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Early Termination of a PK Study Between Dolutegravir and Weekly Isoniazid/Rifapentine

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Background

- Once-weekly isoniazid (INH) with rifapentine (RPT) (wHP) is a 3-month treatment regimen for latent tuberculosis infection (LTBI). This regimen is of interest in the HIV-infected population due to its shortened treatment duration vs. other LTBI regimens.
- Drug interaction data between antiretroviral (ARV) medications and wHP are limited. RPT can induce CYP and UGT enzymes similarly to other rifamycins, which could lead to decreased ARV drug exposure and subsequent treatment failure.
- Coadministration of wHP with raltegravir- or efavirenz-containing ARV regimens is included in both the DHHS and IAS-USA HIV treatment guidelines based on available PK data with RPT. The IAS-USA guidelines also recommend coadministration with dolutegravir (DTG), which is based on extrapolation of PK data with rifampin and the assumption that twice-daily DTG dosing will be necessary to overcome induction by RPT.

Study Objective

- To characterize the effects of wHP on the pharmacokinetics (PK) of DTG, an ARV agent recommended in 1st-line treatment regimens for HIV-infected adults.

Methods

Study Design

- This was an open-label, intrasubject drug-drug interaction study to evaluate the steady-state PK of DTG with wHP in HIV-negative healthy volunteers (n=10)
- This study was approved by the NIAID IRB (ClinicalTrials.gov identifier NCT02771249)

Figure 1. Study Schematic

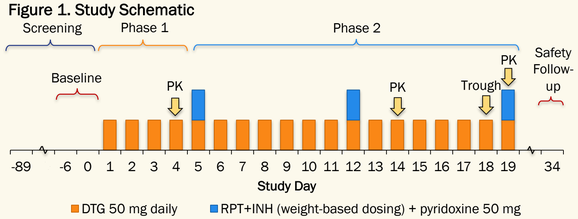


Fig 1. PK sampling at time 0 (pre-dose), 2, 3, 4, 5, 6, 8, 10, and 24 hours post-dose on each PK day. A single trough concentration was collected on Day 18. Safety labs were drawn with the pre-dose samples and 24 hours after each dose of RPT+INH. Weight-based dosing of RPT and INH was as follows: RPT = 750 mg if <50 kg, and 900 mg if >50 kg; INH = 15 mg/kg, max dose 900 mg.

Eligibility Criteria

- **Inclusion:** healthy adult volunteers as determined by medical history, physical exam, and screening labs; 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; concomitant prescription, OTC, herbal, or holistic medications within 5 half-lives of study medications (exceptions for intermittent use of OTC analgesics on non-PK days)

Analytical & Statistical Methods

- DTG plasma concentrations were determined using a UPLC method with fluorescence detection. RPT, 25-desacetyl-RPT, and INH concentrations were determined with previously described HPLC-MS/MS methods (Peloquin CA, et al. *Int J Tuberc Lung Dis* 1999;3:703).
- PK parameters for DTG, RPT, 25-desacetyl-RPT, and INH were determined using non-compartmental methods (Phoenix WinNonlin, v6.4). DTG PK parameters were compared between set PK time points to generate geometric mean ratios (GMR) with 90% CIs. P-values were calculated using 2-tailed paired t-tests.
- Symptom and safety laboratory assessments were graded according to the Division of AIDS AE table (November 2014, v2.0).
- Cytokine assays were performed with plasma samples from PK and follow-up safety visits. Cytokines examined included: IFN-Y, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, and TNF-α (V-PLEX® Proinflammatory Panel 1, Meso Scale Discovery®, Rockville, MD). Other inflammatory markers included sCD14 (R&D Systems, Minneapolis, MN), SCD163 (Aviscera Bioscience, Santa Clara, CA), and CRP (Meso Scale Discovery®, Rockville, MD).

Results

Study Population

- Four subjects were enrolled before study termination:
  - 3 males (2 white, 1 African American), 1 female (Hispanic)
  - Median age 43 years (range 21-46), weight 77.2 kg (range 74.1-95.8)
  - Subject 3 voluntarily withdrew prior to Day 19

Safety Results

- This study was terminated early due to the development of flu-like syndrome and transaminase elevations (Grade 2-4) in 2 subjects, with symptom onset ~8-10 hours after the last doses of DTG, RPT, and INH on Study Day 19 (Figure 2).
- **Subject 1:** experienced N/V, headache, and fever (max 39.1°C) for ~24 hrs after onset. A left-shift in the WBC differential also occurred.
  - Symptoms resolved by 72 hrs post-dose, at which point he developed transaminase elevations
- **Subject 4:** experienced N/V, fever (max 39.5°C), and was hospitalized for orthostatic hypotension (97/50 supine, HR 97; BP 79/51 standing, HR 80;), which required IV fluid resuscitation. A left-shift in her WBC differential also occurred.
  - Transaminase elevations developed ~24 hrs post-dose
  - Acute symptoms resolved by 72 hrs post-dose
- **Other reported AEs:** diarrhea and nausea (grade 1) with DTG alone in subject 1, and headache (grade 1) in subject 3 after the 1st and 2nd HP doses.

