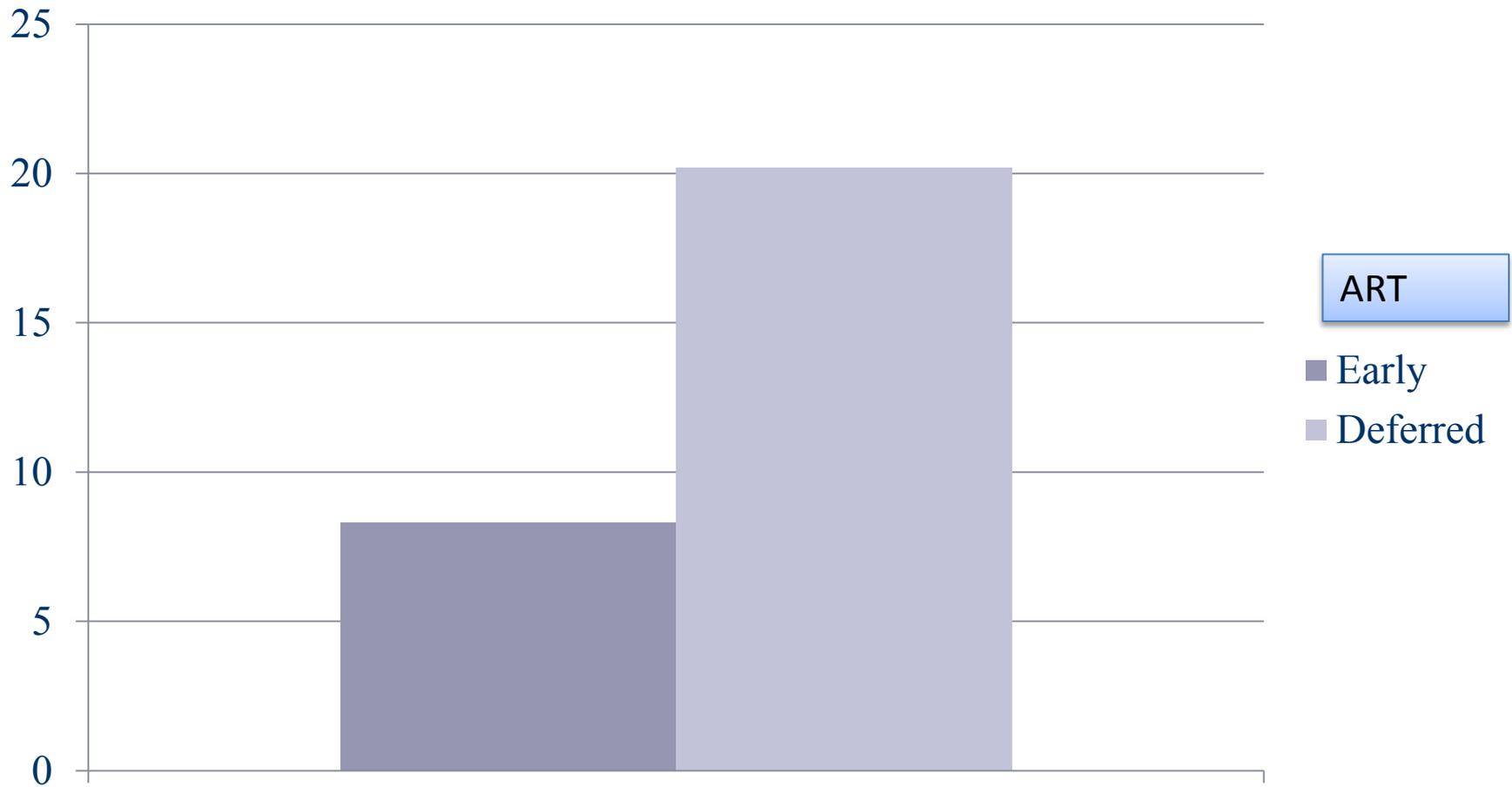
Increased ART coverage & decreased TB in RSA



cART

Mode of action	Restoration of CD4-cell counts and functional immune responses to Mycobacterium tuberculosis¹⁸
Correlate	CD4-cell count
Effect on endogenous reactivation	Likely sustained reduction in patients with increasing CD4-cell counts;
Effect on exogenous re-infection	Likely sustained reduction in patients with increasing CD4-cell counts; however, exogenous re-infection may be proportionately more important
Efficacy with isoniazid resistant	
Risk of generating drug resistance	
Exclude active tuberculosis before starting treatment	Unmasking of tuberculosis or unmasking of tuberculosis immune-reconstitution disease

Tuberculosis in 1st year of life (per 100 patient years)



The CHER Trial: Violari et al. N Engl J Med 2008; 359: 2233-44

IPT for HIV+ children?

- 2 Studies:
 - Madhi: Primary Isoniazid Prophylaxis against Tuberculosis in HIV-Exposed Children. NEJM 2011
 - Zar: Effect of isoniazid prophylaxis on mortality and incidence of TB in children with HIV: Randomised controlled trial. BMJ, 2007

cART and IPT

- INH alone - 0.22 (95% CI 0.09 to 0.53)
- ART alone - 0.32 (95% CI 0.07 to 1.55)
- INH & ART - 0.11 (95% CI 0.04 to 0.32)

South African guideline

Post-exposure IPT 10 mg/kg daily for 6 months is recommended in the following children after exclusion of TB disease

- HIV-uninfected children less than 5 years of age
- HIV-infected children irrespective of age or ART status.

