PESAB09

Pharmacokinetic and 48 week Efficacy of Once-Daily vs Twice-Daily Dolutegravir among patients with Human Immunodeficiency virus/Tuberculosis coinfection receiving rifampicin based tuberculosis therapy: A Randomized control trial

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Background:

- Concurrent use of Rifampicin (RIF) and dolutegravir (DTG) reduce DTG exposure, thus, DTG 50 mg twice-daily is currently recommended.
- Food increases DTG concentrations in healthy volunteers by 33 – 66%.
- Since DTG is currently and massively being scaling up as preferred HIV treatment in many resource limited countries (RLS), therefore, optimal dose of DTG in HIV/TB is urgently needed.
- We therefore investigated the effect of RIF on DTG exposure when dosed at 50 mg once daily with food.
- DTG 50mg once daily maybe more convenient than 50 mg twice daily and generic TLD (tenofovir disoproxil fumarate/lamivudine/doluteravir) could be easily used without adding extra 50 mg DTG.

Methods:

- HIV-NAT 254 (DTG/RIF) study is a RCT to evaluate efficacy and safety of DTG 50 mg QD with food and DTG 50 mg twice daily among 200 HIV/TB receiving RIF in Thailand
- For safety, this study is conducted in 2 steps: step 1 among first 40 participants (included in this analysis) (Figure1).
- DTG concentrations were determined by validated LC-MS/MS.
- PK parameters were estimated by WinNonLin.

Results:

- Table 1 shows demographic data 87.5% were males with median age of 32 years; and median body weight was 60.4 kg.
- Median baseline CD4 was 194 (IQR 46-238) cells/μL. Median baseline HIV-1 RNA was 4.9 (IQR 3.6-5.6) log10copies/mL; 43% had HIV-1 RNA >100,000 copies/mL.
- As expected GMR (90%CI) trough concentration (Ctrough), maximal concentration (Cmax) and area under curve (AUC0-τ) were not within the bioequivalence range of 0.8-1.25: [0.19 (0.1-0.35), 0.72 (0.49-1.06) and 0.42 (0.28-0.64)] respectively. (Table2)
- In addition, 70% and 95% of study and control arm participants had DTG Ctrough>64 ng/mL.
- At week 48, 90% of the participants in the study arm (18/20) and control arm (18/20) had HIV-1 RNA <40 copies/mL using ITT analysis.
- Premature study discontinuation occurred in 3 cases (1 in study arm: RIF-induced cholestasis; 2 in control arm: rash and non-TB).

Table 1: Demographic data of the study participants

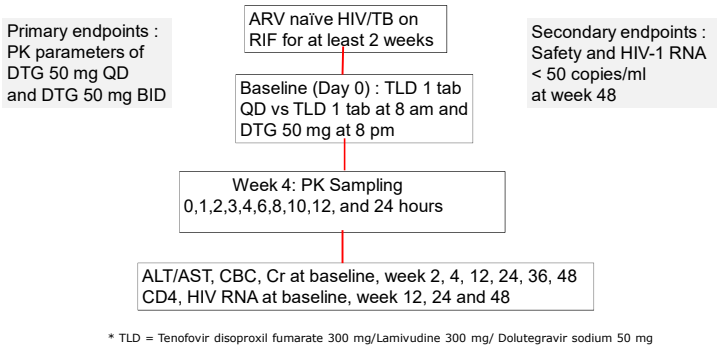
	Total	DTG 50 mg QD with food (n=20)	DTG 50 mg BID (n=20)
Age (years), median (IQR)	36.4 (29.4-48.0)	38.2 (30.4-48.1)	36.3 (28.6-48.5)
Male, n (%)	35 (87.5)	17 (85)	18 (90)
Weight (kg), median (IQR)	60.4 (48.7-64.4)	60.4 (48.8-63.6)	59.6 (48.7-65.6)
Body mass index , median (IQR)	20.5 (18.6-21.7)	20.5 (19.1-21.3)	20.5 (18.2-21.9)
Median (IQR) CD4 cell count	194 (46-238)	211 (49-383)	153.5 (42-237.5)
Median (IQR) HIV1-RNA log10 copies/mL	4.9 (4.2-5.6)	5.2 (4.2-5.6)	4.9 (4.3-5.7)

Table 2 Pharmacokinetic parameters of dolutegravir among 2 doses (dolutegravir 50 mg once daily with food and dolutegravir 50 mg twice daily) in rifampicin treated HIV/TB co-infected patients

	DTG 50 mg QD with food (n=20)	DTG 50 mg BID (n=20)	GMR (90%CI)	P-value
C_{max} (ng/mL)	1818 (1160 - 2849)	2521 (2133-2978)	0.72 (0.49-1.06)	0.16
AUC0-τ (ng·hr/mL)	16356.6 (10226-26161)	38876 (31599-47828)	0.42 (0.28-0.64)	<0.001
C_{trough} (ng/mL)	85 (46-155)	444 (288-684)	0.19 (0.1-0.35)	<0.001
C_{trough} > 64 ng/mL , n(%)	14 (70%)	19 (95%)	-	0.04
C_{trough} >158 ng/mL , n(%)	6 (30%)	18 (90%)	-	<0.001
T_{max} (hr)*	2.5 (1.5-4.5)	2.4 (2.1-2.6)	-	0.90
$t_{1/2\beta}$ (hr) *	5.4 (4.9-6)	5.2 (4.5-6)	1.05 (0.91-1.22)	0.58
CL_{ss}/F (L/hr)	2862 (1778- 4607)	1949 (1515-2506)	1.47 (0.95-2.27)	0.14

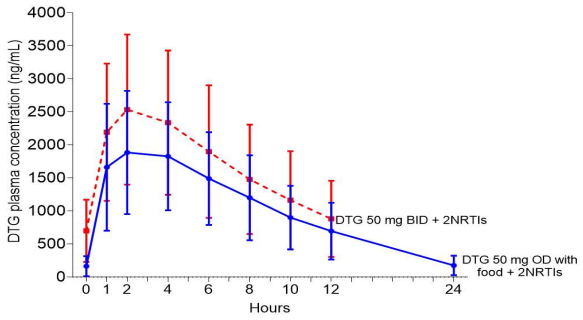
The data is described with Geometric mean (95%CI), GMR: Geometric mean ratio
*Median (minimum-maximum); C_{trough} : trough concentration; C_{max}: maximum concentration; $AUC_{0-\tau}$:area under curve, T_{max}: time to peak concentration; $t_{1/2\beta}$: elimination half-life ; CL_{ss}/F : oral clearance

Figure 1. DTG/RIF PK study design



* TLD = Tenofovir disoproxil fumarate 300 mg/Lamivudine 300 mg/ Dolutegravir sodium 50 mg

Figure 2. 24 hour pharmacokinetic time-curve of dolutegravir plasma concentrations



Conclusions:

- There was substantial reduction in DTG plasma concentrations when co-administered with RIF, However, DTG once-daily regimen with food had robust virological suppression at week 48.
- Larger study of once-daily and twice-daily DTG is underway to confirm this finding.

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