Rilpivirine with Darunavir/Ritonavir; Pharmacokinetics & Safety in HIV Therapy-Naïve Patients.

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Background

Current treatment guidelines recommend the use of NRTI "backbone" plus 3rd agent (PI, NNRTI, InSTI) for initial therapy.

Avoiding nucleos(t)ide use first-line may be considered where there is a concern regarding:

- potential NRTI toxicity (e.g metabolic, renal)
- compromise by resistance mutations

In such situations, the use of an effective two-drug regime offers the potential advantages of:

i. sparing the use of remaining drug classes for the future
ii. reduced toxicity and cost with the use of fewer agents, and
iii. a simple regime, which may aid long-term dosing adherence, particularly when given once-daily.

A combination of ritonavir-boosted darunavir (DRV/*rtv*) and rilpivirine (RPV) could potentially form a once-daily nucleoside-sparing regime for therapy-naïve treatment. RPV is subject to the boosting effect of hepatic cytochrome inhibition (CYP3A4), and in an interaction study in healthy volunteers DRV/*rtv* increased RPV pharmacokinetic (PK) exposures, of a RPV 150mg daily dose, by 80 to 180% without altering DRV or *rtv* significantly.

This study investigates the safety, steady state PK and antiviral activity of RPV/DRV/rtv in therapy-naïve HIV-infected adults.

Methodology

This is a single-arm, open-label 48 week study conducted at Chelsea & Westminster Hospital, London, UK [EUdraCT - 2012-002663-10; Clinicaltrials.gov NCT01736761}.

Previously untreated, HIV-positive adults were enrolled, after written confirmation of their consent, with eligibility screened by medical history, examination (including electrocardiograph), and blood and urine analysis.

Important eligibility criteria:

- aged 18 - 65 years, CD4 > 50 cells/mm^3, HIV-RNA > 1000 copies/mL
- No opportunistic illness, hepatitis B or C infection, or cardiac disease
- Absence of genotypic resistance mutations on screening or prior tests to:
  - darunavir (V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V) or
  - rilpivirine (K101E, K101P, E138A, E138G, E138K, E138R, E138Q, V179L, Y181C, Y181I, Y181V, H221Y, F227C, M230I, and M230L).
- No use of proton-pump inhibitors or H-2 antagonists

Eligible patients commenced treatment with darunavir 800mg, ritonavir 100mg and rilpivirine 25mg once daily, taken with a meal containing at least 520 kcal in the morning.

Samples were obtained for 24h-trough concentrations at weeks 1 & 3, with a formal 24h PK profile at week 4 steady-state (pre-dose, 1, 2, 4, 6, 8, 12 & 24 hour).

Viral response was assessed by HIV-RNA weekly to week 4, fortnightly to week 12 and every 12 weeks to week 48.

ECG morphology assessed at each study visit including QT-corrected$_{Friedericia}$.

Adverse events were monitored by symptom report and assessment of biochemical & haematologic safety parameters.

Results

Table 1. Baseline demographic data

		All	Baseline VL below 100k	Baseline VL above 100k
N		32	16	16
male:female		31:1	15:1	16:0
Age (yr)	mean (SD)	34.3 (8.5)	35.4 (8.4)	33.3 (8.7)
height (cm)		176.8 (7.6)	175.9 (8.6)	177.7 (6.6)
weight (kg)		73.5 (13.4)	73.2 (13.8)	73.8 (13.4)
BMI (kg.m^{-2})		23.4 (3.5)	23.5 (2.9)	23.4 (4.1)

Table 2. Pre-dose concentrations at weeks 1 & 3 and Pharmacokinetic parameters at steady state (week 4)

PK parameter (N = 25)		rilpivirine	darunavir	ritonavir
		GeoMean (95% C.I.)		
C_{trough} (ng.mL^{-1})	Week 1	91 (76 - 106)	2061 (1585 - 2537)	57 (40 - 75)
	Week 3	120 (92 - 148)	2310 (1667 - 2953)	53 (43 - 64)
AUC_{0-24h} (ng.h^{-1}.mL^{-1})		2966 (2704 - 3820)	92504 (82266 - 131107)	5222 (4567 - 7722)
C_{max} (ng.mL^{-1})		183 (165 - 239)	9381 (8392 - 12976)	592 (517 - 1036)
C_{24h} (ng.mL^{-1})		114 (104 - 109)	1799 (1675 - 3048)	47 (40 - 69)

Table 3. Electrocardiograph change in QT-corrected$_{Friedericia}$ interval from baseline.

		Baseline	Week 4 (4 hr post dose)	Individual change from baseline
QT_cF (msec)	median	385.5	390.5	3
	range	(354 - 408)	(357 - 416)	(-16 to +23)

No significant change from baseline and no QT_cF interval greater than 450 msec recorded.