IPT will not select resistance

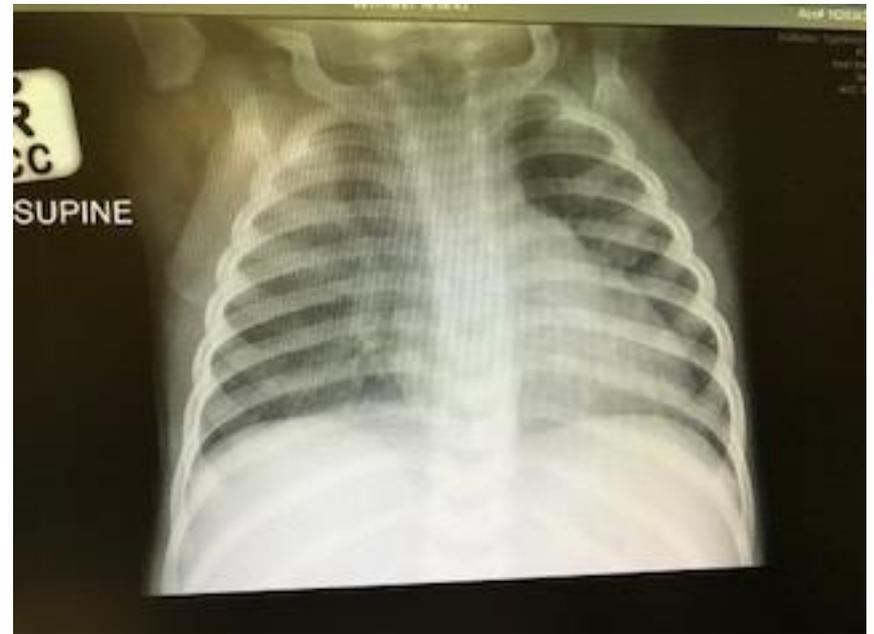
- Must take a good history of the contact
- Try to find the culture result of the contact
- Failure of IPT
 - Resistance in the contact
 - Non adherence

This is nice BUT

- In the DNDi Superboosting study
 - TB treatment started 1st: 70 (73%) of children in the DNDi superboosting study
 - < 3 Months ART Before TB: 12 (12.5%)



6 year old with confirmed TB
PCR positive in early life
Mom and dad defaulting ART



10 month old with confirmed TB
PCR positive after initially testing negative
Mom defaulting ART

High rates of TB in HIV-infected infants and children

- Rates:
 - 53.3 cases/100 patient years in children not on HAART
 - 1596 per 100 000 HIV-infected infants
 - 25-60% of children hospitalized with TB HIV infected
- Mortality:
 - TB-related deaths in 18.8% of HIV- infected Zambian children

Incidence of culture-confirmed TB in HIV-infected and uninfected South African infants (per 100 000 infant population)

	All infants	HIV-uninfected	HIV-infected	Relative risk
All tuberculosis	83.1 (72.9-93.7)	65.9 (56.7-75.3)	1595.9 (1151.3-2131.5)	24.2 (16.9-33.6)
Pulmonary tuberculosis	78.7 (68.6-89.0)	62.5 (53.3-71.7)	1505.6 (1075.2-2022.8)	24.1 (16.7-33.7)
Extra pulmonary tuberculosis	28.2 (22.2-34.4)	22.9 (17.5-28.6)	481.8 (257.0-750.8)	21.0 (10.7-35.0)
Disseminated tuberculosis	16.6 (11.9-21.2)	14.1 (9.7-18.3)	240.9 (86.6-431.7)	17.1 (6.0-33.7)
Miliary tuberculosis	10.9 (7.2-14.7)	9.3 (5.8-12.7)	150.6 (30.8-301.0)	16.2 (3.4-37.1)
Tuberculosis meningitis	9.2 (5.8-12.6)	7.9 (4.7-11.1)	120.1 (27.7-257.9)	15.2 (2.9-38.7)

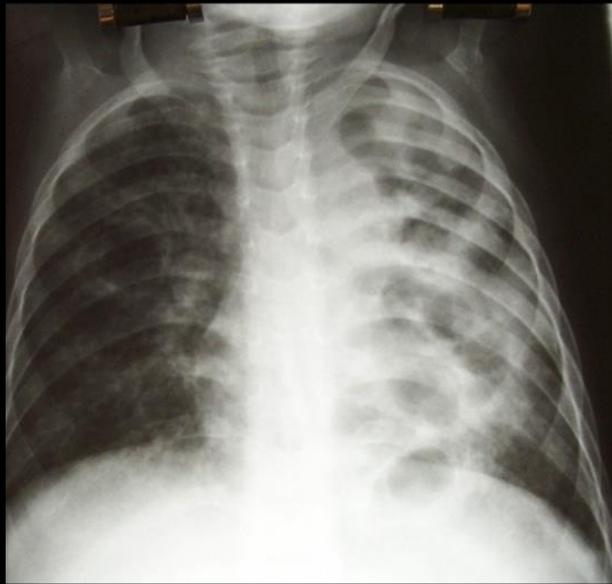
Can we screen for and diagnose TB?

