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Rilpivirine Pharmacokinetics With/Without Darunavir/r in Adolescents and Young Adults

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BACKGROUND & OBJECTIVE

- Rilpivirine (RPV) is a second generation non-nucleoside reverse transcriptase inhibitor (NNRTI).
- Once daily (QD) dosing of RPV is approved at 25 mg for HIV-infected individuals ≥ 18 years of age who are antiretroviral treatment naïve.[1]
- Once daily dosing of RPV makes it an attractive option for HIV-infected adolescents.
- **Primary Objective**: To assess the steady state pharmacokinetics of rilpivirine 25 mg QD with and without darunavir/ritonavir (DRV/r 800/100 mg) or atazanavir/ritonavir 300/100 mg (ATV/r) once daily administered to adolescents and young adults.
- **Secondary Objective:** To assess steady state pharmacokinetics of DRV/r 800/100 mg QD with RPV 25 mg QD administered to adolescents and young adults.

METHODS

Study Design

- **IMPAACT P1058A** is a multi-centered observational study designed to evaluate the PK of antiretroviral drug combinations commonly used by HIV-infected children, adolescents, and young adults [clinicaltrials.gov: NCT00977756].
- Two of the ARV regimens under study in protocol Version 2.0 included:

  Arm P: rilpivirine 25 mg QD + DRV/r 800/100 mg or ATV/r 300/100 mg QD

  Arm Q: rilpivirine 25 mg QD
- The study did not prescribe therapy or provide medications, and did not dictate subject management.
- Eligible subjects included HIV-infected patients ≥12 and <24 years of age on one of the regimens of interest for at least 30 days at an IMPAACT site in the United States.
- Subjects were excluded if they had any clinical or laboratory toxicity of grade 2 or higher, a hemoglobin level of <8.5 gm/dl, or were receiving a drug that might interact with the drugs of interest. A negative pregnancy test was required at enrollment for females of child bearing capacity.
- PK Results were communicated to the local investigator in real-time but there were no protocol-mandated dosage adjustments.
- The study was approved by the Institutional Review Board at each site.

Bioanalytical and Pharmacokinetic Methods

•Plasma samples were collected at 0, 1, 2, 4, 6, 8 ,12 and 24 hours post observed dose at steady-state.

•RPV was quantitated using a validated HPLC method at the IMPAACT Pharmacology Lab at University of California at San Diego (LLOQ 10 ng/mL). DRV was quantitated using a validated LC-MS/MS method at the IMPAACT Pharmacology Lab at University of Alabama (LLOQ 25 ng/mL).

•Pharmacokinetic parameter estimates were determined using a non-compartmental approach with Phoenix WinNonlin version 6.3, Certara USA, Inc., St. Louis, MO.

Statistical Plan

- Previous estimates of the mean RPV AUC in adults is 1.4 - 2.2 mg*h/L[1]; a sample size of 15 individuals per arm yields 80% power to detect a 30% minimum detectable difference from this reported mean, using a rule that declares underexposure to be present if the 90% CI lies entirely below the target interval.
- Sample size was selected to have power to identify situations in which DRV/r led to pharmacokinetic parameter values outside the interval target (T) [of T/1.25 and 1.25 x T].
- Statistical comparisons examined whether the 90% Confidence Interval (90% CI) of the geometric mean (GM) AUC and C_{24h} for each antiretroviral was within 25% of those parameters observed in previous studies demonstrating safety and/or efficacy.

RESULTS

Table 1. Baseline Patient Demographics

Gender	N (%)*
Male	13 (46)
Female	15 (54)
	Median (range)
Age (Yr)	20 (12-23)
Weight (Kg)	67.7 (38.4-115.6)
HIV RNA (log 10 copies/ml)	1.5 (1.2-5.1)
CD4 + T cell count	529 (96-1260)

- **Arm P**: 14 patients receiving RPV 25 mg once daily + DRV/r 800/100 mg once daily had RPV intensive pharmacokinetic data available [*Note: one patient received the RPV and ATV/r but is not included in this analysis]*
- **Arm Q**: 15 patients receiving RPV 25 mg once daily had RPV intensive pharmacokinetic data available
- *one patient received RPV alone and then added DRV/r resulting in inclusion in both groups

Table 2. Rilpivirine Pharmacokinetics without and with administration of Darunavir/r

