PHARMACOKINETICS OF DOLUTEGRAVIR 100 MG ONCE-DAILY WITH RIFAMPICIN

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BACKGROUND

- The WHO estimated in 2015 worldwide there are 10.4 million people infected with TB and 1.2 million (11%) co-infected with HIV
- TB causes 25% of all deaths among HIV-infected individuals
- First-line anti-TB regimen – **rifampicin (RIF)**, isoniazid, pyrazinamide and ethambutol
- Dolutegravir (DTG) – an integrase strand transfer inhibitor
  - 50 mg once-daily for ART-naïve and InSTI-naïve patients
  - 50 mg twice-daily for patients who harbour InSTI-resistant viruses.
- DTG is primarily metabolised by UGT1A1, with CYP3A4 as a minor route
- RIF is a potent CYP3A4 and UGT1A1 inducer

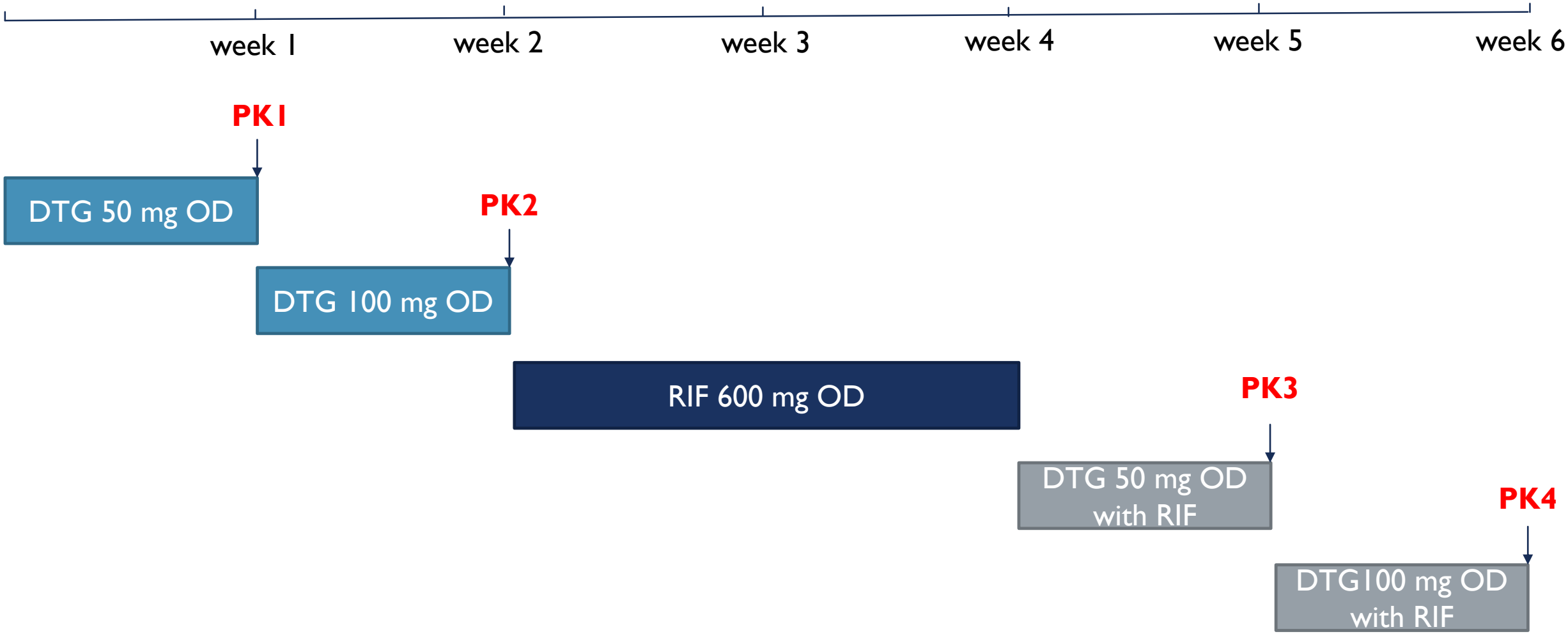
DRUG-DRUG INTERACTION

- RIF can lower the concentration of DTG
- Dooley *et al* (2013) doubled the dose of DTG to 50 mg-daily with RIF in healthy volunteers – modest increased in plasma DTG AUC (33%) and Cmax (18%) compared with DTG once-daily alone
- Interim 24 week analysis from the phase 2 INSPIRING study – DTG 50 mg administered twice-daily with RIF was effective and well-tolerated in HIV/TB co-infected individuals