1. Contact with an index case
2. Positive TST
3. History of symptoms
4. Suggestive signs on the chest radiograph
5. Xpert and culture of respiratory and other specimens

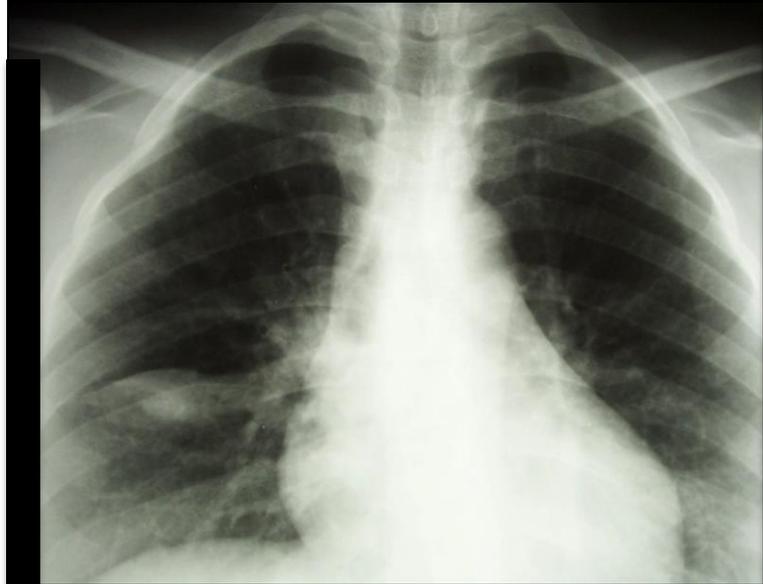
Can we screen for and diagnose TB?

1. Contact with an index case
 1. Time and space sensitive
2. Positive TST
 1. Understanding negative results
 2. Understanding positive results
3. History of symptoms
 1. HIV vs TB symptoms
4. Suggestive signs on the chest radiograph
 1. View all images
5. Xpert and culture of respiratory and other specimens

Shifting Paradigm of TB



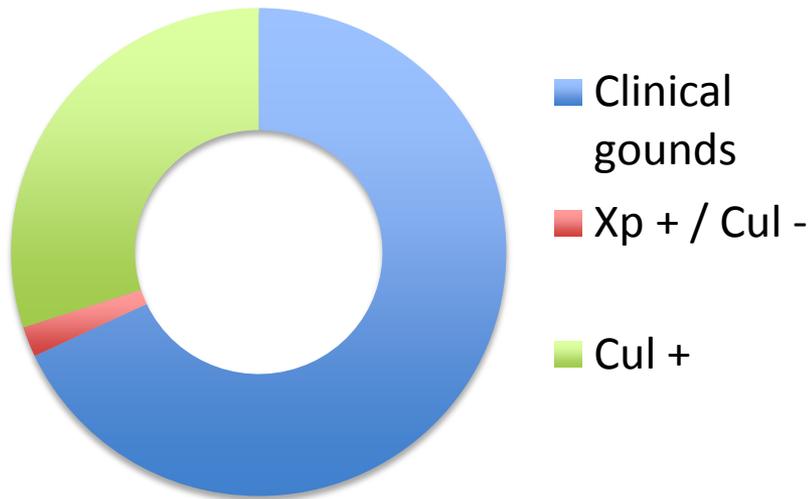
CHILD



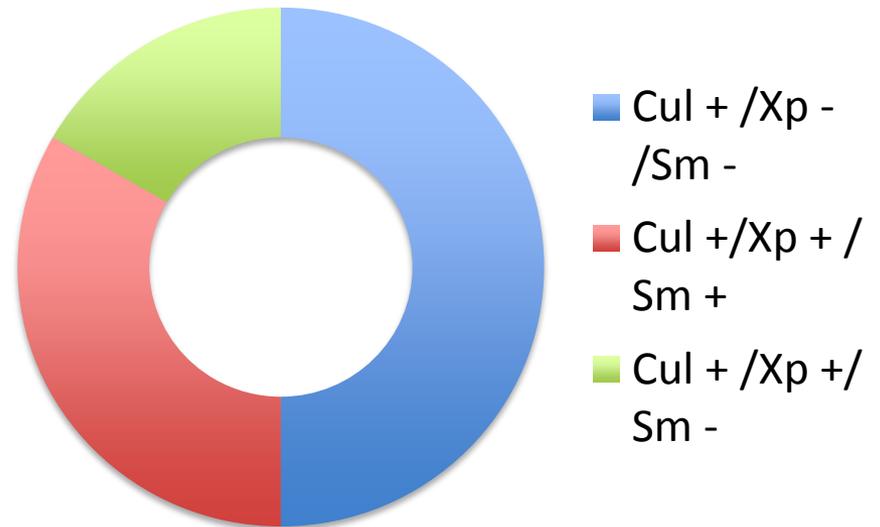
MOM

It is important to contextualize Xpert MTB/RIF for tuberculosis in children

For every 100 children on therapy



For the 30 culture confirmed children



Will LAM Help?

- lipoarabinomannan glycolipid component of the cell wall of M. tuberculosis and other mycobacteria
- Only 1 study showed value
 - Hospitalized adults
 - Low CD4
 - Not in SA
- No study in children showing any effect

Therapeutic considerations in co-infected children

1. Timing of ART
2. Choice of drug regimens
3. Duration of TB treatment
4. Monitoring

Drug Interactions

Rifamycin	Interaction with antiretroviral drugs
Rifampicin	NNRTI ↓60% PIs ↓90% Maraviroc ↓60-70% Raltegravir ↓40% ABC/AZT ↓50%
Rifapentin	Less potent activator No data on ART interaction
Rifabutin	Interaction with PI and EFV that require dose adjustments

Which anti-tuberculosis drugs to use

Rifampicin

- Maximum induction 1 week dose dependent

Rifabutin

- Least induction Phase 1 enzymes and p glycoprotein
- Induce own metabolism
- Substrate CYP3A
- Dosing in adults?
- Dosing in children?