PK Parameters GM (90% CI)	Rilpivirine 25 mg QD (n=15)	Rilpivirine 25 mg QD + DRV/r 800/100 mg QD (n=14)		Ratio of GM RPV With/Without DRV/r
	RPV	**RPV**	**DRV**	
AUC (µg.hr/mL)	2.38 (1.92,2.94)	6.74 (4.89, 9.28)	81.16 (64.56,102.0)	2.83 (1.96, 4.10)
C_{max} (µg/mL)	0.14 (0.12,0.18)	0.39 (0.27, 0.57)	6.40 (5.44,7.53)	2.77 (1.86, 4.11)
C_{last} (µg/mL)	0.08 (0.06,0.10)	0.23 (0.17, 0.32)	2.40 (1.66,3.49)	3.04 (2.10, 4.45)
C_{min} (µg/mL)	0.07 (0.06,0.09)	0.16 (0.09, 0.27)	0.61 (0.25,1.49)	2.16 (1.24, 3.77)
AUC Target range	1.4 to 2.2	1.4 to 2.2	48.8 to 76.3	
C_{min} Target range	0.05 to 0.07	0.05 to 0.07	0.9 to 1.4	

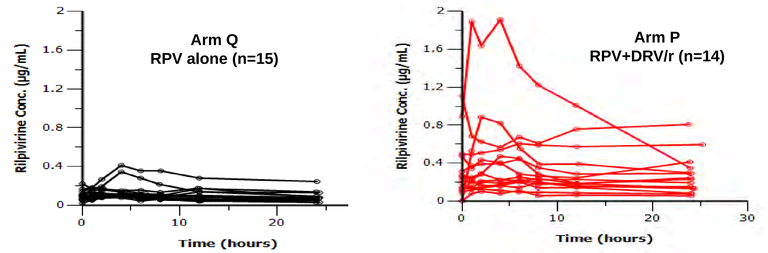

Figure 1: Individual Rilpivirine Concentration versus Time Curves in Adolescents & Young Adults without (Arm Q) and with (Arm P) co-administration of Darunavir/ritonavir

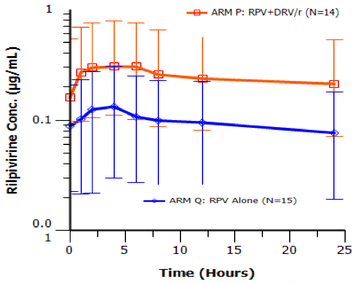

Figure 2: Geometric Mean (90%CI) Rilpivirine Concentration versus Time Curves in Adolescents & Young Adults with (Arm P) and without (Arm Q) co-administration of Darunavir/ritonavir

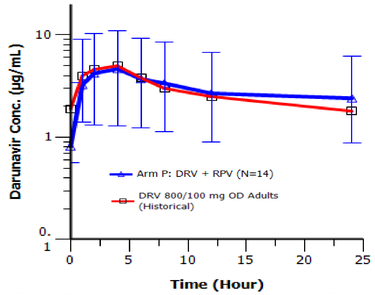

Figure 3: Geometric Mean (90%CI) Darunavir Concentration versus Time Curves in Adolescents & Young Adults with co-administration of Rilpivirine

CONCLUSIONS

- RPV exposure after 25 mg dosing without DRV/r in our cohort, median age 20, was similar to adults, although slightly above the standard AUC range of 1.4 – 2.2 µg.hr/mL (Table 2) .
- Greater variability in concentration time curves was seen in those patients receiving RPV plus DRV/r (Figure 1).
- RPV exposure after 25 mg dosing in conjunction with DRV/r 800/100 mg once daily was two to three fold higher for all tested parameters (AUC, Cmax, Cmin, Clast) when compared to RPV alone (Table 2 and Figure 2).
- DRV exposure after 800/100 mg dosing did not appear to be affected by concomitant RPV use (Table 2 and Figure 3)[2].
- All patients had RPV C_{min} above the RPV half maximal effective concentration (EC_{50}) of 0.03-0.37 ng/mL for wild-type HIV.
- Further studies are required to determine if changes in RPV dose are needed when used in conjunction with DRV/RTV in this age group.

REFERENCES

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2. Kakuda, TN, Brochot, A, van de Casteele, T et. al. Establishing darunavir dosing recommendations in treatment-naïve and treatment-experienced pediatric patients. 13th International Workshop on Clinical Pharmacology of HIV Therapy, Amsterdam, 22-24 April, 2013