OBJECTIVE

- No data on the exposure of DTG 100 mg once-daily with RIF – beneficial because of improved adherence?
- We investigate the exposure of DTG 50 mg and 100 mg once-daily with RIF versus DTG 50 mg and 100 mg alone in healthy volunteers

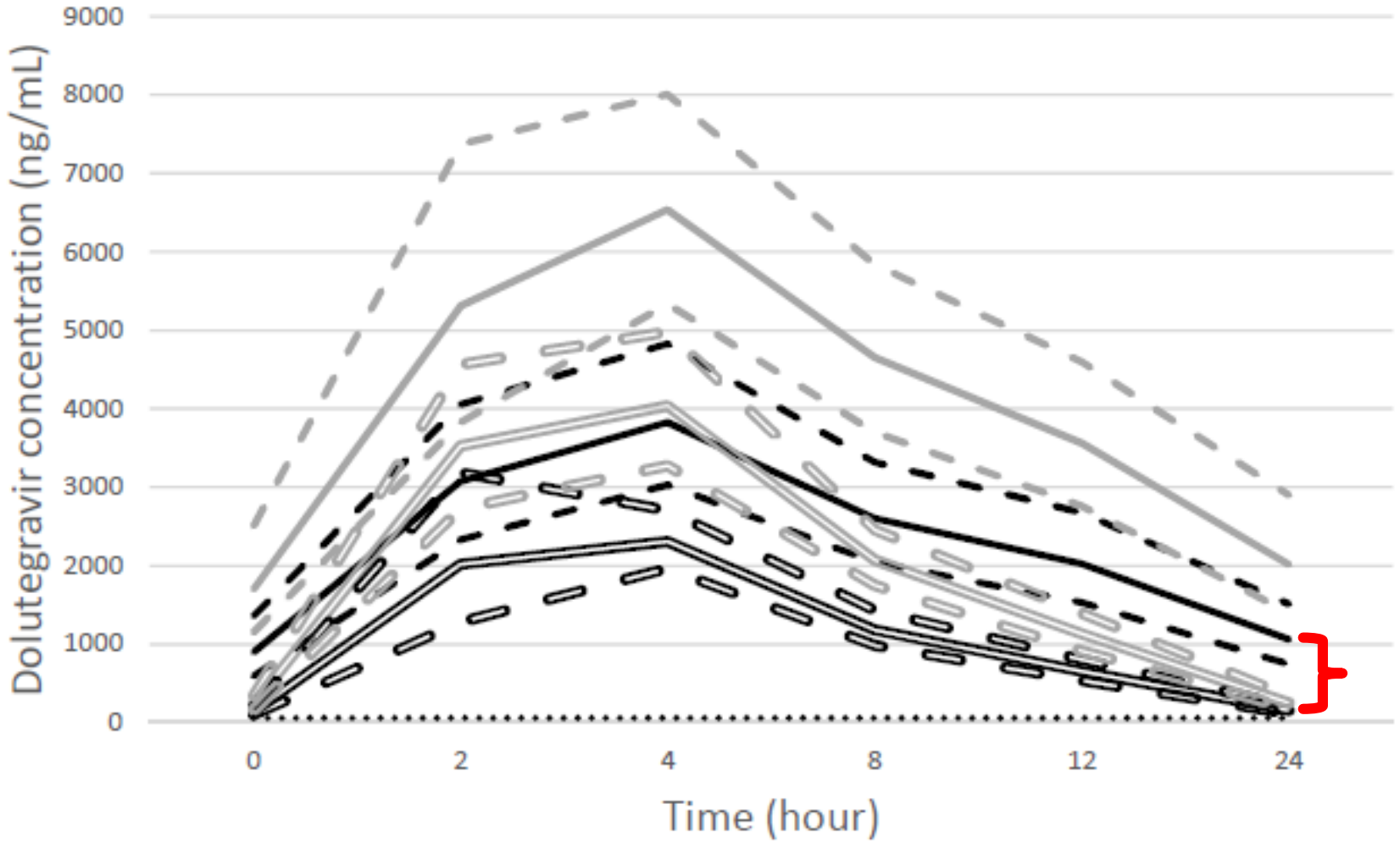
STUDY DESIGN



STUDY POPULATION

- 16 subject screened and enrolled; 14 completed all PK sampling days
- One withdrew consent for personal reason; one stopped the study due to allergic reaction to RIF
- The median (range) : age 32 (22-55) years and BMI 27 (18-32) kg/m^2
- Nine (64%) were male
- 11 (79%) were of white ethnicity, two black Caribbean and one was of ethnic Asian origin

DOLUTEGRAVIR PK CURVES



PK1-black solid line
PK2-grey solid line
PK3-black hollow line
PK4-grey hollow line

Short-dashed lines represents 95% CI

Black dotted line – an in vitro protein-adjusted IC_{90} of 64 ng/mL

STEADY STATE DTG PK PARAMETERS

Pharmacokinetic parameter	50 mg DTG (PK1)	100 mg DTG (PK2)	50 mg DTG with RIF (PK3)	100 mg DTG with RIF (PK4)
C_{max} (ng/mL)	3969 (3213-4903)	6746 (5571-8169)	2569 (2184-3023)	4312 (3546-5245)
CV%	34	31	28	38
C_{24h} (ng/mL)	1061 (745-1509)	2017 (1401-2904)	**156 (115 - 214)**	**251 (187 - 337)**
CV%	59	53	60	56
AUC_{24h} (hr*ng/mL)	52101 (40195-67534)	92306 (72227-117967)	22750 (19012-27222)	38731 (31867-47073)
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GEOMETRIC MEAN RATIOS OF DTG PK PARAMETERS

	GMR (90% CI)				
