Pharmacokinetics of dolutegravir with and without darunavir/cobicistat in healthy volunteers

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BACKGROUND

Novel HIV treatment strategies, including NRTI-free dual therapies, are increasingly being investigated.1 Aimed at reducing ART toxicity and costs, results have been promising, particularly during the maintenance phase of treatment. The integrase inhibitor, dolutegravir (DTG), combined with boosted darunavir (DRV), both potent and with high resistance barriers, potentially offers a powerful yet safe and tolerable ART dual therapy regimen. The DUALIS PK sub study has shown that when DTG 50mg once-daily (OD) and DRV/ritonavir (r) 800/100mg OD are co-administered, adequate steady-state drug concentrations of both drugs are achieved2 (Median Cmax were 3427ng/mL for DTG and 6170ng/mL for DRV, Median Cmin 637ng/mL for DTG and 1245ng/mL for DRV and Median AUICmax were 28609 ng*h/mL for DTG and 49920 ng*h/mL for DRV). In earlier studies, DTG trough concentrations doubled when switching from DRV/r to DRV/cobicistat (c), in contrast to a 38% decrease with DRV/r twice daily.3 However, no formal interaction studies between DTG and DRV/c have been published to date. We aimed to describe the steady-state PK of DTG 50mg OD and of DRV/c 800/100mg OD when co-administered in healthy volunteers.

METHODS

This phase 1, open label, 57 day, cross over, pharmacokinetic (PK) study, included healthy volunteers aged 18-65years, who were randomized to one of two groups, as below. All doses were administered once daily. Each group underwent intensive PK sampling (0-24 hours post-dose) on days 14, 35 and 56 and DTG/DRV/c concentrations were measured by validated Liquid Chromatography–Mass Spectrometry methods.4,5

RESULTS

Study population

25 healthy volunteers were screened, 21 attended baseline and 20 completed all PK phases (11 in group 1 and 9 in group 2; 1 subject withdrew for personal reasons). Median age was 35.5 years (range 24-63), 13 participants were female and median BMI was 27 (range 20-31). 13 subjects described themselves as Caucasian, 6 as Black African/Caribbean and 1 as White and African. The studied drugs were well tolerated, with no grade 3 or 4 side effects or laboratory abnormalities.

Pharmacokinetics

Table 1 describes the PK parameters of DTG and DRV/c when administered alone or together in the co-administration phase, in both groups combined.

Table 1: DTG, DRV and Cobi steady state pharmacokinetic (PK) parameters, expressed as geometric mean (GM), 90% confidence intervals (CI), coefficient of variation (CV) and GM Ratios (GMR, alone/co-administered)

Pharmacokinetics

• Duranavir/cobicistat

DRV GM (DRV+c/DTG versus DRV/c alone) and 90%CI for Cmax, AUC and Cmin were 0.90 (0.83-0.98), 0.93 (0.86-1.00) and 0.93 (0.79-1.11) and for cobicistat Cmax, AUC and Cmin were 0.96 (0.89-1.04), 0.98 (0.88-1.08) and 0.98 (0.79-1.22).

Cmax remained 7- to 32-fold above the protein-adjusted IC90 (>84ng/mL) for dolutegravir and 1.6 to 11-fold above the protein-adjusted EC90 (200ng/mL) for darunavir for all subjects (except for one participant with Cmin1,428 ng/mL but Cmax, 185 ng/mL). Figures 1 and 2 illustrate DTG and DRV GM at all time points in relation to the DTG IC90 and DRV EC90.

Discussion

Concentrations of DTG during co-administration with DRV/c decreased by 10% and those of DRV with DTG by 7%. GM minimum concentrations (Cmin) for both drugs stayed well above the protein-adjusted IC90 (DTG) and IC90 (DRV) at all time points; suggesting this combination can be prescribed safely in the treatment of HIV-1, including in patients harbouring resistance that benefit from optimal antiretroviral exposures.