POPULATION PHARMACOKINETIC ANALYSIS OF DOLUTEGRAVIR IN HIV/TB CO-INFECTED PEOPLE WITH AND WITHOUT RIFAMPICIN

Rajendra Singh,[1] Hardik Chandasana,[1] Kelly E. Dooley,[2] Richard Kaplan,[3] Noluthando Mwelase,[4] Beatriz Grinsztejn,[5] Eduardo Ticona,[6] Marcus Lacerda,[7] Omar Sued,[8] Elena Belonosova,[9] Mounir Ait-Khaled,[10] Konstantinos Angelis,[11] Dannae Brown,[12] Christine L. Talarico,[13] Allan R. Tenorio,[13] Michael R. Keegan,[10] Michael Aboud,[10] for the INSPIRING study group

[1]Clinical Pharmacology Modeling Simulation, GlaxoSmithKline, Collegeville, PA, USA; [2]Center for Tuberculosis Research, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [3]Desmond Tutu HIV Foundation, Cape Town, South Africa; [4]Clinical HIV Research Unit, Johannesburg, South Africa; [5]Instituto de Pesquisa Clínica Evandro Chagas FIOCRUZ, Rio de Janeiro, Brazil; [6]Hospital Nacional Dos de Mayo, Universidad Nacional Mayor de San Marcos, Lima, Peru; [7]Instituto Leônidas & Maria Deane (Fiocruz)/Tropical Medicine Foundation Dr Heitor Vieira Dourado, Manaus, Brazil; [8]Fundación Huésped, Buenos Aires, Argentina; [9]Regional Center for Prevention and Treatment of AIDS and Infectious Diseases, Russia; [10]ViiV Healthcare, Brentford, UK; [11]GlaxoSmithKline, Stockley Park, Uxbridge, UK; [12]ViiV Healthcare, Abbotsford, VIC, Australia; [13]ViiV Healthcare, Research Triangle Park, NC, USA

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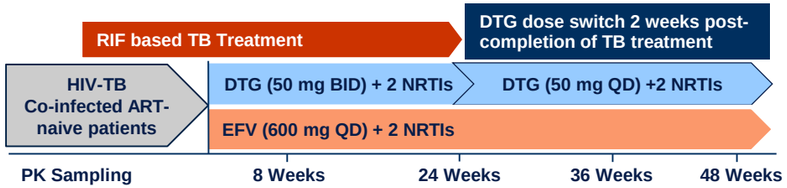
Introduction

- Dolutegravir (DTG) based regimens are recommended by the World Health Organization (WHO) as preferred 1st and 2nd line treatments.
- DTG is a substrate of UGT1A1 and CYP3A4, both of which are induced by the anti-TB medicine rifampicin (RIF). Characterizing the efficacy, safety, and PK to establish the best dose of DTG in patients with TB is a high priority. A prior study in healthy participants showed that the reduction in DTG concentrations was compensated by increasing DTG dosage from 50 mg once daily (QD) to 50 mg twice daily (BID).
- INSPIRING (NCT02178592), a Phase IIIb, noncomparative, active control, randomized, open-label study of DTG in HIV-1 infected, ART-naive adults with drug-sensitive TB, demonstrated high efficacy and good immunologic response of DTG 50 mg BID during concomitant RIF-based TB therapy (Dooley et al, 2019).
- The objective of this analysis was to characterize the population pharmacokinetics (PopPK) of dolutegravir in HIV/TB co-infected patients and identify cofactors, e.g. use of the enzyme inducer RIF, that influence DTG PK.

Methods

Figure 1. Schematic Representation of Study Design



- The subjects received DTG with and without TB treatment (isoniazid, rifampin, pyrazinamide, ethambutol) for 52 weeks.
- Pre-dose plasma samples were collected at Weeks 8, 24, 36, 48 and post-dose samples at Weeks 8 and 36.
- A nonlinear mixed-effects modeling approach was used for the population pharmacokinetic analysis (NONMEM version 7.3; ICON, Ellicott City, MD). The population PK model of DTG was developed with 430 plasma concentrations from 65 participants.
- The final model was used to compute individual estimates of steady-state AUC(0-τ), Cmax, and Cτ for all subjects included in the population PK analysis with and without RIF treatment by an empirical Bayes estimation method.

