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PK & Safety of Darunavir/Cobicistat with Once-Weekly Isoniazid/Rifapentine

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BACKGROUND

- Once-weekly isoniazid (INH) with rifapentine (RPT) for 3 months (3HP) is a recommended treatment for latent tuberculosis infection (LTBI) in PWH.[1,2]
- Drug-drug interactions between 3HP and ARVs are of concern, notably subtherapeutic ARV exposures due to induction of metabolizing enzymes by RPT, resulting in limited options for the concomitant use of 3HP with ARVs.
- There are currently no data on the pharmacokinetics (PK) of boosted protease inhibitors in combination with 3HP.

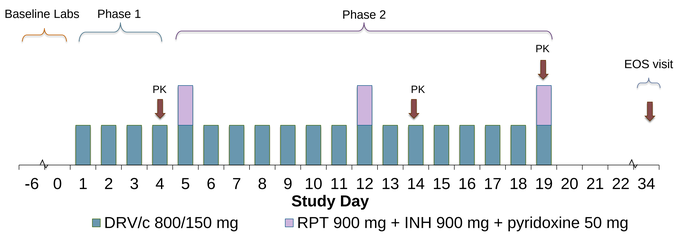
OBJECTIVE

- To examine the PK and safety of darunavir boosted with cobicistat (DRV/c) when co-administered with 3HP.

METHODS

- This was an open-label, fixed sequence, 2-period crossover study in healthy volunteers (Figure 1) (NCT02771249).
- Eligibility Criteria:
  - Inclusion: persons without HIV age 18-65 years, weight 45-120 kg, BMI 18-30; negative for HIV, TB, and hepatitis A/B/C infection; no alcohol consumption while on study
  - Exclusion: known hypersensitivity to study medications; use of concomitant prescription, OTC, herbal, or holistic medications within 5 half-lives of study medications (except for intermittent use of select OTCs)

Figure 1. Study Schematic



- DRV concentrations were quantified using a validated LC-MS-MS method.
- PK parameters were calculated using noncompartmental methods (Phoenix WinNonlin, Certara®, Inc.).
- Geometric mean ratios (GMR) with 90% confidence intervals (CIs) were calculated and compared between phases using mixed effects models.
- Adverse events (AEs) were graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric AEs (Version 2.0, November 2014).

DRV exposures were **significantly decreased** with 3HP coadministration. Concomitant use of DRV/c with 3HP should be avoided.

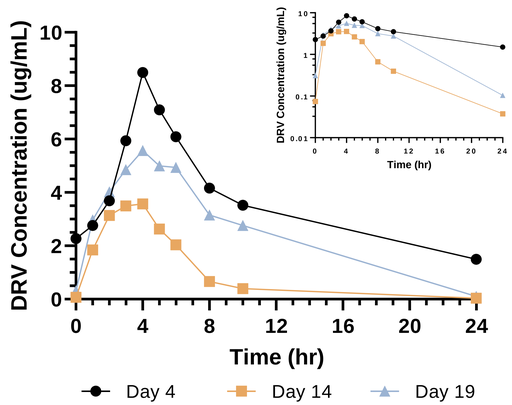
RESULTS

- 13 participants were enrolled (Table 1)
  - 2 withdrew after the Day 4 PK
  - 1 withdrew after the Day 14 PK

Table 1. Participant Demographics

Characteristic	
Sex, n(%)	
Male	10 (77%)
Female	3 (23%)
Race, n(%)	
White	8 (62%)
Black	3 (23%)
Other	2 (15%)
Ethnicity, n(%)	
Hispanic/Latino	2 (15%)
Age (yr), median (range)	25 (21-45)
Weight (kg), median (range)	71 (62-85)

Figure 2. DRV Concentration-Time Curves



Data presented as mean concentrations by nominal time. Results reflect concentration profiles from 13 participants on Day 4, 11 participants on Day 14, and 10 participants on Day 19.

