UPDATE ON TB PREVENTIVE THERAPY TRIALS IN CHILDREN

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WHO TPT – which regimens to use in which situations? consolidated quidelines on tuberculosis Module 1: Prevention Tuberculosis preventive treatment Children <2 • Preferred regimen: **3RH** years* • If paediatric FDC not available: 6H (World Health Organization Children <25 • Preferred regimen: **3RH** • If paediatric FDC not available: **6H** (dispersible tab) or kg (up to 8-10 **3HP** (adult formulations) years) Older children •3RH (adult FDCs) or (>25 kg) 3HP (>2y) / <u>1HP (>13y</u>) (adult formulations) •**6H** (dispersible tab) or Children living For children on EFV-based ART only: **3RH** with HIV or •If <u>able to swallow tablets</u>: **3HP (>2y) / 1HP (>13y)** Neonates: No data available, expert opinion recommended Courtesy of Annemieke Brands, WHO

Trends in provision of TPT to eligible <5 contacts



PRIORITY 1: 3 HP +-ARVS



TBTC Study 35 : Phase I/II Dose Finding and Safety Study of Rifapentine and Isoniazid in HIV-Infected and HIV-Uninfected Children with LTBI (FDA IND # 141932)





3 HP in children across age spectrum - also < 2 years, HIV: PK and safety

- Primary Objective: To establish, through population PK modelling, the dose of RPT that will achieve the target adult exposures from TBTC Study 26 in children aged 0-12 years receiving novel child-friendly INH/RPT formulations
- Primary End point: Dosing algorithm derived by simulation of optimal RPT doses in children, using nonlinear mixed effects models, and using age and/or weight banding approaches





Sanofi

IMPAAC

Minimum evaluable number of participants per age group and by HIV status*						
Cohort	Age	Total number	Number HIV- infected**	Number HIV- uninfected		
1	\geq 4 to \leq 12 years	12	6	6		
2	≥ 24 months to < 4 years	12	6	6		
3	≥ 12 to < 24 months	18	-	18		
4	0 to < 12 months	18	-	18		
	Total	60	12	48		

*Protocol allows enrollment **of up to 72** children total to achieve the minimum numbers of evaluable participants **Up to 6 total HIV-infected children may be enrolled in cohorts 3 and 4 if integrase inhibitors (e.g. dolutegravir, raltegtavir) become available in South Africa, for a maximum total of 18 HIV-infected participants

TBTC Study 35 Timeline

- Enrolment completed for interim analysis: cohorts 1, 2 (12-2 years)
- 6 participants needed in each of cohorts 1 and 2 (2-12 years) with completed week 1 PK sampling and week 12 safety evaluation
- 16 children enrolled in cohorts 1, 2 (March 2020)
- Interim analysis: PK and safety completed
- Interim review targets:
 - PK: Median AUC is not >25% below adult target, and not >75% above adult target
 - Safety: No Dose limiting toxicity (defined as 2 or more suspected adverse reactions to INH or RPT of Grade 3 or higher, at a given dose)
- Re-opening: cohorts 3, 4 (<2 years): delayed due to nitrosamine impurity: Q1 2021? Requires FDA, in country approval
- Data on < 2 year olds: 2021?</p>

3HP, 1HP and ARV Interactions in Children



ARV	ЗНР
NVP	 Interaction not known in adults or children
LPV/r	Anticipated interactionNo plan to evaluate
EFV	 No dose adjustment needed in adults

- Children: TBTC S35
- <u>DoLPHIN Study</u>: Well tolerated, safe. No dose adjustment necessary.
 - Children: DoLPHIN Kids

Courtesy: Nicole Salazar-Austin



Farenc, et al. CROI 2014; Podany et al. Clin Infect Dis 2015; Dooley, et al. CROI 2019;