Timing in relation to TB therapy?

“Any child with active TB disease [not yet on ART] should begin TB treatment immediately, and start ART as soon as tolerated in the first 8 weeks of TB therapy, irrespective of the CD4 count and clinical stage”

(Strong recommendation, very low quality of evidence).

Delaying HAART

Delaying HAART

- Increased mortality
- Increased risk of virological failure
- Important in specific conditions ie meningitis
- Decreased risk of IRIS
- Decrease pill burden
- Lower risk of adverse drug reactions

Early HAART

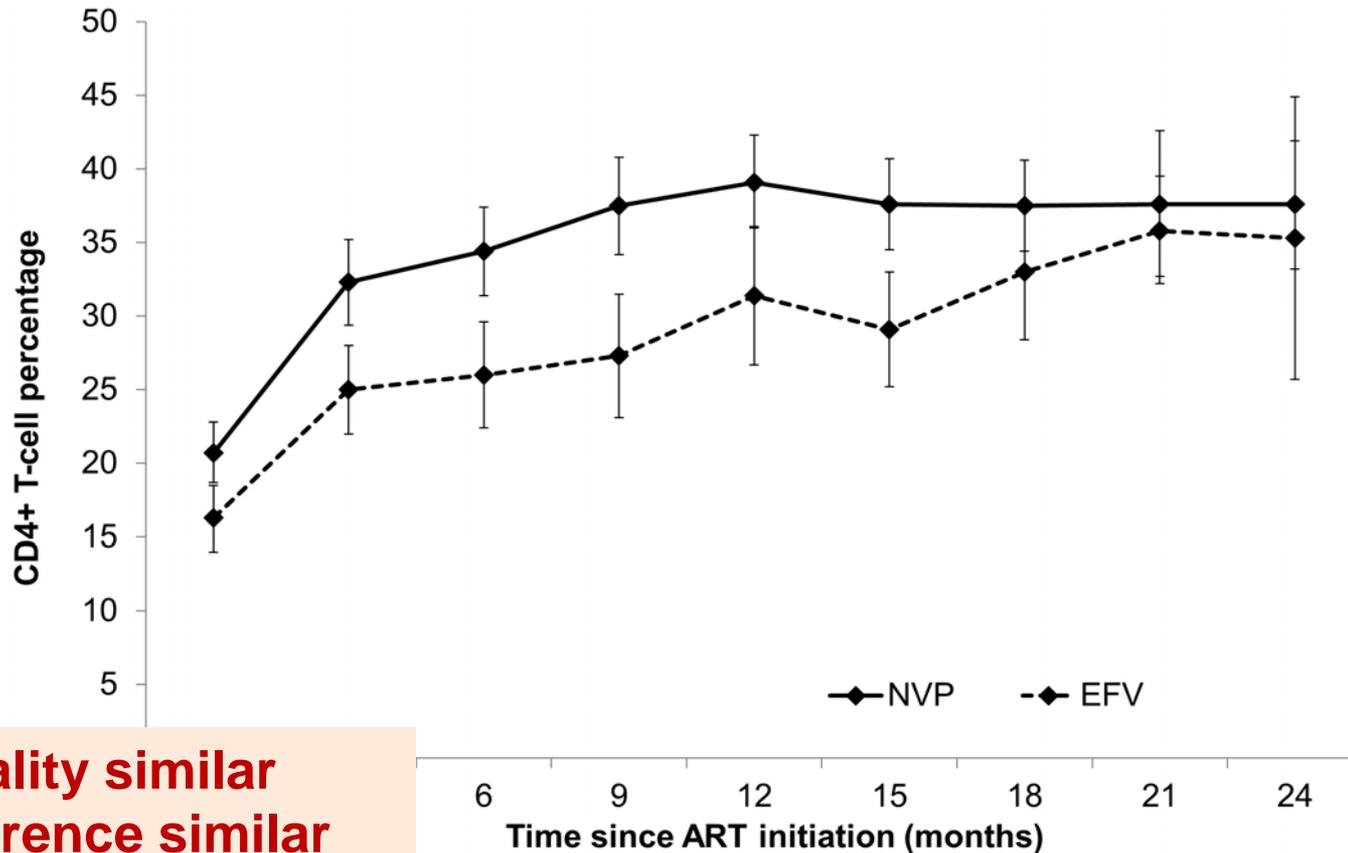
- Increase IRIS
- Increased pill burden
- Increase risk drug reactions
- **Reduced mortality**

EFAVIRENZ

- Doses were low regardless of RMP exposure and suggested weight based doses were modified
- FDA approved for children < 3 years
- Resistance risk in low resource settings

Effectiveness of Efavirenz-Based Regimens in Young HIV-Infected Children Treated for Tuberculosis: A Treatment Option for Resource-Limited Settings

Janneke H. van Dijk^{1,2}, Catherine G. Sutcliffe³, Francis Hamangaba¹, Christopher Bositis⁴, Douglas C. Watson⁵, William J. Moss^{3*}

