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Twice-Daily Dolutegravir With a 4-Month Rifapentine-Based Regimen for HIV-Associated Tuberculosis

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for the A5406 study team

Background and Rationale

WHO consolidated guidelines on tuberculosis

Treatment of drug-susceptible TB using 4-month regimens

Recommendation 6.

People aged 12 years or older with drug-susceptible pulmonary TB, may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide[8] (conditional recommendation, moderate certainty of evidence) – new recommendation.

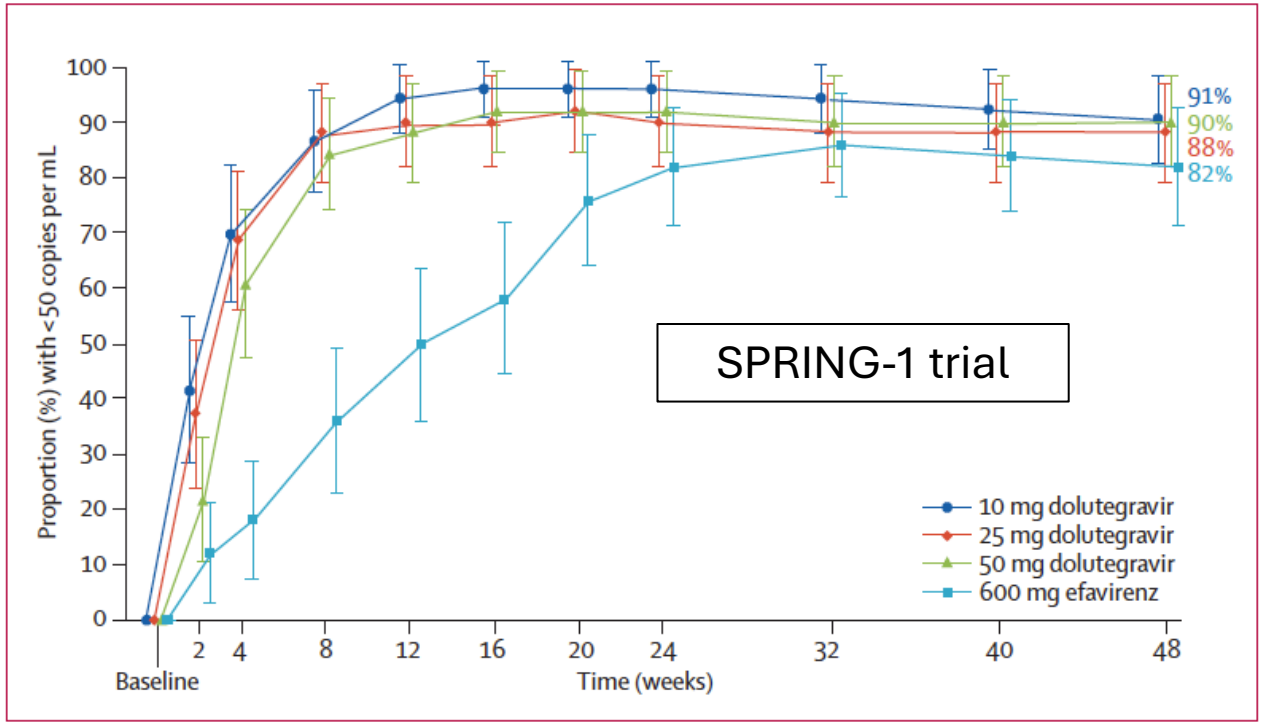
- DTG used as first line ART, but RPT increases DTG clearance (dose-related)
- Twice-daily DTG overcomes the drug-drug interaction effect with:
  - Rifampicin - healthy volunteers and patients
  - RPT 600 mg - 1HP
- Effect of daily RPT 1200 mg on DTG unknown, but may be more pronounced
- **Important to demonstrate safety and adequate exposures of twice-daily DTG among patients with HIV-TB to support implementation of 4-month regimen**

Williamson, et al. Antimicrob Agents Chemother 2013; 57(12): 6366-9.; Griesel, et al. Lancet HIV. 2023;10(7):e433-e441.
Kawuma, et al. Antimicrob Agents Chemother. 2022;66(6):e0021522.; Podany, et al. Clin Infect Dis. 2024;79(4):983-989.

