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Evaluation of Single and Multiple Dose Pharmacokinetics of Ritonavir in Subjects with Mild or Moderate Hepatic Insufficiency

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ABSTRACT

Background: Ritonavir is primarily metabolized by CYP3A. Hepatic insufficiency (HI) may reduce ritonavir clearance. The purpose was to evaluate ritonavir pharmacokinetics (PK) in subjects with mild or moderate HI.

Methods: For Study 1, there were 6 HIV+ subjects each in the control and mild HI groups; for Study 2, there were 6 subjects without HIV each in control and moderate HI groups. In Period 1, subjects received a single 600 mg ritonavir dose, followed by 48 h sampling. In Period 2, a 400 mg dose was administered BID to the HI groups and a 500 mg dose BID to the control groups. On Day 14, plasma samples were collected for 12 h. Ritonavir total concentrations and plasma protein binding were measured. Noncompartmental methods were used for PK and ANOVA/ANCOVA for statistical comparisons, with dose normalization to 500 mg BID at steady state (SS).

Results: At SS, mean % bound ranged from 98.2 to 98.8 with no difference between the groups ($p \geq 0.14$). Therefore, ritonavir pharmacokinetics was analyzed using total concentrations. After a single 600 mg dose, the mild HI group had a 26% higher AUC (p=0.03) compared to the control group; the moderate HI group had a similar AUC, but 44% lower C_{max} (p=0.02) compared to the control group. At SS, dose-normalized AUC (85 ± 29 *vs.* 79 ± 35 µg•h/mL, p=0.4), C_{max} (13 ± 6.3 *vs.* 12 ± 4.9 µg/mL, p=0.7), and C_{min} (2.6 ± 1.2 *vs.* 1.9 ± 0.9 µg/mL, p=0.16) in mild HI group were similar to those in control group. Both dose-normalized AUC (41 ± 18 *vs.* 66 ± 24 µg·h/mL, p=0.08) and C_{max} (6.1 ± 2.0 *vs.* 10 ± 3.7 µg/mL, p=0.05) in the moderate HI group were 61% of those in the control group; however, C_{min} was similar between groups (1.6 ± 1.3 *vs.* 1.7 ± 0.9 µg/mL, p=0.6). The T_{max} for the moderate HI group at SS was prolonged compared to the control group (6.7 *vs.* 4.3 h, p=0.04). The somewhat lower ritonavir concentrations and prolonged T_{max} at SS in moderate HI group may be due to reduced ritonavir absorption. Adverse event rates were similar between groups.

Conclusions: Based on PK observations, there appears to be no need to reduce the ritonavir dose in mild or moderate HI.

INTRODUCTION

- Norvir® (ritonavir, RTV) is an HIV protease inhibitor (PI) that is approved for the treatment of HIV infection.
- At clinical doses of 400-600 mg BID, RTV in combination with nucleoside analogues with/without other PIs has demonstrated profound reduction in viral RNA levels and substantial increases in CD_4 cell counts.
- RTV is primarily eliminated by hepatic CYP450 (CYP3A) metabolism.
- Elimination of RTV may be reduced in patients with hepatic insufficiency (HI).
- RTV appears to induce its own metabolism; enzyme induction could be affected in patients with HI.

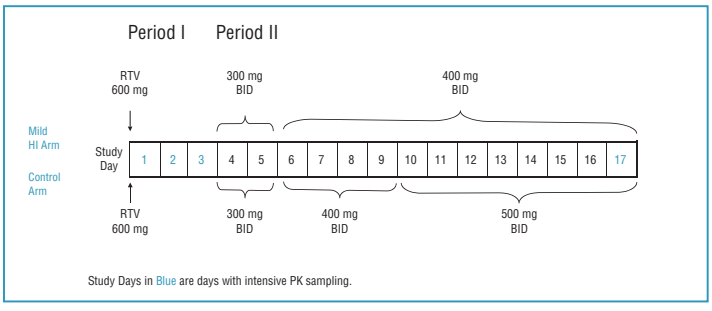
OBJECTIVE

- To assess the effect of mild or moderate HI on the single- and multiple-dose pharmacokinetics of RTV.