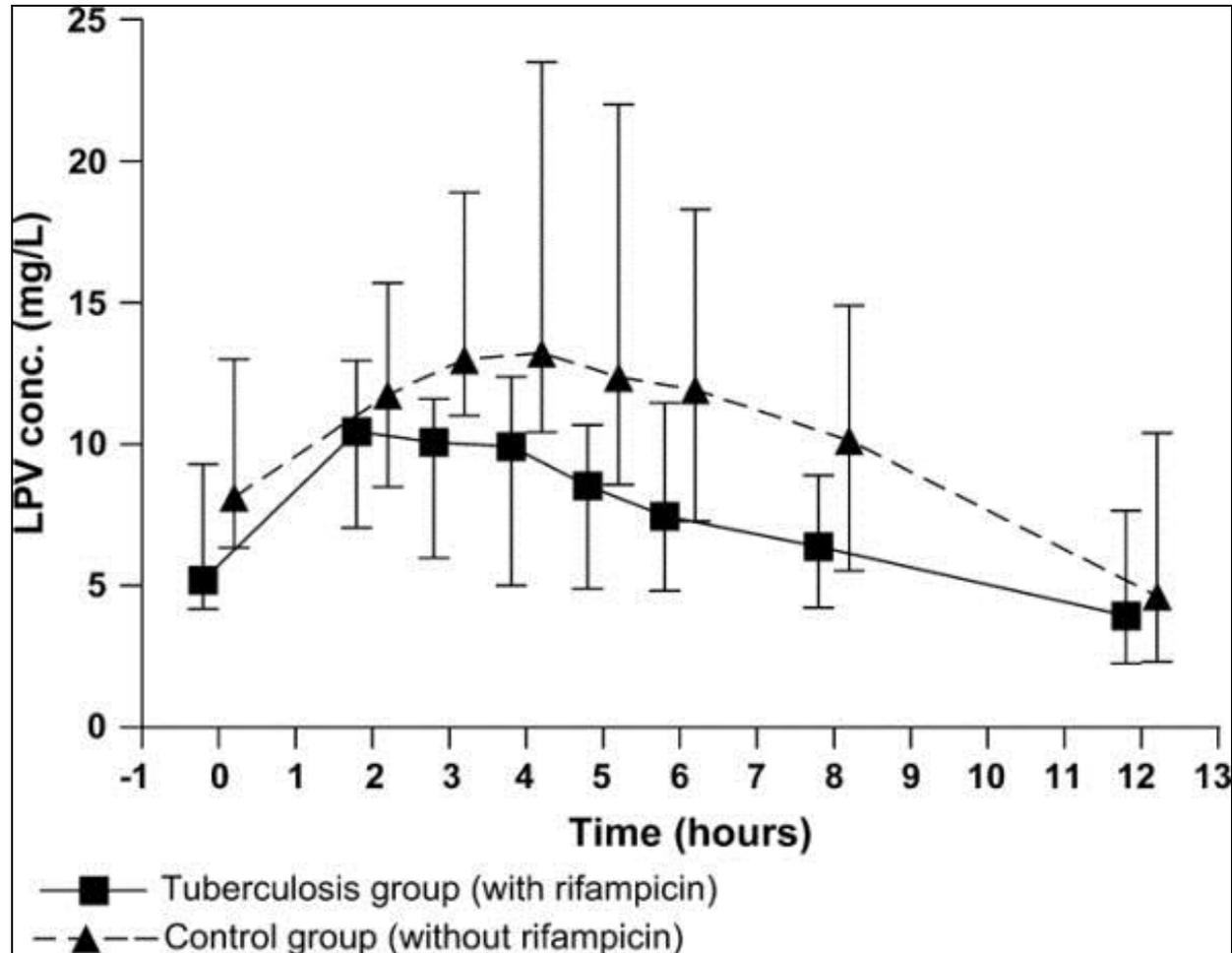


- Mortality similar
- Adherence similar
- EFV: better viral control
- ?A/E

Boosted PI: double dose LPV/r

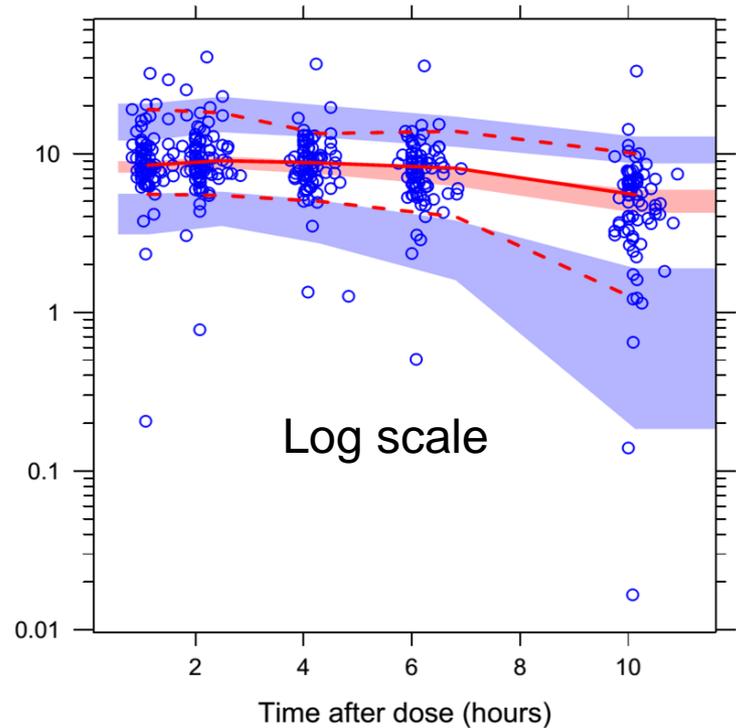
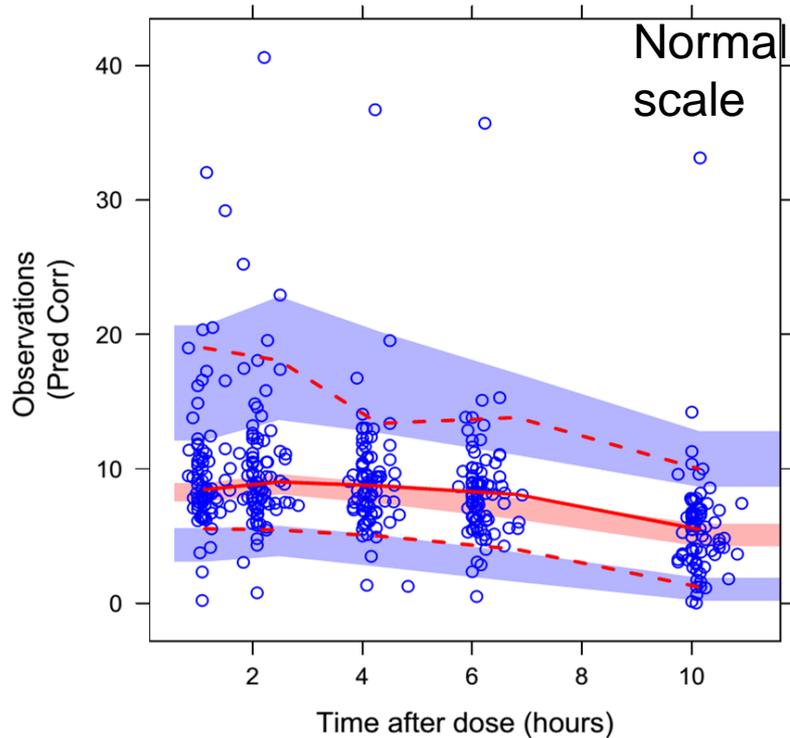
	TB/HIV- double LPV/r	Controls	P- value
Age (yr)	1.25	1.59	0.60
Cpre (mg/L)	0.63	4.25	0.0001
Cmax (mg/L)	4.45	7.94	0.006

Boosted PI: Super-boosted LPV



n=15 per cohort

Modeled PK n=80, non inferiority



Visual predictive check: the model was used to re-simulate the dataset



Observed concentrations

50th centile

5th & 95th centiles

Modeled from simulation

50th centile

5th & 95th centiles

Super-boosting is not without issues

- Taste
- Logistics
 - Shelf life
- Consequences of not super-boosting
 - Failure WITH resistance

What about resistant TB and the “newer” ART



ART and RIF

- Atazanvir – Use rifabutin
- Dolutegravir – no pediatric data BD in stead of daily dose
- Raltegravir – No pediatric data doubling the daily dose

Estimated total TB cases in children	1 million (10% global total)
TB deaths <ul style="list-style-type: none">• HIV-• HIV+	81 000 55 000
TB infections	6.6 million



What is needed for novel pediatric MDR-TB treatment?

- Injectable sparing shorter regimen: 6-9 months
- Data on optimal use of 2nd line drugs: FQN, clofazamine, PAS, Linezolid?
- Adult PK targets defined
- Inclusion of novel drugs: data on dosing, safety needed (bedaquiline, delamanid, PA-824) – need for phase I studies
- Formulations: SLD, novel drugs

Short course - Drug resistance