Hypothesis: DTG BID will be adequate

Dolutegravir 50mg twice daily will provide adequate exposures when dosed with rifapentine1200mg:

- Lower bound of the 95% confidence interval around model-based DTG C_{min} > 0.158 µg/mL
- Adequate to maintain viral suppression



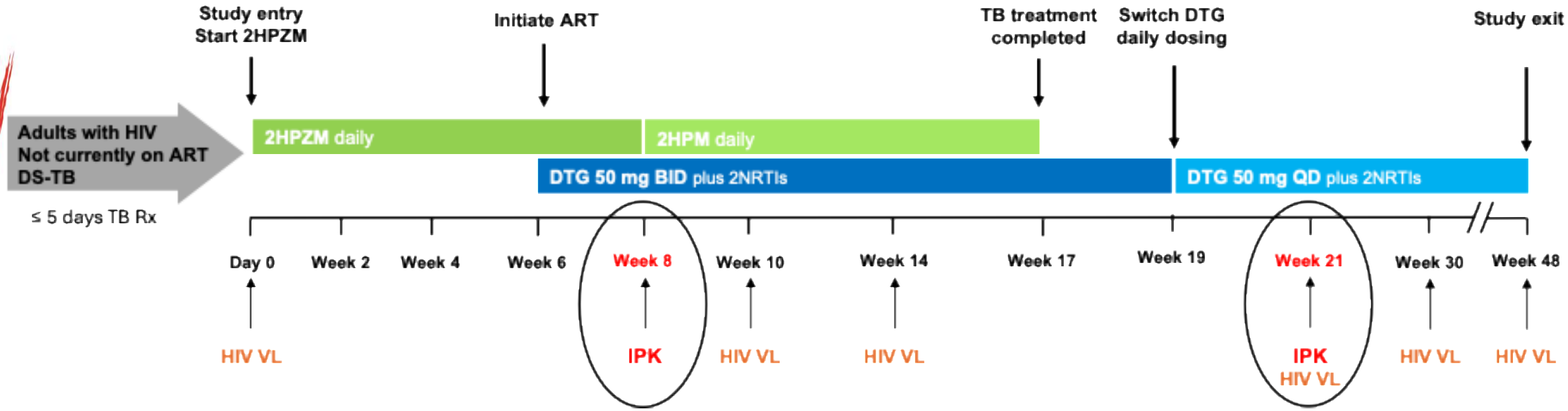
	Median	5th percentile
Cmin	0.300 µg/mL	0.158 µg/mL
C_{min}/IC_{90}	4.7	2.5

van Lunzen, et al. Lancet Infect Dis. 2012;12(2):111-8.