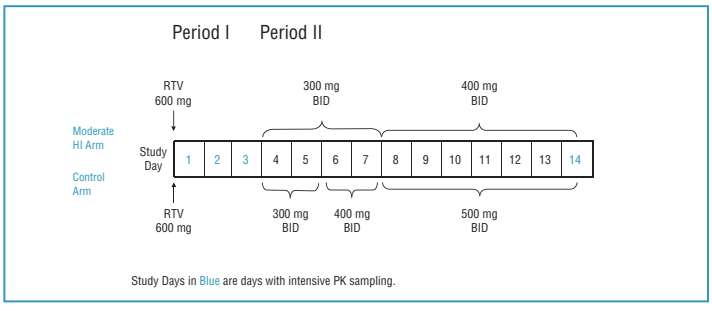
STUDY DESCRIPTION

- Two Phase I, open label, single center studies.
- Study 1: HIV-infected subjects with normal hepatic function (control, n=6) and subjects with mild HI (Child-Pugh score 5-6, n=6).
- Study 2: HIV-negative subjects with normal hepatic function (control, n=6) and subjects with moderate HI (Child-Pugh score 7-9, n=6).
- Subjects were confined throughout the study.
- RTV was dosed with food; dose was administered shortly after breakfast on intensive PK study days.

Study 1 Design



Study 2 Design



METHODS

- On Study Day 1 (Period I), plasma samples were collected pre-dose and through 48 hours post dose for RTV.
- On the last study day of Period II (after at least 10 days of multiple dosing), plasma samples were collected during a 12-hour dosing interval in both Studies 1 and 2.
- RTV concentrations were measured by LC/MS/MS. Lower limit of quantitation (LLOQ)=1.0 ng/mL.
- Plasma protein binding was determined by ultrafiltration using [^{14}C] RTV.
- Noncompartmental methods were used for PK and analysis of variance (ANOVA) or analysis of covariance (ANCOVA) for statistical comparisons, with dose normalization to 500 mg BID for HI arms at steady state.

DEMOGRAPHICS

- Study 1: 12 Subjects (6 control and 6 mild HI) completed.
- Study 2: 12 Subjects (6 control and 6 moderate HI) completed.

	Study 1			Study 2	
	Control	Mild HI Single Dose*	Mild HI Multiple Dose*	Control	Moderate HI
Age† (yrs)	39.5 (30–52)	39.2 (32–45)	38.5 (32–45)	54.0 (48–60)	53.8 (49–62)
Weight† (kg)	75.4 (64.7–94.3)	74.7 (60.0–96.8)	76.5 (60.0–96.8)	85.4 (73.9–108.4)	84.2 (69.4–99.8)
Height† (cm)	175 (158–193)	172 (166–175)	175 (170–185)	169 (158–180)	168 (155–180)
Race (n)	5 White 1 Black	6 White	6 White	5 White 1 Black	6 White
Gender (n)	5 Male 1 Female	6 Male	6 Male	5 Male 1 Female	5 Male 1 Female
HBV + (n)	0	2	2	0	0
HCV + (n)	1	4	4	0	3

* One subject discontinued from the study after the single dose period for personal reasons. An additional subject was enrolled as a replacement for multiple dosing period.
† Age, weight and height presented as mean (range).

RESULTS

Protein Binding Results

At steady state, mean % free RTV ranged from 1.2 to 1.8 (% bound 98.2 to 98.8) with no difference between HI and control arms within each study (p≥0.14), therefore RTV PK was analyzed using total concentrations.