- Who
 - Probable or confirmed MDR-TB in which resistance to second-line drugs is unlikely
 - Probable or confirmed MDR-TB with no previous second-line drug treatment in the child or source case
- Not in
 - Children with known resistance to any component of the shortened regimen except isoniazid
 - Children whose source cases have known resistance to any component of the shortened regimen except isoniazid

Short course - Drug resistance

4-6 months intensive phase

1. Kanamycin / **Amikacin**
2. Moxifloxacin / **Levofloxacin**
3. **Prothionamide**
4. Clofazimine
5. Pyrazinamide
6. **High dose INH**
7. Ethambutol

5 months continuation phase

- 1.
2. Moxifloxacin/ **Levofloxacin**
- 3.
4. Clofazamine
5. Pyrazinamide
- 6.
7. Ethambutol

Other drugs

Repurpose

- Terizidone
- PAS
- Linizolid
- Meropenem
- Co-amoxiclavlanic acid

New

- Delamanid
- Bedaquilin

Delamanid: 6 more than 20kg

- Who
 - Confirmed MDR-TB when a four-drug regimen plus pyrazinamide cannot be constructed owing to resistance or significant intolerance
 - Probable MDR-TB with a source case with known or suspected additional resistance to second-line agents
 - Confirmed or probable MDR-TB with a high risk of treatment failure
- Dose
 - >35 kg: 100 mg twice daily
 - 20–34 kg: 50 mg twice daily
- Monitoring
 - Baseline: ECG to assess QTc interval and albumin in addition to standard MDR-TB assessments
 - Follow-up: Monthly ECG to assess for QTc prolongation
- Safety with ART not studied in children – DDI possibly not important