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• Aim

- To assess the safety, tolerability and pharmacokinetics of three months of once-weekly isoniazid and rifapentine (3HP) among infants, children and adolescents living with HIV taking DTG and 2 NRTI
- Design:
 - Single arm Phase I/II PK and Safety study of DTG-based ART and once-weekly rifapentine plus isoniazid (3HP) in CALHIV (<18 years) on ART with suppressed viral load who have indication for TPT
- Timeline
 - DTG + ABC/3TC daily x4 weeks (With regimen switch and EFV washout if needed)
 - DTG + ABC/3TC daily + 3HP x12 weeks
 - Post treatment access to pediatric DTG (if needed)
- Regimens:
 - Group 1: weight-based DTG dose **BID** + weight-based HP dose \rightarrow interim analysis (n=20)
 - Group 2: DTG, dose **TBD** + ABC/3TC + 3HP \rightarrow PK, confirm dosing (n=40-60)
- In protocol development
- Funded by UNITAID IMPAACT4TB
- Results anticipated in late 2023



Dolphin Kids Study Timeline





DOLPHIN Kids Timeline Dependent On:

- 1. Nitrosamine impurity and child friendly formulation
- 2. Availability of dosing for children < 2 from TBTC S35 (on track)



PRIORITY 2: 1 HP, ARVS

1 HP: EFFICAY AND SAFETY: ONE MONTH OF DAILY RIFAPENTINE/ISONIAZID TO PREVENT TB IN PEOPLE WITH HIV: BRIEF-TB/A5279 : Brief Rifapentine-Isoniazid Efficacy for TB Prevention NCT01404312

A Shorter Regimen to Prevent HIV-Related Tuberculosis



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One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis

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1 HP vs. 3 HP adults and adolescents: IMPAACT4TB

- Safety, tolerability, effectiveness of 1 HP vs. 3 HP in adults, adolescents, HIV
- Preferences for TB PT regimens
- Paediatric study needed?



1 HP: children, HIV

IMPAACT P2024

- 1 HP: priority gaps for children: Data on PK and safety of 1 HP in HIVinfected and uninfected children (daily RFPT dosing vs. once weekly for 3 HP), formulations.
- PK and safety of 1 HP in HIV+ and HIV- children <15 years of age
- HIV+ on DTG (rollout, bd) or EVF based regimens
- Paediatric DTG formulation; will use adult 150 mg until paediatric formulation available
- Effect of crushing extemporaneous formulation work planned, bridging PK with paediatric formulation
- Pragmatic weight banded recommendations when crushed
- Timeline: open 2021? Formulation questions



Priority 2 cross-cutting: RFPT formulation development work challenges and progress

"FDA works to mitigate shortages of rifampin and rifapentine after manufacturers find nitrosamine impurities"

- "To mitigate or avoid shortages and to help ensure patients have access to these necessary medicines, FDA will not object to certain manufacturers temporarily distributing rifampin containing 1-methyl-4-nitrosopiperazine (MNP) or rifapentine containing 1-cyclopentyl-4-nitrosopiperazine (CPNP) above the acceptable intake limits until they can reduce or eliminate the impurities."
- "The acceptable intake limits are 0.16 parts per million (ppm) for MNP in rifampin and 0.1 ppm for CPNP in rifapentine. The agency will not object to certain manufacturers temporarily distributing rifampin containing MNP below 5 parts per million (ppm). The agency also will not object to certain manufacturers temporarily distributing rifapentine containing CPNP below 14 ppm. FDA will not object to these higher exposures to maintain patient access to these life-saving medications."