Study Design

48-week, open-label, single-arm, multicenter pharmacokinetic study

- n = 30
- 4 sites: Thailand and South Africa



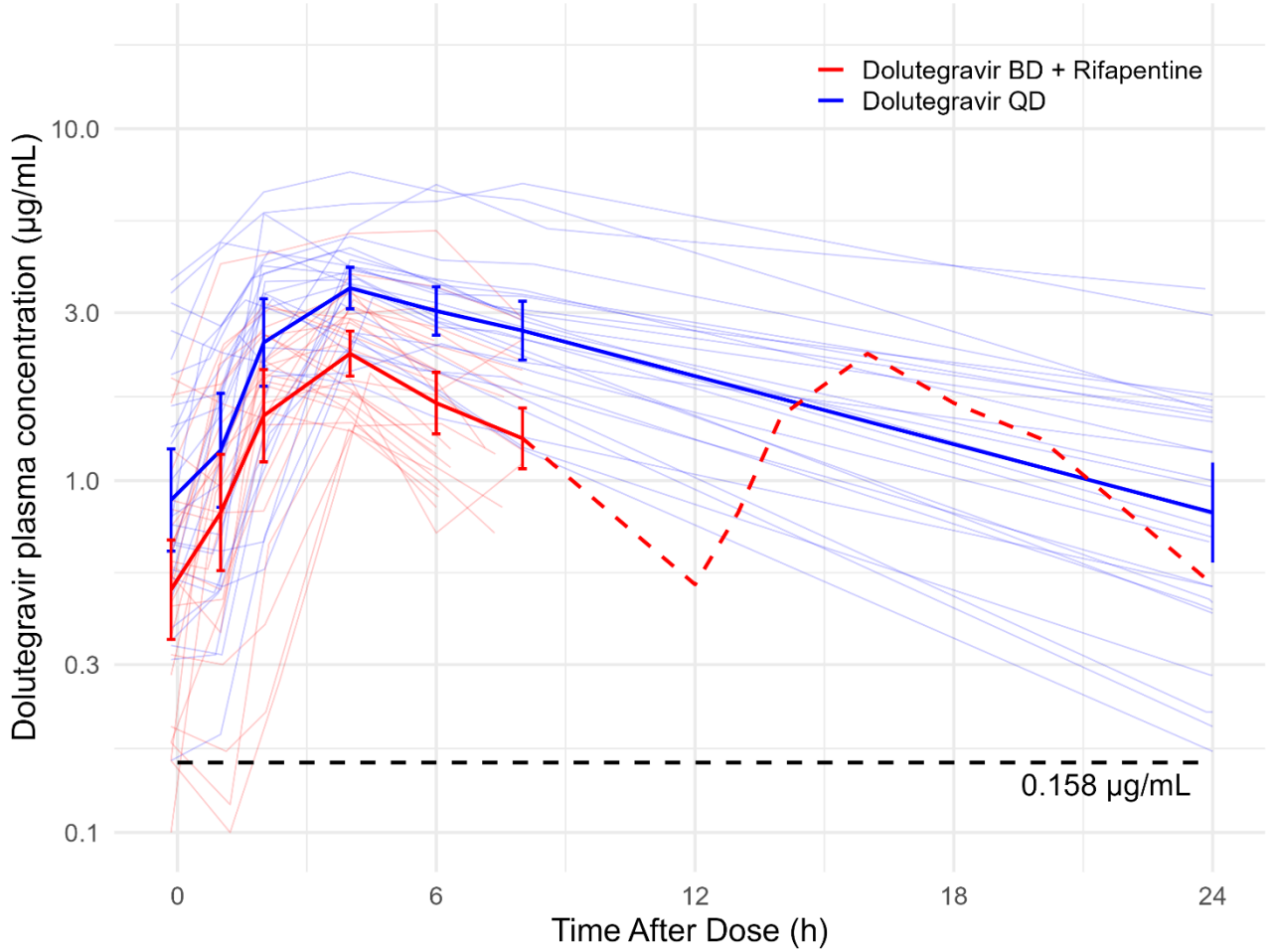
Intensive plasma PK samples collected at pre-dose, 1, 2, 4, 6, 8-10, and 24 hours post-dose
DTG PK estimated from NCA and NLME modelling

Baseline Characteristics

- **50 patients screened**
- **30 enrolled (19 ineligible, 1 did not return); 1 withdrawal (RPT hypersensitivity)**
- **29 included in safety set (took one dose of DTG with HPMZ)**

Characteristic	Result (n = 30)
Age (years), median (Q1, Q3)	35 (32, 38)
Female sex, n (%)	13 (43%)
Country, n (%) - South Africa - Thailand	 27 (90%) 3 (10%)
BMI (kg/m^2), median (Q1, Q3)	19 (18, 23)
HIV RNA (cp/mL), median (Q1, Q3)	96911 (15345, 237538)
CD4 ($10^6/L$), median (Q1, Q3)	185 (135, 357)
Days on TB treatment prior to entry, median (min, max)	3 (1, 5)