PK parameter	100 mg DTG vs 50 mg DTG (PK2/PK1)	100 mg DTG + RIF vs 50 mg DTG + RIF (PK4/PK3)	50 mg DTG + RIF vs 50 mg DTG (PK3/PK1)	100 mg DTG+ RIF vs 100 mg DTG (PK4/PK2)	100 mg DTG + RIF vs 50 mg DTG (PK4/PK1)
C_{max}	1.70 (1.56-1.85)	1.68 (1.43-1.97)	0.65 (0.55-0.75)	0.64 (0.55-0.74)	**1.09 (0.97-1.21)**
C_{24h}	1.90 (1.74-2.08)	1.60 (1.40-1.84)	0.15 (0.13-0.17)	0.12 (0.10-0.15)	**0.24 (0.20-0.28)**
AUC_{24h}	1.77 (1.61-1.94)	1.70 (1.49-1.95)	0.44 (0.37-0.52)	0.42 (0.35-0.50)	**0.74 (0.64-0.86)**

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76%

CONCLUSIONS

- Dooley et al showed lower DTG concentrations both without and with RIF: discrepancies may originate from whether DTG was administered in the fasted state or with food
- Maximum induction of RIF achieved at three weeks
- Drug absorption reached saturation limit in the range of 50 – 100 mg DTG; RIF has no additional effect on the saturation limit of DTG absorption
- RIF significantly reduced DTG 100 mg once-daily C_{24h} by 76% and 50 mg once-daily by 85% compared with 50 mg DTG once-daily alone
- DTG C_{24h} in all study subjects remained 2-14 fold above the *in vitro* protein adjusted IC_{90} of 64 ng/mL (but <300 ng/mL in the majority of subjects

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Imperial College London

Chelsea and Westminster Hospital NHS
NHS Foundation Trust

St Stephen's
CLINICAL RESEARCH

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