RPT impurity and development of child friendly formulations

- Does production of the pediatric friendly formulation further increases the nitrosamine levels in the dispersible tablet?
- Analyses expected November 2021
- Further increase in nitrosamine impurity: Sanofi would need to refine the manufacturing process, delay in :
 - 1. Trial preparations of a pediatric friendly formulation
 - 2. Marketable Pediatric Friendly Formulation
- Sanofi: Paediatric formulation development work on hold for several months until impurity issue resolved
- Impurity in API: 2 sources globally: both affected (Sanofi, Macleods)
- Impact on clinical routine access and trials?
- Benefit of clear TCC after resolution of impurity issues: TB PADO

Formulation landscape

- 150 mg unscored tablet. Non-dispersible. Commercial product. Licensed down to 2 years: 3 HP
- Sanofi: Water-dispersible FDC tablet: 150 mg RPT/150 mg INH; mango flavoured and water-dispersible RPT-only 100-mg and 20-mg tablets. Trial formulations. Not scored: trial formulations (not commercial products)





Dosing Predictions for 3HP

	Rifapentine Unscored 150 mg		Rifapentine Scored 150 mg		Isoniazid ⁺ Scored 100 mg	
Weight band	Tabs	Dose in mg (mg/kg)	Tabs	Dose in mg (mg/kg)	Tabs	Dose in mg (mg/kg)
3-4 kg	1	150 (37-50)	0.5	75 (18-25)	1	100 (25-33)
5-6 kg	1	150 (25-30)	0.5	75 (12-15)	1.5	150 (25-30)
7-9 kg	1	150 (17-21)	1	150 (17-21)	2	200 (22-28)
10-15 kg	2	300 (20-30)	2	300 (20-30)	3	300 (20-30)
16-23 kg	3	450 (19-28)	3	450 (19-28)	5	500 (21-32)
24-30 kg	4	600 (20-25)	4	600 (20-25)	6	600 (20-25)
>=31 kg	5	750 (17-24)	5	750 (17-24)	6	600 (13-19)

⁺ isoniazid dose predictions based on 25 mg/kg recommendation for < 10 kg, and for 10+ kg sourced from *Radtke et al. ERJ 2020*

3HP AUC prediction with proposed weight-band dosing



Adult target is predicted AUC with 900 mg dose from adult PK model¹

TB PADO: Ideal RFPT formulation characteristics

- **Strength**: 150 mg single formulation
- Dispersible
- **Scored:** 75: 75 mg (minimum "ease of use" as minimum, ideally functional).
- Palatable
- Long shelf life
- Modeled PK data can update EOI: dispersible, scored 150 mg
- Industry: target 1 priority paediatric formulation for WHO PQ once impurity issues resolved: multiple indications, durable.
- Standalone RFPT removes complexity with FDC

PRIORITY 3:DR-TB

Contacts of multidrug-resistant tuberculosis patients

7. In selected high-risk household contacts of patients with multidrug-resistant tuberculosis, preventive treatment may be considered based on individualized risk assessment and a sound clinical justification. (Conditional recommendation, very low certainty in the estimates of effect)

Justification and evidence

This recommendation was added in the 2018 update of the guidelines. Ahead of this a systematic review of the effectiveness of preventive treatment for contacts of people with MDR-TB conducted for the 2015 LTBI guidelines was updated (14).

The updated review comprised 10 studies (6 newly identified and 4 from the previous review) that allowed comparisons between participants who received preventive treatment for MDR-TB and those who did not (see PICO 10 in **Annex 2**). Because of clinical heterogeneity among the studies, a meta-analysis could not be performed. Of the 10 studies, one was excluded because only isoniazid monotherapy was used, and an additional five studies were excluded as fewer than 20 participants completed preventive TB treatment. Therefore, the quality of the evidence was based on only four studies. No active TB was reported in either the intervention or the control group in one study (34), while one person with active TB due to a drug-susceptible strain that was different from the presumed source was reported in another study (35). The remaining two studies addressed the efficacy of preventive treatment (36),(37). In one cohort of 119 contacts, 104 with LTBI initiated fluoroquinolone-based preventive treatment, of whom 93 (89%) completed treatment, and none developed active TB; while 3 of 15 (20%) contacts who refused treatment developed MDR-TB (OR 0.02, 95% CI 0.00; 0.39) (26). In the other study, confirmed or preventive TB developed MDR-TB (OR 0.02, 95% CI 0.00;

