CS 5019: Phase I/II Dose Finding and Safety Study of Daily Rifapentine and Isoniazid for one month (1HP) for tuberculosis preventive therapy in HIV-infected and uninfected children

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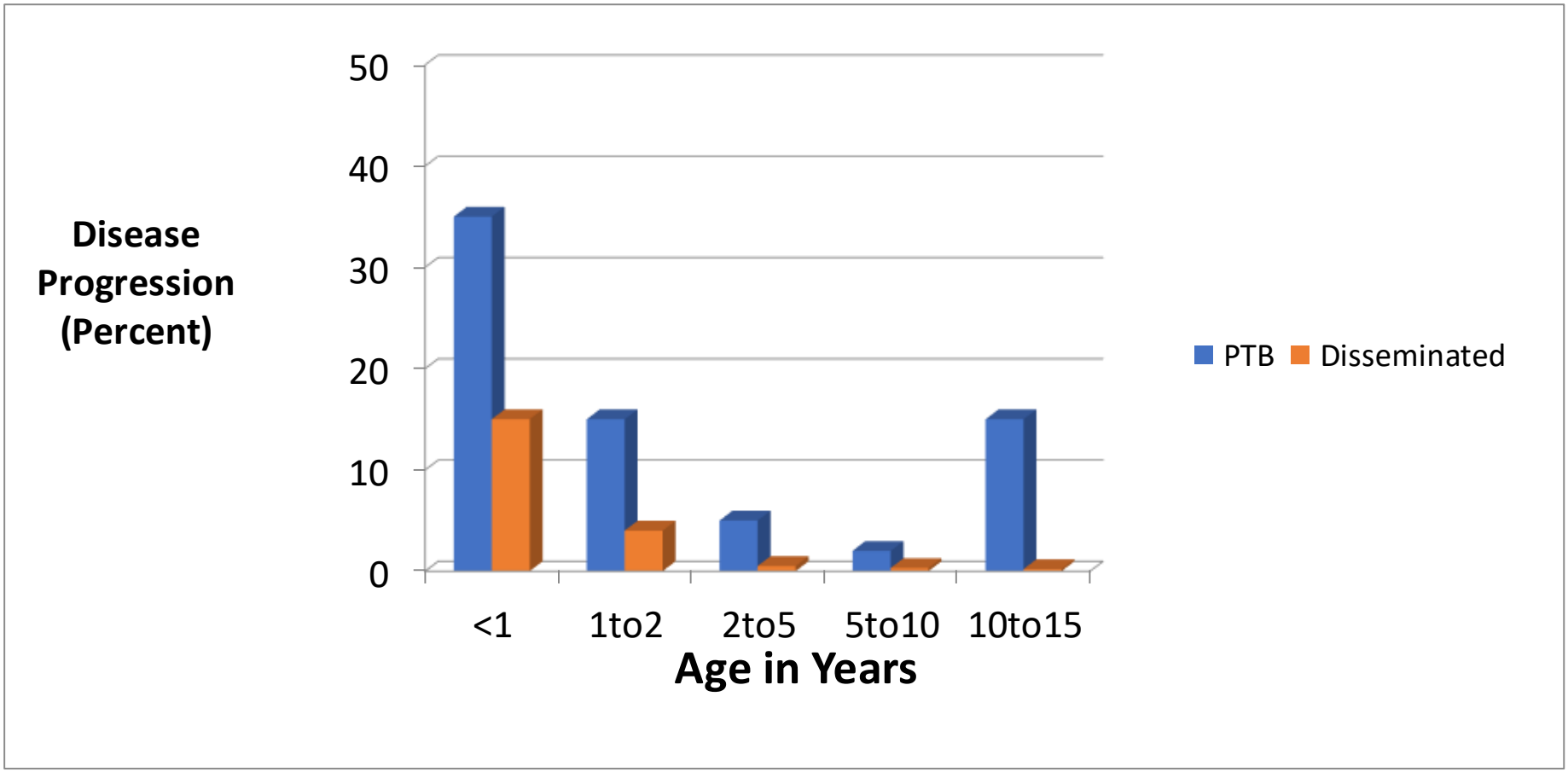
IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Background and Rationale