Table 1. Summary of Major AEs in Subjects 1 & 4

Adverse Events	Highest Grade	
	Subject 1	Subject 4
Flu-like syndrome		
Nausea	2	1
Vomiting	1	1
Headache	1	1
Dizziness/lightheadedness	1	2
Tachycardia	1	1
Fever	1	3
Chills	0	2
Orthostatic hypotension	0	3
Rash	0	1
Lab abnormalities		
Absolute lymphocyte decrease	4	4
ALT elevation	2	3
AST elevation	2	4
Direct bilirubin elevation	3	3

Safety Results

Figure 2. Lab Trends in Subjects 1 & 4 during the Study Period

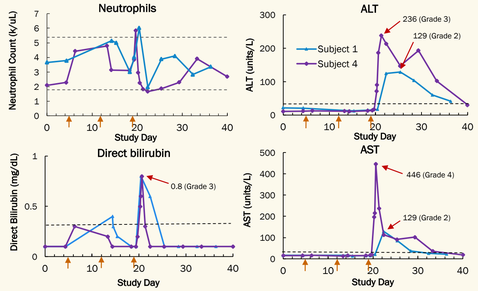


Fig 2. Orange arrows = administration of wHP; dashed line = reference range. Left shifts (top left) were observed in both subjects following the development of flu-like syndrome. Transaminase elevations (right) developed 24-72 hours after the final doses of DTG, RPT, and INH, and took 2-3 weeks to resolve. Transient increases in direct bilirubin (bottom left) were observed after the 1st and 2nd doses of wHP.

Figure 3. Select Inflammatory Markers in Subjects 1 & 4 during the Study Period

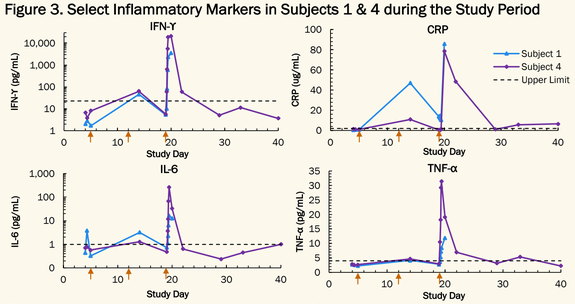


Fig 3. Orange arrows = administration of wHP. Posthoc evaluations of inflammatory markers revealed transient increases in IFN-Y, CRP, IL-6, and TNF-α after the 2nd doses of HP, with significant increases in all markers during the flu-like syndrome events after the 3rd HP dose.

PK Results

Figure 4. RPT, 25-desacetyl RPT, and INH Plasma Concentration vs. Time Curves by Subject on Day 19

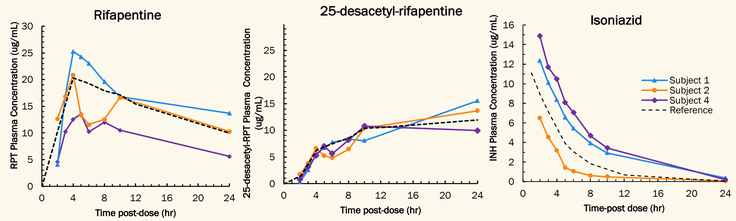


Fig 4. RPT, 25-desacetyl-RPT, and INH levels were examined following the development of flu-like syndrome in subjects completing all doses of study medications. Exposure to RPT (left) and its active metabolite (middle) were similar to reference PK data in healthy volunteers across all subjects, with subjects 1 & 4 having the highest and lowest exposures, respectively. INH exposure (right) was ~67-92% higher in subjects 1 & 4 than available reference PK data in healthy volunteers and LTBI patients. Reference data was estimated from published references using Plot Digitizer (v2) and plotted for comparison (Dooley et al. *Antimicrob Agents Chemother* 2008; 52: 4037-4042. Weiner M, et al. *Am J Respir Crit Care Med* 2002; 167(10):1341-7; Weiner M, et al. *Am J Respir Crit Care Med* 2004;169(11):1191-7).

PK Results

Figure 5. DTG Plasma Concentration vs. Time Curves by Subject

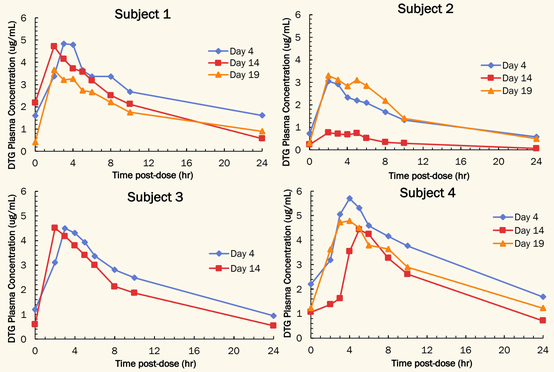
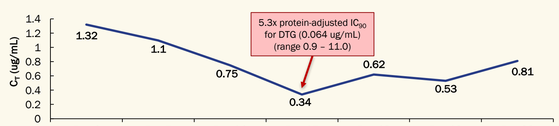