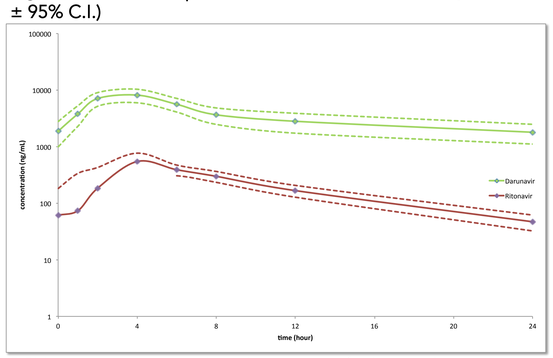
Adverse Events

Three serious adverse events were recorded during the study, none of which were deemed by the investigator to be related to study medication:

i. Admission to hospital for treatment of prostatitis complicated by peri-urethral abscess.
ii. Overnight admission to hospital to treat dehydration and confusion caused by recreational drug intoxication.
iii. Laparotomy and bowel resection with temporary stoma to repair rectal trauma.

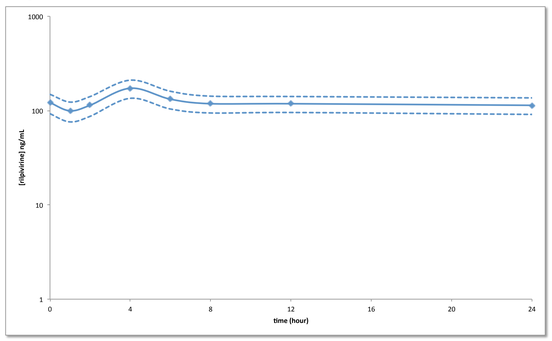
There were no other adverse events > Grade 2 severity. Two patients experienced an transient self-limiting generalised rash (without mucosal involvement) which resolved with continued dosing.

Figure 1. 24 hour PK profile of darunavir and ritonavir (GeoMean ± 95% C.I.)



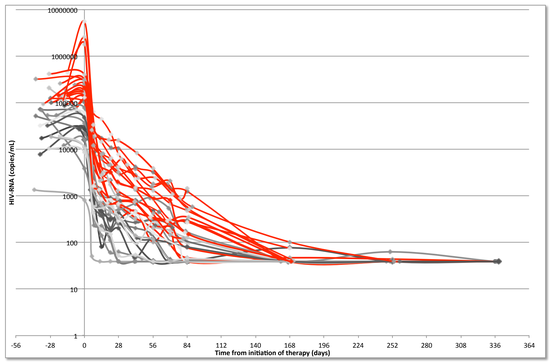
DRV exposure was within the range of observed in previous patient PK studies.✚

Figure 2. 24 hour PK profile of rilpivirine (GM ± 95% C.I.)



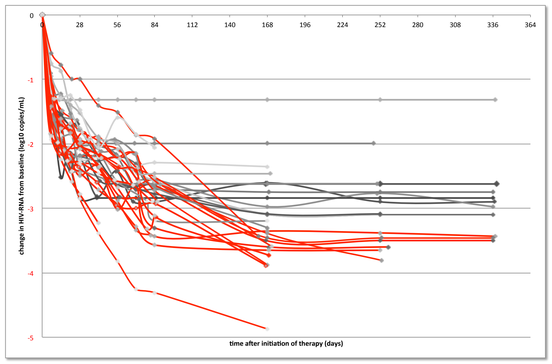
RPV exposure was approximately 45% higher than that determined in ECHO and THRIVE studies; however, interestingly all AUC_{0-24h} were within the range observed within their pooled PK substudies (723 - 4065 ng.h^{-1}.mL^{-1})❖

Figure 3. Viral load; individual patient plot of absolute HIV-RNA over study period; those with baseline viral load above 100,000 copies/mL in red.



Day 168, n= 26; Day 252, n=15; Day 336, n=10

Figure 4. Individual patient plot of HIV-RNA log-change from baseline over time; those with baseline viral load above 100,000 copies/mL highlighted in red.



Comparing those with a pre-treatment viral load - below versus above 100,00 copies/mL: median VL reduction (log10 copies/mL) was 2.0 versus 2.2 at day 28 and 2.3 versus 2.5 at day 56, respectively.

Conclusion

The combination of DRV/rtv and RPV was well tolerated, giving RPV exposure (AUC0-24h) within the range of values seen in ECHO and THRIVE. Similarly DRV exposure was comparable with historic data in patients (ARTEMIS, ODIN). Good initial virologic response data, independent of baseline viral load and tolerable safety data supports further efforts to confirm the effectiveness of this nucleoside-sparing combination.

References

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