- CALHIV and HEU are at high risk of TB exposure and subsequent progression to TB disease
- TB Preventive therapy (TPT) is highly efficacious at reducing this risk
  - Limited effectiveness due to long durations of therapy
- 1HP, an ultra-short course TPT regimen (28 days of rifapentine (RPT) and isoniazid (INH)), could improve initiation and completion of TPT
  - BRIEF-TB (A5279) showed 1HP was safe and non-inferior to 9H in HIV-infected persons ≥13 years

Age related TB disease risk in children



Marais et al. Int J Tuberc Lung Dis. 2004

Background and Rationale

- The dosing and safety of daily RPT for treatment for prevention in children <13 years is not known
- DDI between daily RPT and pediatric ART regimens is also unknown
- Globally, most common pediatric ART regimens include: LPV/r (<3 years) and EFV (≥3 years)
  - Plan to study LPV/r and EFV to ensure immediate relevance of findings
- Anticipate dosing of DTG soon, but delayed global availability of RAL and DTG
  - Plan to study RAL & DTG to ensure long-term relevance of data
  - Understand enrollment may be limited

Background and Rationale

- **RPT is a potent inducer of the cytochrome P450 system (CYP3A4) and key drug transporters (UGT1A), similar to Rifampin (RIF)**
- **LPV/r metabolized by CYP3A4**
  - RIF results in significant reduction in plasma LPV concentrations requiring boosted ritonavir 1:1 with LPV
  - Anticipate DDI
- **EFV**
  - No anticipated DDI; 1HP did not significantly lower EFV levels in adults
- **RAL / DTG metabolized by CYP3A4 and UGT1A**
  - Weekly RPT & DTG is safe in adults living with HIV (CROI 2019), despite initial concerns in healthy volunteers
  - Daily RPT with RAL or DTG not yet studied in adults (DTG studies planned), daily RIF with RAL or DTG require double dosing of RAL and DTG in adults
  - Anticipate DDI

Ren, et al. JAIDS 2008; Podany, et al, CID 2015; Dooley, et al. CID 2019; Dooley, et al. CROI 2019

Hypotheses

1. Model-based daily dosing of RPT, adjusted through an adaptive design, in children <15 years, will result in exposures similar to those seen in adults receiving 1HP in BRIEF-TB (A5279)
2. 1HP will be a safe and well-tolerated regimen in HIV-infected, HEU and HUU children treated for the prevention of TB

Study Design

- Phase I/II, single arm dose finding and safety study with an adaptive design to evaluate the PK, safety and tolerability of 1HP (daily RPT/INH for 28 days)
- Enrollment will occur over 12-18 months
- One year follow-up for TB incidence
  - *For participant safety, not efficacy*

Population

- HIV-infected and HIV-uninfected children 0 to 14 years
- Either documented TB infection or recent close exposure to an adult DS-TB index case
- Participants will be enrolled in 3 age cohorts, in parallel (no age de-escalation)

Age Cohort	Ages
1	≥6 to <15 years
2	≥3 to <6 years
3	0 to <3 years

Sample Size

Age Cohort	HIV+ on LPV/r	HIV+ on EFV	HIV+ on RAL or DTG	HIV negative	Total
0 to <3 years	12	0	24	12	~36
≥3 to <6 years	0	12		6	~24
≥6 to <15 years	0	12		6	~24
Total	12	24	24	24	84