Figure 6. Steady-state DTG C_T Levels[a] throughout the Study



	Day 4 (n=4)	Day 5 (n=4)	Day 14 (n=4)	Day 15 (n=4)	Day 18 (n=4)	Day 19 (n=3)	Day 20 (n=3)
% Decrease vs. Day 4		-16.4%	-42.7%	-74.4%*	-53.2%*	-59.9%	-38.3%

Fig 6. C_T = concentration at the end-of-the-dosing interval [a]Reported as geometric mean of the time 0 (pre-dose) sample on the specified study day. % decrease based on the GMR of specified time point vs. Day 4 C_T value. *p<0.05

Table 3. Individual & Summary DTG PK Parameters with GMR Comparisons vs. Day 4 (DTG Alone)

Subject	C_{max} (ug/mL)	$AUC_{24hr,SS}$ (h*ug/mL)	$t_{1/2}$ (hr)	CL_{SS}/F (L/h)	V_Z/F (L)
DTG Alone (Day 4)					
1	4.8	64.1	17.3	0.78	19.5
2	3.1	33.0	9.7	1.51	21.3
3	4.5	55.2	11.1	0.91	14.5
4	5.7	77.8	12.0	0.64	11.1
Geo Mean	**4.4**	**54.9**	**12.2**	**0.91**	**16.1**
DTG 2 days after the 2nd dose of HP (Day 14)					
1	4.7	49.4	7.6	1.01	11.1
2	0.8	7.3	6.4	6.83	63.0
3	4.5	44.3	7.7	1.13	12.5
4	4.4	48.4	7.2	1.03	10.8
Geo Mean	**2.9**	**29.7**	**7.2**	**1.69**	**17.5**
DTG with the 3rd dose of HP (Day 19)					
1	3.7	43.1	12.2	1.16	20.5
2	3.3	36.5	8.6	1.37	17.1
4	4.8	63.5	11.0	0.79	12.5
Geo Mean	**3.9**	**46.4**	**10.5**	**1.08**	**16.3**
Day 14 vs. 4					
GMR [90% CI]	0.66 [0.31, 1.43]	0.54 [0.27, 1.10]	0.59* [0.46, 0.75]	1.85 [0.91, 3.77]	1.09 [0.48, 2.50]
Day 19 vs. 4					
GMR [90% CI]	0.88 [0.65, 1.20]	0.85 [0.55, 1.29]	0.83 [0.65, 1.06]	1.18 [0.77, 1.80]	0.98 [0.73, 1.32]

*p<0.05
Individual PK data reported as geometric means
Key: C_{max} = maximum (peak) concentration; $AUC_{24,SS}$ = area-under-the-concentration-time curve from time 0–24 hr, V_{SS}/F = apparent volume of distribution at steady-state, CL_{SS}/F= apparent oral clearance at steady state; $t_{1/2}$ = elimination half-life

Table 2. PK Parameters of RPT, 25-desacetyl-RPT, and INH

Subject	$AUC_{0\text{-}24h}$ (ug*hr/mL)	C_{max} (ug/mL)	$t_{1/2}$ (hr)
RPT[a]			
1	376.2	25.4	n/a
2	317.8	21.0	n/a
4	205.0	13.6	n/a
25-desacetyl-RPT[a]			
1	217.9	15.6	n/a
2	218.1	13.7	n/a
4	199.1	10.9	n/a
INH			
1	79.9	12.4	4.8
2	25.2	6.5	3.9
4	91.6	14.9	5.2

Key: 25-desacetyl-RPT = 25-desacetyl-rifapentine (active metabolite); $AUC_{0\text{-}24h}$ = area-under-the-concentration-time curve from 0–24 hrs; C_{max} = maximum concentration; $t_{1/2}$ = elimination half-life
[a]$t_{1/2}$ not reported as sampling only available through 24 hours post-dose

Conclusions

- Serious toxicities were observed in 2 of 3 subjects who received 3 doses of wHP with once daily DTG, resulting in early termination of our study. Flu-like syndrome was reported in <4% of subjects in clinical trials receiving wHP alone for LTBI treatment, with serious reactions accounting for ~0.3% of AEs (Sterling T, et al. *Clin Infect Dis* 2015; 61(4):527-35. Sterling T, et al. *AIDS* 2016;30(10):1607-15). Hepatotoxicity was reported in ~0.4-1% of patients in these studies.
- Limited PK data from these subjects revealed decreased DTG exposure and C_T values following initiation of wHP. Exposure to RPT and its metabolite were similar to reference PK data for all subjects. INH exposure was higher than expected in the 2 subjects that developed flu-like syndrome.
- The mechanisms behind the reactions observed in these subjects are unknown. Cytokine assays revealed increases in a number of inflammatory markers, including CRP, TNF-α, IL-6, and most notably IFN-Y, a proinflammatory cytokine that is primarily produced by lymphocytes.
- Additional investigations are in progress, including pharmacogenetic testing for acetylator status and screening for anti-INH and anti-RPT antibodies. These efforts may help provide additional insight into the mechanism of these toxicities.

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