Figure 1. Protein Binding: Individual and Mean ± SD % Free Ritonavir, Single Dose

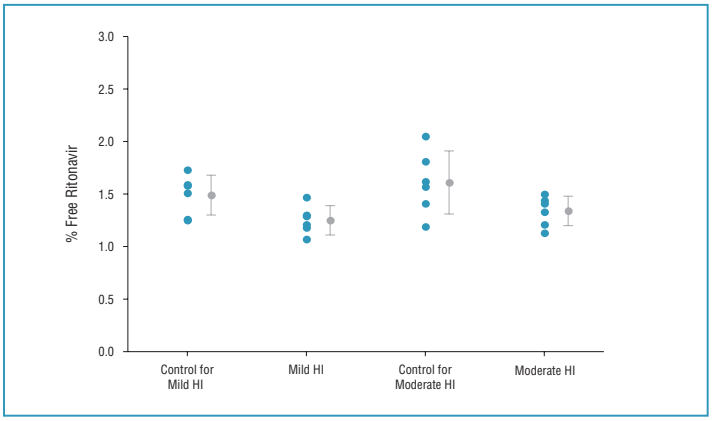


Figure 2. Protein Binding: Individual and Mean ± SD % Free Ritonavir, Multiple Dose

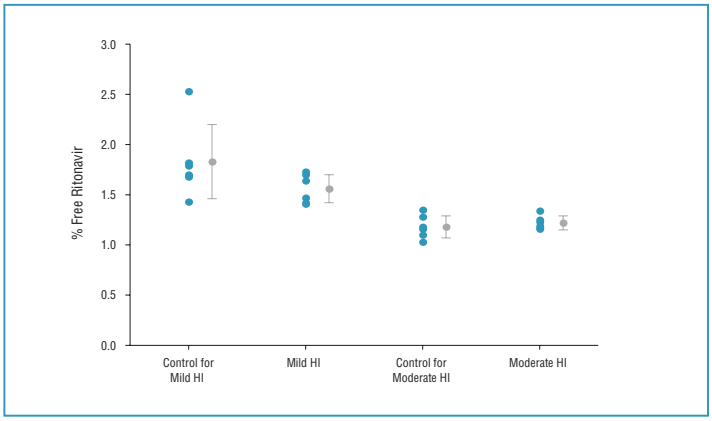


Table 1. Effect of Mild Hepatic Insufficiency on Ritonavir PK (Mean ± SD)

	Study Day 1 Single Dose		Study Day 17 Multiple Dose (BID)		
	Mild HI 600 mg (n=6)	Control 600 mg (n=6)	Mild HI 400 mg (n=6)	Mild HI, Normalized to 500 mg (n=6)	Control 500 mg (n=6)
C_{max} (µg/mL)	13.8 ± 3.0	12.3 ± 1.9	10.4 ± 5.0	13.0 ± 6.3	12.2 ± 4.9
C_{min} (µg/mL)	–	–	2.06 ± 0.94	2.58 ± 1.18	1.87 ± 0.89
C_{trough} (µg/mL)	–	–	3.88 ± 1.43	4.85 ± 1.79	3.34 ± 1.69
AUC_{12} (µg•h/mL)	–	–	68.1 ± 23.3	85.1 ± 29.1	78.6 ± 35.3
AUC_{∞} (µg•h/mL)	126.5 ± 21.7*	99.8 ± 17.6	–	–	–
$t_{1/2}$^ (h)	4.9 ± 0.5	4.6 ± 0.9	–	–	–
CL/F+ (L/h)	4.9 ± 1.0	6.2 ± 1.1	6.4 ± 1.8	–	7.4 ± 2.9

* Statistically significantly different from Control (ANCOVA with body weight as a covariate, p<0.05).
^ Presented as harmonic mean and pseudostandard deviation; statistical tests based on β.
+ Parameter not tested statistically.