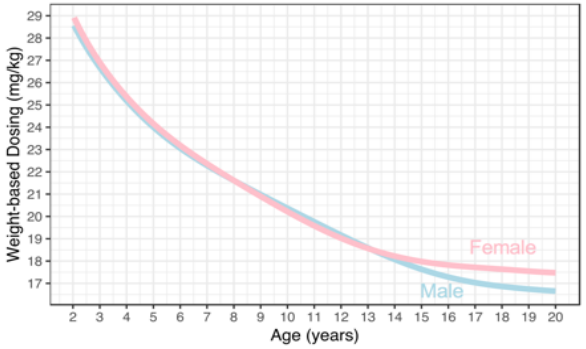
Rationale

- Age groups to be studied largely reflect ART regimens used globally
  - LPV/r-based ART for children < 3y and EFV ≥ 3y
- We anticipate limited enrollment of participants on RAL or DTG
  - Built in flexibility in RAL/DTG enrollment
- Sample size simulations ongoing and will be updated in the future protocol

1HP Regimen

- Sanofi-Aventis' water-dispersible tablets
  - fixed dose formulation (1:1 RPT:INH) + RPT standalone (2 strengths)
- RPT dosing derived from:
  - *Estimated* AUC targets from BRIEF-TB
  - Autoinduction parameter from adult clinical trials including pulmonary TB patients and healthy volunteers
  - Age and weight dependent maturation function for clearance (TBTC S26 kids)
  - Food effect and bioavailability parameter (RPT absorption food-dependent)
- Standard daily dosing of INH for children
- Initial RPT Dosing:

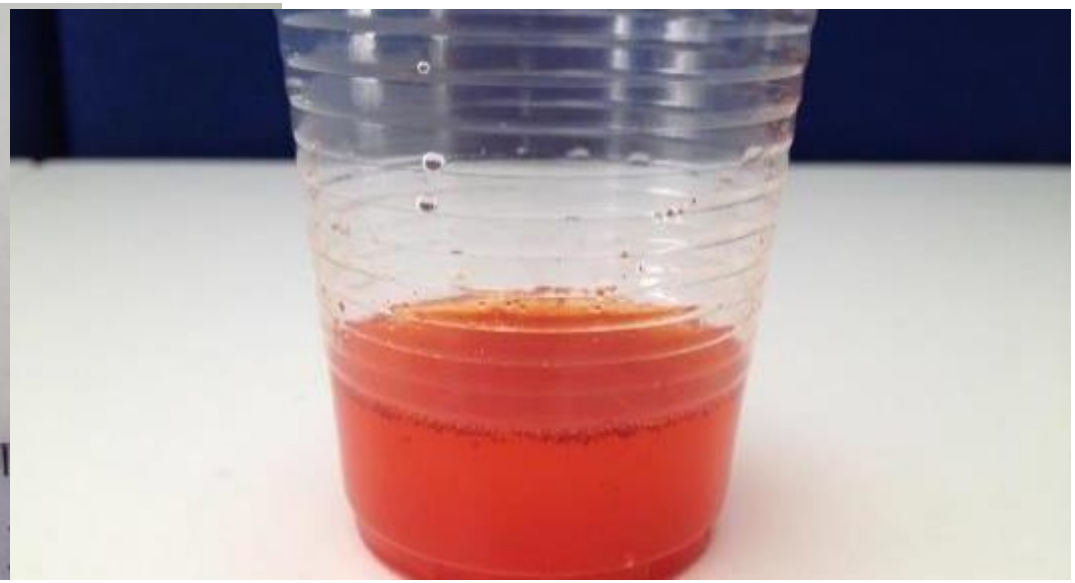
Age Cohort	Initial RPT Dose	INH Dose
≥6 to <15 years	18 mg/kg	10-15 mg/kg
≥3 to <6 years	20 mg/kg	
Birth to <3 years	23 mg/kg	



Weiner et al. JPIDS 2014; Savic et al; Clin Pharmacol Ther 2017;
Savic et al. Antimicrob Agents Chemother, 2014.