Markedly reduced DTG exposure with RPT



Model estimates

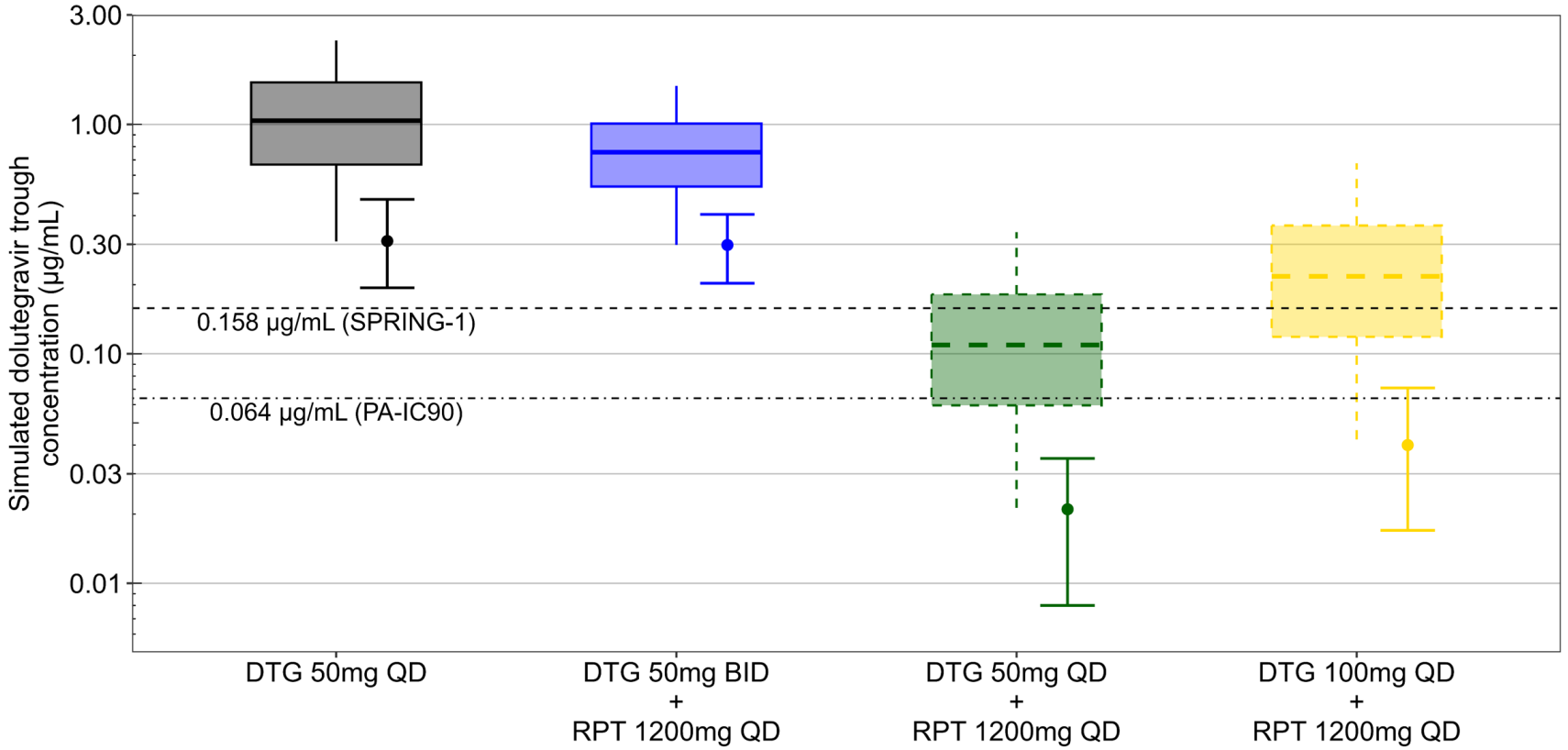
clearance — 2.27-fold (95% CI: 1.90-2.54)

Bioavailability — 23.5% (95% CI: (36.1 –9.23)

NCA

Parameter	Dolutegravir BD + Rifapentine (%GCV)	Dolutegravir QD (%GCV)	GMR (90% CI)
N	26	26	24
C_{trough}	0.51 (93%)	0.81 (96%)	0.60 (0.49–0.74)
AUC_{0-24} (µg·h/mL)	33.5 (46%)	47.2 (50%)	0.69 (0.61–0.78)