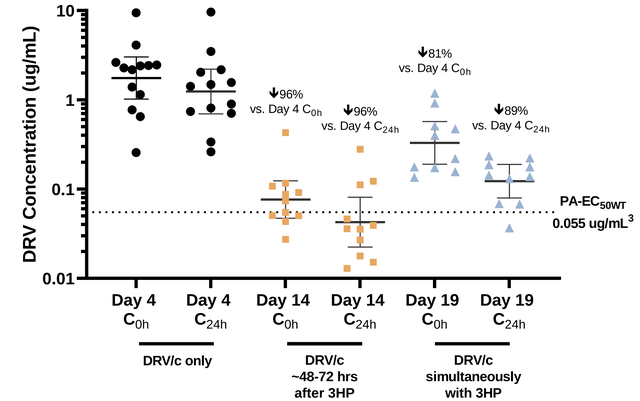
Table 2. PK Parameters for DRV, when given as DRV/c Alone and in Combination with 3HP

PK Parameter	DRV/c alone (Day 4) (n=13)	DRV/c + 3HP (Day 14) (n=11)	DRV/c + 3HP (Day 19) (n=10)	Day 14 vs. Day 4* (GMR [90% CI])	Day 19 vs. Day 4* (GMR [90% CI])	Day 14 vs. Day 19* (GMR [90% CI])
$AUC_{0\text{-}24h}$ (hr*ug/mL)	82.6 (59.9%)	23.1 (56.8%)	49.4 (37.6%)	0.29 (0.24, 0.35)	0.64 (0.53, 0.78)	0.45 (0.37, 0.55)
C_{max} (ug/mL)	7.86 (42.2%)	4.53 (45.7%)	6.22 (39.3%)	0.59 (0.50, 0.69)	0.83 (0.70, 0.98)	0.71 (0.60, 0.84)
T_{max} (hr)	4.0 (2.7-4.0)	3.0 (2.0-4.0)	3.4 (2.0-4.3)	-1.0 (-2.0 to 1.0)	-0.33 (-3.0 to 0.2)	0.0 (0.0, 0.04)
C_{0h} (ug/mL)	1.75 (112%)	0.08 (82.0%)	0.33 (90.1%)	0.04 (0.03, 0.07)	0.19 (0.11, 0.34)	0.22 (0.13, 0.40)
C_{24h} (ug/mL)	1.24 (122%)	0.04 (122.0%)	0.12 (66.2%)	0.04 (0.02, 0.06)	0.11 (0.07, 0.18)	0.33 (0.19, 0.54)
$t_{1/2}$ (hr)	10.8 (85.0%)	4.44 (31.2%)	3.37 (11.3%)	0.45 (0.37, 0.56)	0.35 (0.28, 0.43)	1.31 (1.05, 1.64)
CL_{ss}/F (L/hr)	9.68 (59.9%)	34.6 (56.8%)	16.2 (37.6%)	3.44 (2.87, 4.12)	1.55 (1.29, 1.88)	2.21 (1.83, 2.68)
V/F (L)	151.3 (53.1%)	221.8 (78.9%)	78.8 (34.8%)	1.54 (1.23, 1.93)	0.53 (0.42, 0.67)	2.89 (2.29, 3.65)

$AUC_{0\text{-}24h}$ = area under the concentration time curve from time 0 through 24 hours post-dose; C_{max} = maximum concentration; C_{0h} = time 0 (pre-dose) concentration; C_{24h} = concentration at 24 hours post-dose; $t_{1/2}$ = half-life; CL_{ss}/F = apparent oral clearance at steady-state; V/F = apparent volume of distribution. Data for each phase presented as geometric mean (geometric CV%) except for T_{max} (reported as median [IQR]); phase comparisons presented as GMR (90% CI) except for Tmax (reported as median (IQR) difference).
*All GMR comparisons were statistically significant (p <0.05).

RESULT (CONTINUED)

Figure 3. Geometric mean (95% CI) DRV Trough Concentrations



See Table 2 for 90% CIs. All paired comparisons were statistically significant (p<0.05).

Safety Results

- Nearly all AEs related to study drugs were mild or moderate in severity.
  - 69 AEs were reported, of which 51 were possibly or probably related to study medication(s).
  - The most common AEs were CNS (n=12) or GI (n=8) related.
- Only one grade 3 or higher AE occurred, which was a grade 3 transient direct bilirubin increase deemed possibly related to DRV/c and INH and probably related to RPT.

CONCLUSIONS

- DRV $AUC_{0\text{-}24h}$ and C_{24h} were decreased by up to 71% and 96%, respectively, following 3HP initiation. Multiple trough concentrations fell below the DRV PA-EC_{50} of 0.055 ug/mL for wildtype virus.
- Temporal relationships between 3HP coadministration and the extent of induction or mixed inhibition/induction of DRV metabolism were identified.
- Coadministration of DRV/c with 3HP should be avoided.

ACKNOWLEDGEMENTS

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