Results

- The PK of DTG following oral administration were adequately described by a one compartment model with absorption lag time (tlag) and first order absorption and elimination.
- The population estimate of apparent volume of distribution (V/F) and absorption rate (Ka) were 28.9 L and 2.02 hr-1, respectively, and tlag was fixed to 0.263 h.
- Comedication with strong enzyme inducer RIF significantly altered CL/F of DTG and it increased by ~2-fold. The estimates of clearance (CL/F) with and without rifampicin were 1.09 L/hr and 2.36 L/hr, respectively (Table 1).
- The diagnostic plots for the final model (Figure 2) indicated that the model adequately described the data.

Table 1. Population Parameter Estimates

$CL/F=1.09 * (WT/70)^{0.75} * (AGE/33)^{0.256} * (ALBU/34)^{-0.863}$ (Without RIF)

$CL/F=2.36 * (WT/70)^{0.75} * (AGE/33)^{0.256} * (ALBU/34)^{-0.863}$ (With RIF)

$V/F=28.9 * (AGE/33)^{0.256} * (ALBU/34)^{-0.863}$

	NONMEM Estimates		Bootstrap Estimates	
	Estimate	RSE%	Median	95% CI
CL/F (L/hr)	1.09	7	1.09	0.98-1.23
V/F (L)	28.9	10	28.66	24.81-34.02
Ka (1/hr)	2.02	35	1.90	1.27-3.64
Tlag (hr)	0.263	Fixed	0.263	Fixed
CL/F (L/hr) ~ WT	0.750	Fixed	0.750	Fixed
CL/F (L/hr) with RIF	2.36	7	2.38	2.13-2.62
AGE on CL/F and V/F	0.256	50	0.250	0.001-0.47
ALBU on CL/F and V/F	-0.863	27	-0.869	-1.27- (-0.49)
Inter-Individual Variability (IIV)				
CL /F	0.05	22	0.05	0.02-0.11
V/F	0.05	57	0.07	0.01-0.19
IOV on CL/F	0.14	12	0.14	0.09-0.21
Residual Variability				
Proportional	0.076	26	0.074	0.04-0.11
Additive	0.198	36	0.186	0.06-0.32

Figure 2. Goodness of Fit Plots

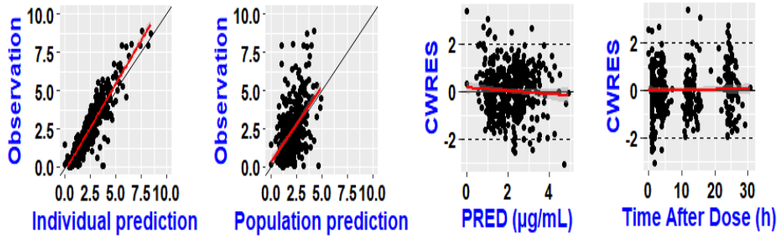


Table 2. Summary of Individual Steady-State PK Parameters

Statistics	AUC(0-tau) (hr*µg/mL)	Cmax (µg/mL)	Ctrough (µg/mL)
Dolutegravir (50 mg BID) with Rifampicin (n=65)			
Geomean (95% CI)	46.8 (42.8-51.7)	3.97 (3.67-4.3)	1.24 (1.05-1.48)
Dolutegravir (50 mg QD) without Rifampicin (n=47)			
Geomean (95% CI)	52.6 (46.2-59.9)	4.34 (3.92-4.81)	1.24 (0.993-1.55)

Ctrough for BID dosing was 12 hr and for QD dosing was 24 hr

Conclusions

- The PK of DTG is described by a linear one-compartment PK model in HIV/TB co-infected patients.
- Co-administration with the enzyme inducer RIF increased DTG CL/F by 2-fold. DTG BID dosing (50 mg) with RIF was adequate to achieve comparable exposure (AUC and Ctrough) as 50 mg QD administration without RIF (Table 2).
- The effects of age, albumin, and body weight as covariates on DTG PK were statistically significant based on objective function values but were not clinically significant and didn't require dose adjustment.

Reference: Dooley KE, Kaplan R, Mwelase N, et al. "Dolutegravir-based antiretroviral therapy for patients co-infected with tuberculosis and HIV: a multicenter, noncomparative, open-label, randomized trial." *Clinical Infectious Diseases* (2019).