Simulated dolutegravir trough concentrations



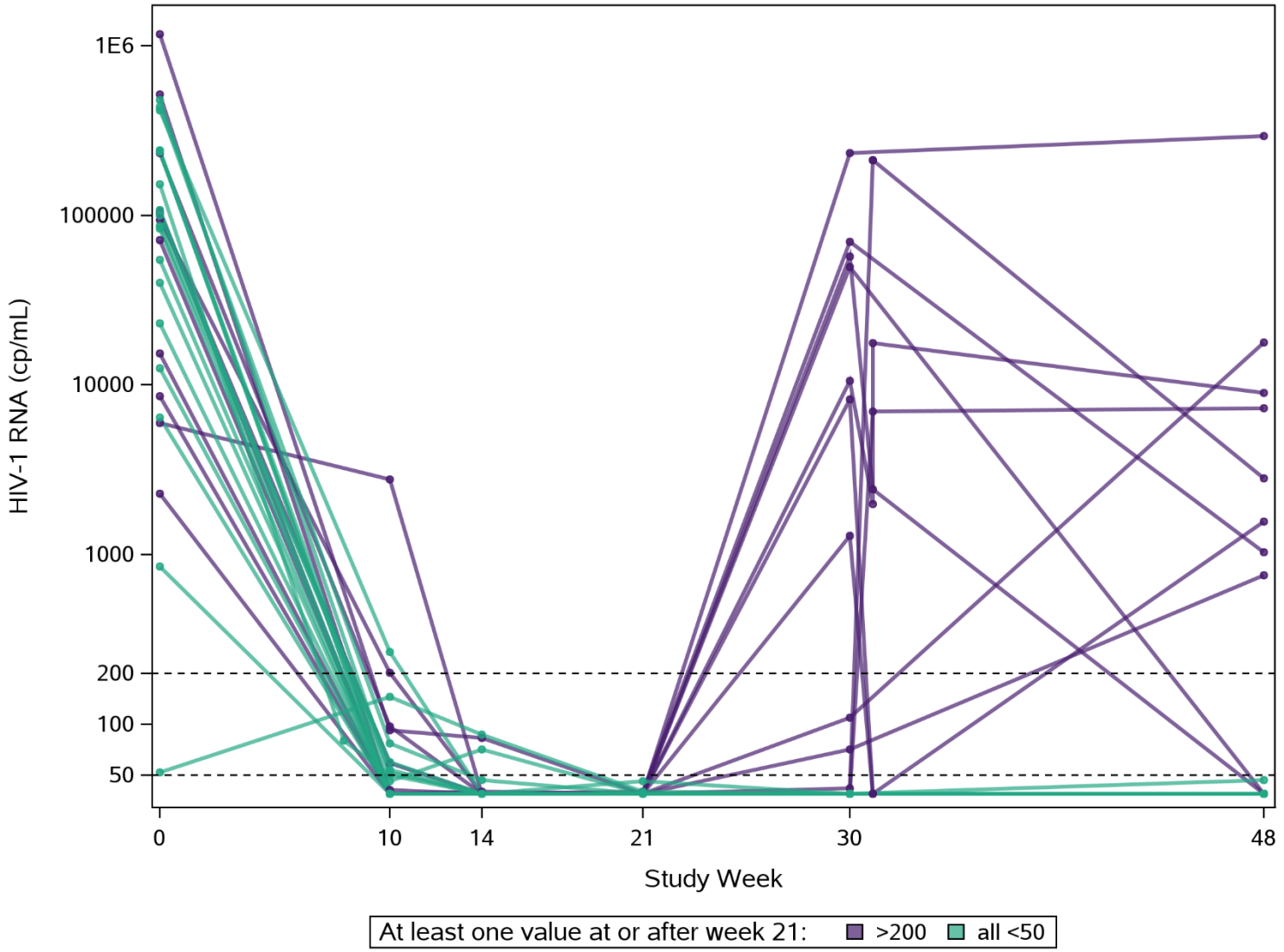
> 0.158 µg/mL (%)	99.1 (96.0 – 99.9)	99.4 (97.2 – 100)	31.3 (17.1 – 46)	63.6 (48.3 – 76.8)
> 0.064 µg/mL (%)	100 (99.2 – 100)	100 (99.7 – 100)	72.1 (56.9 – 84.0)	89.4 (78.8 – 96.0)
5th percentile C_{trough} (µg/mL)	0.310 (0.194 – 0.471)	0.298 (0.203 – 0.405)	0.0197 (0.008 – 0.035)	0.039 (0.017 – 0.071)

Simulation:

- In silico population of 10,000 individuals with resampled covariates
- Provided different dosing regimens
- Repeated 1,000 times to quantify uncertainty

Excellent virologic response on TB treatment

- **All participants suppressed by week 21 (~4 months of ART)**
- 11 had VL > 200 after week 21
  - 6 confirmed
  - 5 off ART
  - 6 poor adherence
  - 1 known re-suppressed



No safety concerns

- Grade ≥3 adverse events occurred in 20.7% (n=6) while on both antituberculosis and HIV treatment
- Single participant with rifamycin hypersensitivity reaction prior to starting ART
- Single SAE and study drug discontinuation: C. diff colitis
- No attributable liver events

Conclusions

- DTG clearance markedly increased by RPT 1200mg co-administration
- Twice-daily DTG dosing with RPT-based TB treatment:
  - Provided therapeutic exposures in all individuals
  - Safe
  - Achieved virologic suppression
- Findings support use of DTG BID (+ 2NRTIs) during RPT-based TB therapy