Child-friendly formulations for delivery of 3 HP in children

- Water-dispersible FDC tablet: 150 mg RPT/150 mg INH
- Water-dispersible RPT-only tablets (20 and 50 mg)



ART Targets and ART Dosing

- **LPV/r**
  - Goal LPV concentration: $AUC_{0\text{-}12}$ > 81 mg*h/L at 14, 28, 42 and 56 days
  - Dose Adjustment: boosted ritonavir 1:1 with LPV
- **EFV**
  - Target: Mid-interval EFV concentration: >1mg/L at 14 and 28 days
  - No dose adjustment
- **RAL**
  - Target: Median C_{12h} with RPT is ≥ 75 ng/mL and the median AUC_{12} with RPT is between 6.2 and 20 mg*h/L at 14, 28, 42 and 56 days
  - Double dose RAL (2-times RAL dose BID)
- **DTG**
  - Target: Median C_{τ} ≥300µg/mL at 14, 28, 42 and 56 days
  - Double dose (DTG dose given BID)

Ren, et al. JAIDS 2008; Podany, et al, CID 2015; van Lunzen Lancet ID 2012;
Eron, et al. Lancet ID 2011; P1101 protocol version 3

Primary Objectives

1. To establish the dosing of daily RPT, through population PK modeling, that will achieve target adult exposures, as observed in BRIEF-TB ($AUC_{0\text{-}Tss}$), in both HIV-infected and HIV-uninfected children
2. To evaluate the safety and tolerability of daily RPT given in combination with daily INH over 28 days

Secondary and Exploratory Objectives

Secondary Objectives:

- To explore the effect of covariates on the PK of RPT and desacetyl-rifapentine (des-RPT), when given in combination with INH, once-daily for 28 days
  - Covariates: age, weight, sex, ethnicity, HIV infection, and nutritional status
- In HIV-infected children, to evaluate the impact of RPT on the PK of ART (LPV/r, EFV, RAL and DTG).
- To evaluate the palatability and acceptability of daily RPT/INH administered over 28 days
- To evaluate adherence to 1HP during the 28-day study period

Exploratory Objectives

- To evaluate the proportion of HIV-infected participants on ART with suppressed viral load at baseline and at week 8
- To evaluate incident TB (safety) over 12 months of follow-up in children treated with 1HP

Primary Endpoints

PK

- Primary population PK parameters of RPT and des-RPT including
  - Maximum serum concentration (C_{max})
  - Area-under-the-curve ($AUC_{0\text{-}Tss}$)
  - Time to C_{max} (T_{max})
  - Half-life ($t_{1/2}$)
  - Oral clearance (CL/F)
  - Volume of distribution (Vd)

Safety

- Treatment-related adverse event ≥ grade 3 over the 28-day treatment period.
- Permanent discontinuation of study drug due to a treatment-related adverse event over the 28-day treatment period.
- All-cause adverse event (AE) ≥ grade 3 over the 28-day treatment period
- Drug-related serious adverse event (SAE)
- All-cause SAE
- Cumulative number and proportion of children with drug-related grade 2 AE

Secondary & Exploratory Endpoints

Secondary

PK

- PK parameters of EFV, LPV/r, RAL and DTG among participants taking these ARV's at baseline and at days 14, 28, 42, and 56 days, taking CYP2B6 genotype (EFV users only) into account

Acceptability / Palatability

- Palatability and acceptability scores of the study regimen (quantitative) among child participants.
- An in-depth understanding of the acceptability of the study regimen (qualitative) among families and providers.
- Adherent to >95% of 1HP doses over the 28-day treatment period using a combination of Wisepill data and caregiver/self-report.

Exploratory

Efficacy

- Virologic suppression (<20 copies/mL) for participants on ART at week 8

Safety

- Incident TB over 12 months of follow-up

Potential Sites

- All sites will be solicited
  - At least 6-8 sites will be selected based on experience with pediatric TB PK studies
- Domestic and international sites
- Range of TB burden: high, medium, low

Additional Key Considerations

- Pharmaceutical support will be sought from Sanofi
- Complements TBTC Study 35 (3 HP in HIV-infected and infected children): opens Q3 2019 in South Africa
- Complements proposed IMPAACT maternal 1 HP vs. 3 HP studies

Discussion Points

- Age versus weight cohorts
- How to best include assessment of INSTI in study
- Sample size