Bedaquiline > 12 years > 33 kg

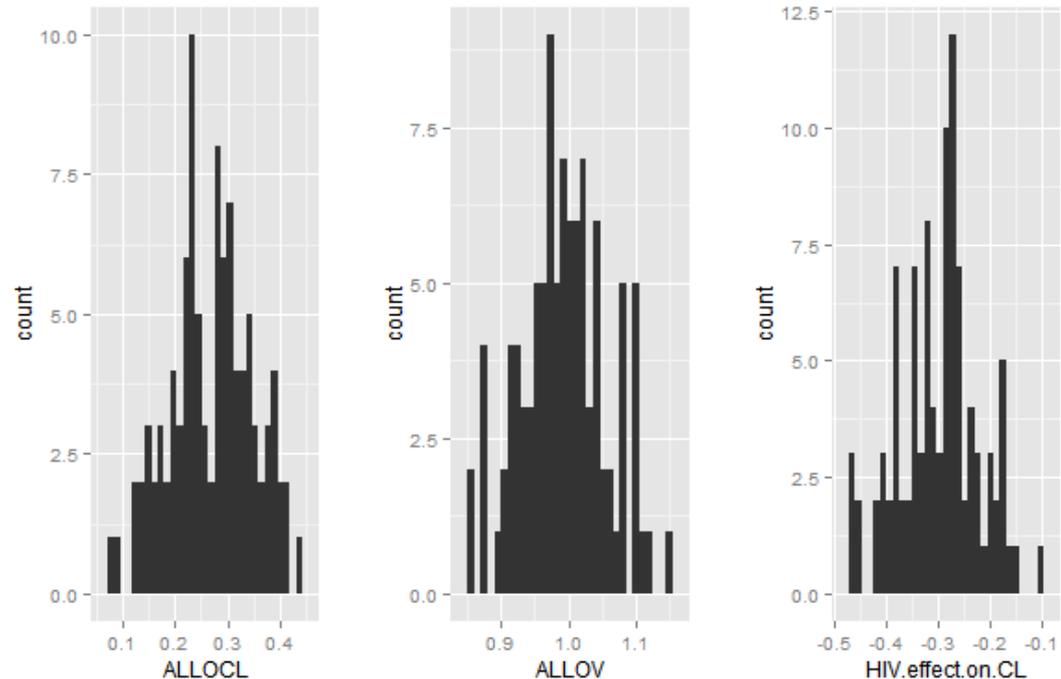
- Who > 12 and > 33 kg
 - Confirmed MDR-TB in whom a four-drug regimen plus pyrazinamide cannot be constructed because of resistance or significant intolerance and where delamanid is not available
 - Probable MDR-TB with a source case with known or suspected additional resistance to second-line agents and where delamanid is not available
- Dose
 - 400 mg daily for 14 d followed by 200 mg given three times weekly for an additional 22 weeks
- Monitoring with ECG



Results: -30% in CL of HIV

parameter	mean	stdev	95%CI_low	95%CI_upp
ALLOCL	0.2700	0.078	0.1169	0.422
ALLOV	0.992	0.064	0.8671	1.117
HIV.effect.on.CL	-0.300	0.076	-0.447	-0.15

Power: 88% found a statistically significant effect of HIV on CL when simulating 30% lower CL
N=54 total children,
minimum 18 HIV-infected



Simulating BDQ and M₂ PK in paediatric patients with/without HIV

Linizolid

- Who
 - Some MDR cases especially meningitis
 - Confirmed or probable MDR-TB as part of the core second-line regimen
- Dose - entire course of treatment as long as the child tolerates it
 - Children >12 yr: 10 mg/kg once daily
 - Children ,12 yr of age: 10 mg/kg twice daily
- Monitoring
 - FBC and peripheral nervous system