Figure 3. Mild Hepatic Insufficiency: Mean (SD) Ritonavir Concentration-Time Profiles, 600 mg Single Dose

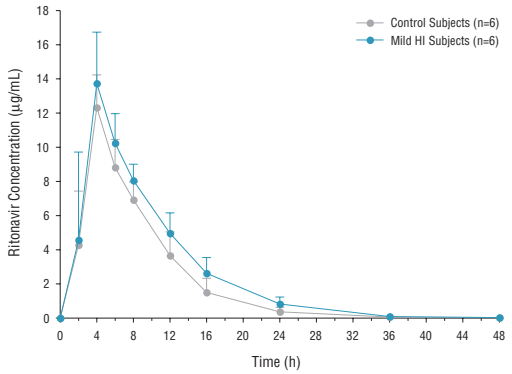
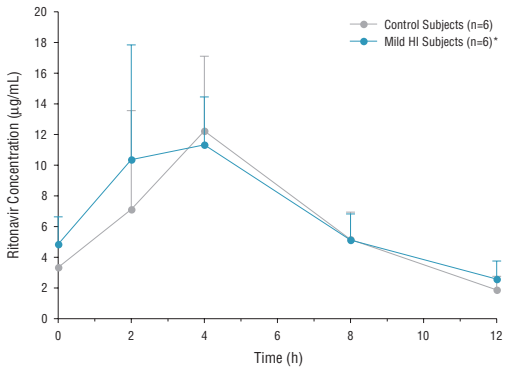


Figure 4. Mild Hepatic Insufficiency: Mean (SD) Ritonavir Concentration-Time Profiles, 500 mg BID



* Mild HI subjects received 400 mg BID; concentrations normalized to 500 mg BID.

Table 2. Effect of Moderate Hepatic Insufficiency on Ritonavir PK (Mean ± SD)

	Study Day 1 Single Dose		Study Day 14 Multiple Dose (BID)		
	Moderate HI 600 mg (n=6)	Control 600 mg (n=6)	Moderate HI 400 mg (n=6)	Moderate HI, Normalized to 500 mg (n=6)	Control 500 mg (n=6)
T_{max} (h)	4.7 ± 1.6	4.7 ± 1.0	6.7 ± 2.7*	–	4.3 ± 0.8
C_{max} (µg/mL)	8.11 ± 2.93*	14.44 ± 4.92	4.84 ± 1.56*	6.05 ± 1.95	9.99 ± 3.67
C_{min} (µg/mL)	–	–	1.29 ± 1.02	1.61 ± 1.28	1.72 ± 0.94
C_{trough} (µg/mL)	–	–	1.95 ± 1.31*	2.44 ± 1.63	3.87 ± 1.51
AUC_t (µg•h/mL)	100.9 ± 36.5	108.4 ± 32.2	–	–	–
AUC_{12} (µg•h/mL)	–	–	32.4 ± 14.7*	40.5 ± 18.4	66.3 ± 24.4
AUC_{∞} (µg•h/mL)	101.9 ± 37.4	108.6 ± 32.3	–	–	–
$t_{1/2}$^ (h)	5.7 ± 1.0	6.2 ± 0.4	–	–	–
CL/F+ (L/h)	6.8 ± 3.0	5.9 ± 1.7	14.8 ± 6.8	–	8.8 ± 4.5

* Statistically significantly different from Control (ANOVA or ANCOVA, $p<0.05$).
^ Presented as harmonic mean and pseudostandard deviation; statistical tests based on β.
+ Parameter not tested statistically.

Figure 5. Moderate Hepatic Insufficiency: Mean (SD) Ritonavir Concentration-Time Profiles, 600 mg Single Dose