WHO 2020 guidelines

	ТВ-СНАМР	V-QUIN	PHOENIx
Intervention	LVF (novel paediatric dispersible formulation) vs. placebo daily for 6 months	LVF vs. placebo daily for 6 months	DLM vs standard dose INH daily for 26 weeks
Design	Cluster randomized; superiority Community-based	Cluster randomized; superiority Community-based	Cluster randomized; superiority Community-based
Target Population	 0-4 years regardless of IGRA or HIV status Only study powered for efficacy in children 	 Adults and adolescents TST + Small group children 	 HIV + Children <5 yrs TST/IGRA + > 5 y
Assumptions	LVF decreases TB incidence from 7% to 2.8% 80% power 1.3 contacts/HH	LVF decreases TB incidence by 70% from 3% untreated 80% power	DLM decreases TB incidence by 50% from 5% to 2.5% 90% power
Sample size	650 Households 1009 contacts	1326 Households 2785 contacts	1726 Households 3452 contacts
Sites	South Africa DTTC, Shandukani, PHRU Matlosana, MRC CTU	Viet Nam NTP	ACTG & IMPAACT sites
Timelines to open	N=598 enrolled Interim analysis: Q4 2020	Fully accrued Results: Q2 2022	N=424 enrolled
Funder, PI	UNITAID BMRC/Wellcome Trust, SA MRC SHIP	Australian MRC Fox, Nguyen	ACTG/IMPAACT

TB CHAMP



Primary

 Is levofloxacin given daily for 6 months effective in preventing TB and/or all-cause mortality in high-risk child household contacts of MDR-TB cases?

Secondary:

- Toxicity and tolerability of Levofloxacin in children?
- Mortality?
- Adherence?
- Levofloxacin resistance for incident TB cases?
- Levofloxacin cost-effectiveness and acceptability to prevent MDR-TB in child and adolescent household contacts?
- Where? 3 South African sites: Cape Town, Johannesburg, Klerksdorp

STUDY PROTOCOL



Levofloxacin versus placebo for the prevention of tuberculosis disease in child contacts of multidrug-resistant tuberculosis: study protocol for a phase III cluster randomised controlled trial (TB-CHAMP)

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COVID-19 trial IMPACT: South Africa

- All sites paused to accrual in March 2020
- Active follow-up in all children continued; selected face to face visits
- Previous pause in August 2019 (funding): accrual re-opened in October 2019
- Re-opened: July 2020
- Interim analysis on track

Other COVID-19 effects

- TB case detection in SA declined by 30%
- TB contact management implementation in children negatively impacted
- Access to child and maternal health: EPI vaccines, nutrition, deworming, intercurrent infections, HIV services
- Poverty

A5300B/IMPAACT2003B

<u>P</u>rotecting <u>H</u>ouseholds <u>On Exposure to N</u>ewly Diagnosed <u>Index</u> Multidrug-Resistant Tuberculosis Patients

(A5300B/I2003B/PHOENIx)

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







PHOENIX Objectives

Primary Objectives

Among HIV+ and other child, adolescent, and adult HH contacts of MDR TB patients at high risk of developing TB, to compare:

- 1. The efficacy of (once daily) DLM vs. INH for preventing confirmed or probable active TB
- 2. 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
 - HIV+ HHCs
 - Each high-risk group
- 2. Efficacy in preventing
 - Confirmed MDR TB
 - All-cause mortality
 - Confirmed or probable TB and all-cause mortality



PHOENIX Study Sites

 \star 16 sites activated \star 4 sites not activated



Botswana (1) Brazil (1) Haiti (1) Kenya (1) India (2) Peru (2) South Africa (8) Tanzania (1) Thailand (2) Zimbabwe (1)







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- James Seddon







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