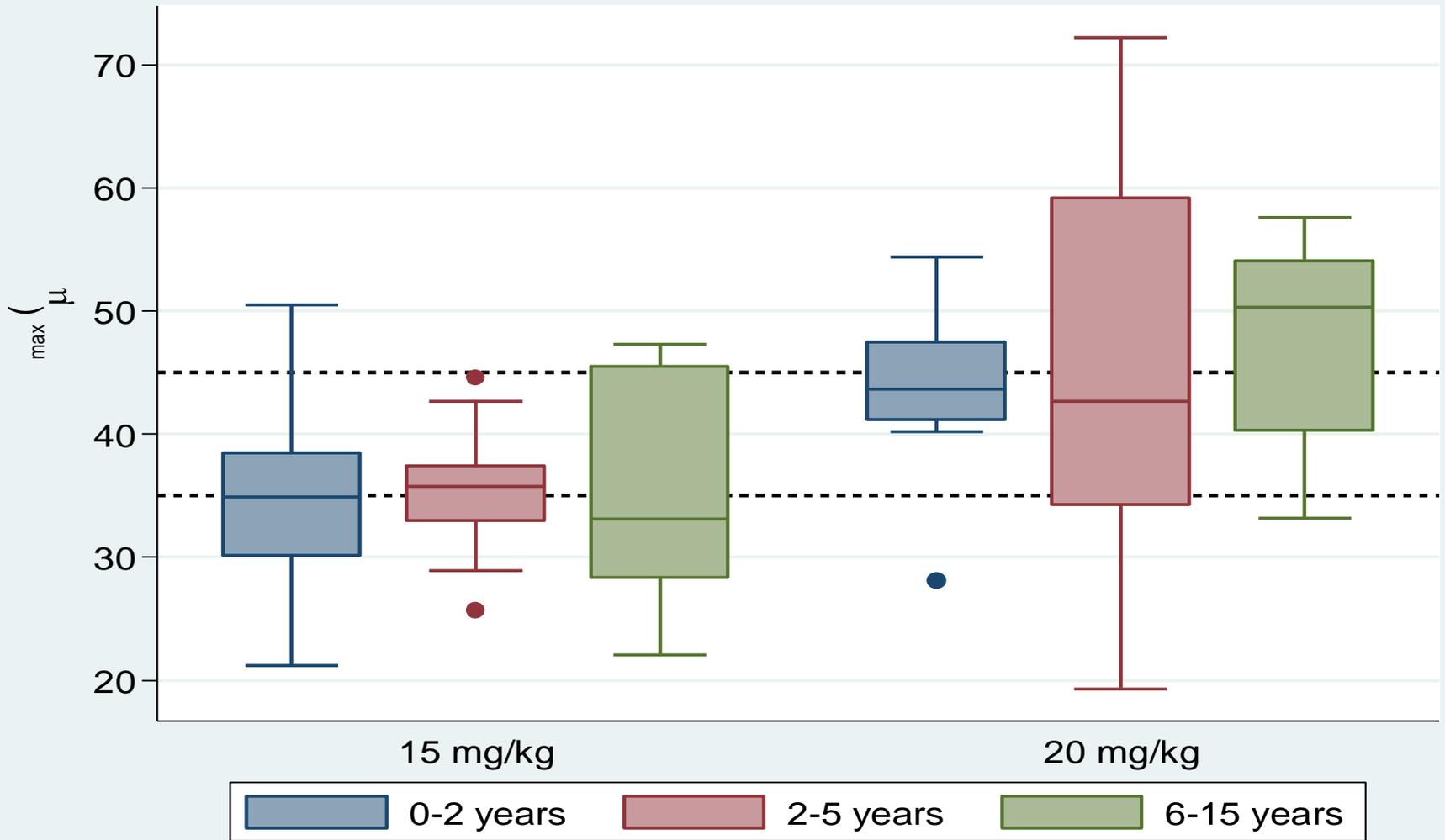
Clofazimine

- Who
 - Confirmed or probable MDR-TB as part of the core second-line regimen
- Dose
 - 2–3 mg/kg given daily for a maximum daily dose of 100 mg or every other day in smaller children (gelcaps cannot be split)
- Monitoring
 - Skin
 - ECG

Amikacin

- Recommended WHO dose – 15-30mg/kg IM
- Preliminary data from our group on amikacin PK in 28 children: IM dose of 20mg/kg: median C_{\max} of 47.1 $\mu\text{g/mL}$, higher than proposed adult target C_{\max} of 35-45 $\mu\text{g/mL}^*$ in >70% of children
- We evaluated PK of once daily IM amikacin at 20 vs. 15 mg/kg
- Analyses on safety and clinical outcomes with higher and lower dose pending

**Peloquin CA. 2002;62(15):2169-83*



Amikacin median concentration (IQR) in different age groups at doses of 15mg/kg and 20mg/kg IM daily

Amikacin: Conclusions

- Age had a significant influence on IM amikacin by total exposure; not by C_{\max} ; no effect by HIV or nutritional status
- To achieve target adult C_{\max} of at least 35 $\mu\text{g}/\text{mL}$: amikacin dose 18-20mg/kg
- Majority of children achieved a C_{\max} of $>35 \mu\text{g}/\text{mL}$ at 20mg/kg daily: care not to exceed this dose unless TDM is available. Hearing loss is associated with cumulative amikacin exposure
- Previous studies showed 25% children had hearing loss*

Levofloxacin

- FQN cornerstone of MDR-TB regimens
- Active enantiomer of ofloxacin
- Fast and complete absorption - F is high: 99%
- Low protein binding 24-38%
- Elimination half-life 6-8 hours in adults
- Mainly renally cleared, very little metabolism
- Toxicity: hepatic
- Few earlier popPK studies in children

Levofloxacin: Conclusions

- 20mg/kg dose more closely approximates adult exposures than 15mg/kg
 - But still low
 - Safety data at this dose being analyzed
- Despite low exposures, outcomes good
- More optimal doses may improve outcomes further or facilitate shorter or injectable sparing regimens
 - Important for bridging to novel regimens

Levofloxacin – 100mg dispersible tablet



Pharmacokinetics of moxifloxacin

Summary of pharmacokinetic parameters of moxifloxacin in children with multidrug-resistant TB (n=23), and published values in adults with TB

	C_{max} ($\mu\text{g/ml}$)		AUC_{0-24} ($\mu\text{g}\cdot\text{h/ml}$)		$t_{1/2}$ (h)	
	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)
Children (7-15y (10mg/kg dose))	23	3.08 (2.85-3.82)	12	23.3 (19.2-24.2.3)	12	4.14 (3.45-6.11)
Adult Summary (400mg dose)		3.3 (3.1-6.1)		33.6 (31.6-60.0)		6.5 (4.9-9.9)

Adverse events in children with 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)

Acknowledgements

- Anneke Hesselning