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A5406 investigators

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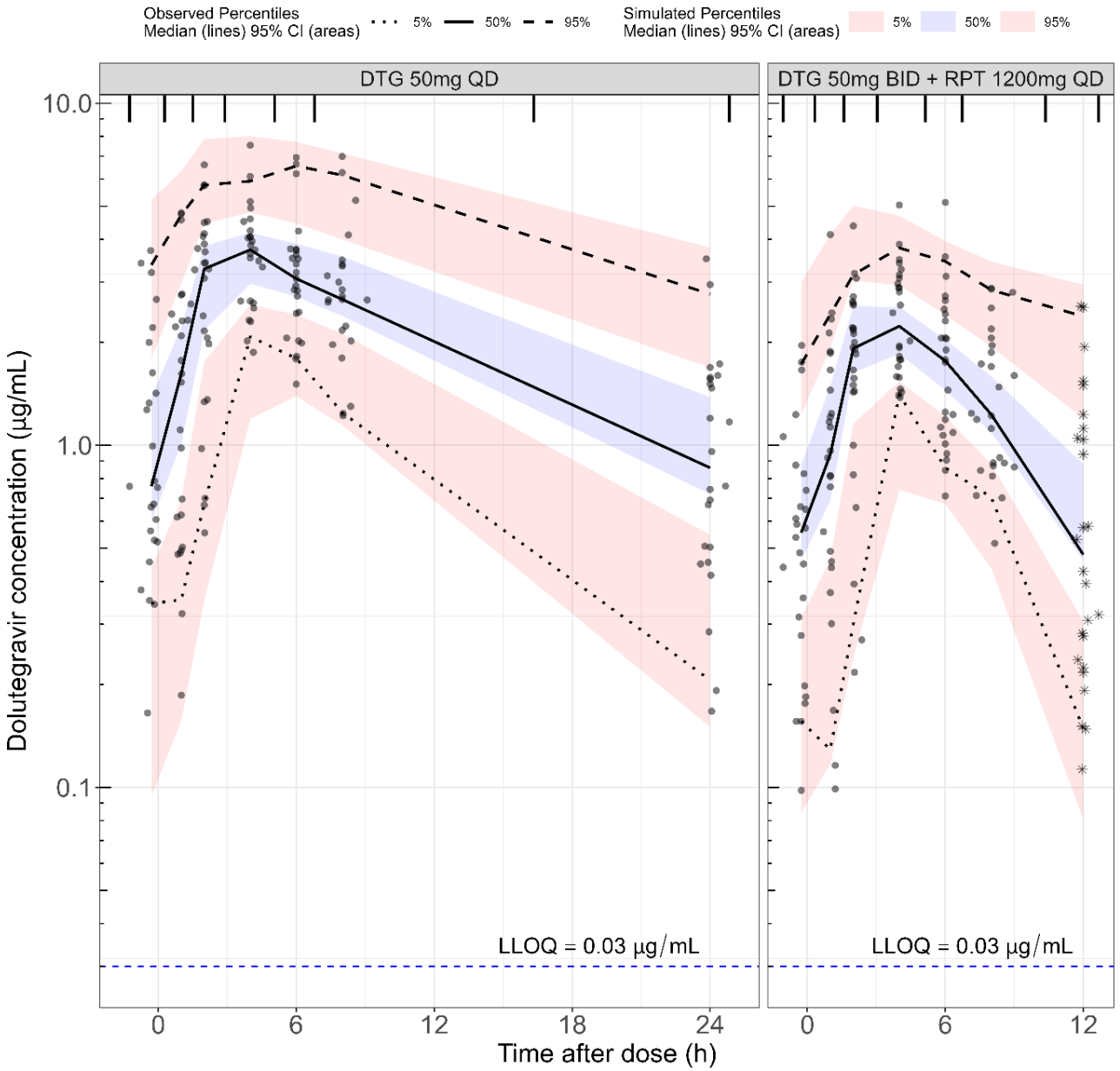
Supplementary

Key objectives and outcomes

Primary: adequacy of DTG exposure when dosed with RPT	
Objective	**Outcome measure**
Proportion of participants with model-predicted DTG Cmin above 158 ng/mL	Individual model-predicted lower bound of the 95% CI of the Cmin 5th percentile (compared with the efficacy target of 158 ng/mL)

Secondary: DDI effect of RPT on DTG	
Objective	**Outcome measure**
Characterize the drug-drug interaction between RPT 1200 mg and DTG BID	Model-predicted DTG PK parameters
Compare DTG exposures when dosed with daily RPT (at 50 BID) with the standard DTG 50 mg QD dose alone	Secondary PK parameters of DTG BID with RPT and DTG QD without RPT (compute GMR)

PK model



* 24 h concentrations plotted at 12 h in the BID arm

- **1-compartment model**
- **Absorption transit compartments**
- **Effects on clearance:**
  - **Rifapentine**
  - **Unconjugated bilirubin**
- **Effects on bioavailability:**
  - **Rifapentine**