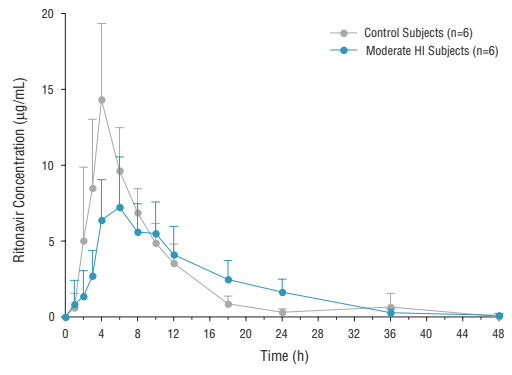
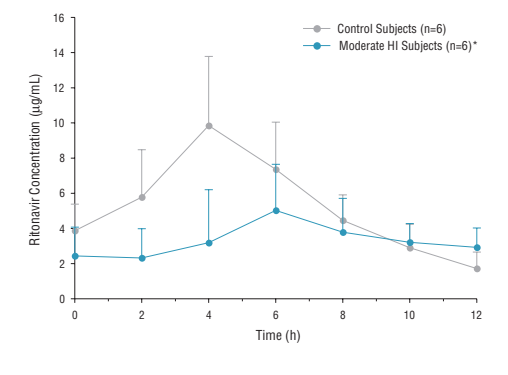
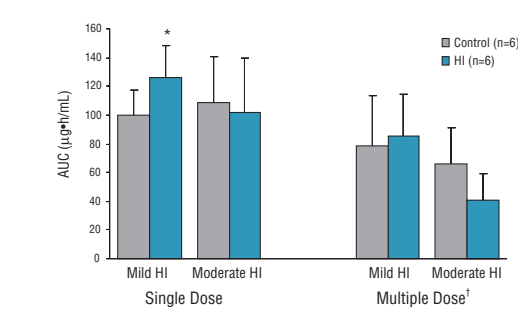


Figure 6. Moderate Hepatic Insufficiency: Mean (SD) Ritonavir Concentration-Time Profiles, 500 mg BID



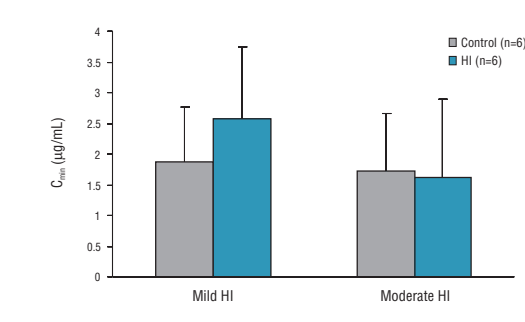
* Moderate HI subjects received 400 mg BID; concentrations normalized to 500 mg BID.

Figure 7. Mean (SD) AUC, Single Dose and Multiple Dose



* Statistically significantly different from control, $p < 0.05$.
† Multiple Dose AUC is normalized to 500 mg BID in HI subjects. For Single Dose: AUC_{∞}; For Multiple Dose: AUC_{12}.

Figure 8. Mean (SD) C_{min}, Multiple Dose



Normalized to 500 mg BID in HI subjects. There was no statistically significant difference between HI subjects and control subjects.

Safety

- There were no apparent differences between the subjects with HI and control subjects with respect to adverse events.
- No subjects were discontinued from either study due to adverse events.
- Most common adverse events included diarrhea, circumoral parasthesia, taste perversion, and flatulence. All adverse events were considered to be mild or moderate in severity.
- A few subjects with HI experienced hepatic transaminase elevations above those at baseline; the contribution of RTV to these elevations is uncertain.

DISCUSSION

- Protein binding of RTV appeared to be unaffected by mild or moderate HI.
- It has been reported that liver disease has a differential effect on P450 isozymes. The protein amount and activity of CYP3A4 are somewhat preserved in patients with mild to moderate disease,[1-3] which may explain the observed results in the current two studies.
- The somewhat lower RTV concentrations and prolonged T_{max} at steady state in moderate HI group may be due to the reduced absorption of RTV.
- C_{min}, an important PK parameter that is associated with sustained anti-viral effects of RTV,[4] was not statistically different between HI subjects and those with normal hepatic function with or without dose normalization.

CONCLUSIONS

- Based on PK observations, there appears to be no need to reduce the RTV dose in patients with mild or moderate HI.
- It would be prudent to monitor hepatic transaminases in patients with HI that are receiving RTV.

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