



# Ritonavir Pharmacokinetics in Subjects 60 Years or Older

C.E. Klein, Y-L. Chiu, J. Li, R. Rode, B. Bernstein, G.J. Hanna  
Abbott Laboratories, Abbott Park, IL, USA

P4.1/07

## Abstract

**Background:** The introduction of antiretroviral therapy has been associated with significantly improved survival with a resultant older treated population. Information on the pharmacokinetics of antiretroviral agents in older individuals is limited. A review of ritonavir clinical studies conducted by Abbott was performed to assess whether ritonavir exposure changes with increasing age.

**Methods:** Fifteen subjects aged 60 years or older underwent extensive ritonavir pharmacokinetic assessment (n=9) or had ritonavir trough concentrations obtained (n=6), many on multiple occasions, as part of different clinical studies. The studies assessed ritonavir doses of 200 mg to 600 mg, administered as a single dose, twice daily or three times daily, often with another protease inhibitor including saquinavir, indinavir or nelfinavir. Individual pharmacokinetic parameters for subjects  $\geq 60$  years old were compared to average values for subjects  $< 60$  years old on the same dosing regimen in each particular study. Trends in dose-adjusted AUC and  $C_{max}$  by age were also assessed.

**Results:** Ritonavir pharmacokinetic parameters in older subjects were similar to those observed in younger subjects. Of the 11 occasions of intensive pharmacokinetic sampling, the AUC was within  $\pm 20\%$  of the average AUC in younger subjects for 8 occasions,  $>20\%$  on 2 occasions and  $<20\%$  on one occasion. The 2 individuals who each had AUC  $>20\%$  on one occasion also had AUC within  $\pm 20\%$  on a separate occasion. On average, the AUC of subjects  $\geq 60$  years old was 7.2% higher than that of younger subjects. The average trough concentration was 13.5% lower in subjects  $\geq 60$  years old than that of the younger subjects. Regression analysis suggests there is no relationship between either dose-adjusted AUC or  $C_{max}$  and age ( $p \geq 0.1987$ ).

**Conclusions:** This assessment of ritonavir in a range of dosing regimens suggests that the pharmacokinetics of ritonavir do not differ between older and younger subjects.

## Background

- The introduction of antiretroviral therapy has been associated with significantly improved survival with a resultant older treated population.
- Information on the pharmacokinetics of antiretroviral agents in older individuals is limited.
- Norvir (ritonavir) is an HIV protease inhibitor developed by Abbott that is licensed for the treatment of HIV infection.
- Clinical trials with ritonavir at a dose of 600 mg BID alone or in combination with nucleoside analogues have demonstrated profound reductions in viral RNA levels and substantial increases in CD4 cell counts among patients across a wide spectrum of HIV disease.
- A review of ritonavir clinical studies conducted by Abbott was performed to assess whether ritonavir exposure changes with increasing age.

## Methods

### 1) Ritonavir doses of 200 mg TID–600 mg BID (Studies #1–#9)

- Nine subjects  $\geq 60$  years of age and 175 subjects  $< 60$  years of age underwent extensive ritonavir pharmacokinetic assessment in Studies #1–#7. Fifteen subjects  $\geq 60$  years of age had ritonavir trough concentrations obtained in Studies #1–#9, many on multiple occasions, as part of different clinical studies.
- The studies assessed ritonavir doses of 200 to 600 mg, administered as a single dose, twice daily or three times daily, often with another protease inhibitor including saquinavir, indinavir or nelfinavir.
- Individual pharmacokinetic parameters for subjects  $\geq 60$  years old were compared to the average values for subjects  $< 60$  years old on the same dosing regimen in each particular study. Trends in dose-adjusted AUC and  $C_{max}$  by age were also assessed.

### 2) Ritonavir doses of 100 mg–133 mg as an enhancer in lopinavir/ritonavir regimens (Study #10)

- In order to assess the potential impact of age on ritonavir pharmacokinetics when administered as a pharmacokinetic enhancer, we obtained the ritonavir pharmacokinetic parameters in 50 HIV-infected subjects from a lopinavir/ritonavir study. In this study, subjects received ritonavir 100 mg or 133 mg BID as a component of co-formulated lopinavir/ritonavir. Trends in dose-adjusted AUC and  $C_{max}$  by age were assessed.

## Demographics

A summary of the demographic data for subjects who had ritonavir pharmacokinetic assessments is presented in Table 1 and Table 2.

**Table 1. Demographic Summary – Ritonavir Doses Ranging from 200 mg TID to 600 mg BID (Studies #1–#9)**

	Subjects ≥60 years old (n = 15)		Subjects <60 years old (n = 893)	
	Mean ± SD	Min – Max	Mean ± SD	Min – Max
Age (years)	62 ± 2	60–67	37 ± 8	19–59
Weight (kg)	75.0 ± 12.8	46.0–92.5	75.1 ± 12.4	36.3–143.8
Sex	12 males (80%), 3 females (20%)		817 males (91%), 76 females (9%)	
Race	13 white (87%), 1 black (7%), 1 other (7%)		756 white (85%), 70 black (8%), 67 other (8%)	

**Table 2. Demographic Summary – Ritonavir Doses of 100 mg–133 mg as an Enhancer in Lopinavir/ritonavir Regimens (Study #10)**

	Subjects ≥60 years old (n = 4)		Subjects <60 years old (n = 46)	
	Mean ± SD	Min – Max	Mean ± SD	Min – Max
Age (years)	61 ± 1	60–63	40 ± 7	25–55
Weight (kg)	69.8 ± 5.3	63.0–74.0	72.0 ± 10.3	48.9–91.0
Sex	4 males (100%)		37 males (80%), 9 females (20%)	
Race	4 white (100%)		39 white (89%), 5 black (11%), 2 other (4%)	

## Result 1

- Of the 11 occasions of intensive pharmacokinetic sampling performed in 9 subjects, the AUC of older (≥60 years of age) subjects was within ± 20% of the average AUC in younger (<60 years of age) subjects for 8 occasions, >20% on 2 occasions and <20% on one occasion (see Table 3). The 2 individuals who each had AUC >20% on one occasion also had AUC within ± 20% on a separate occasion. On average, the AUC of older subjects was 7.2% higher than that of younger subjects.

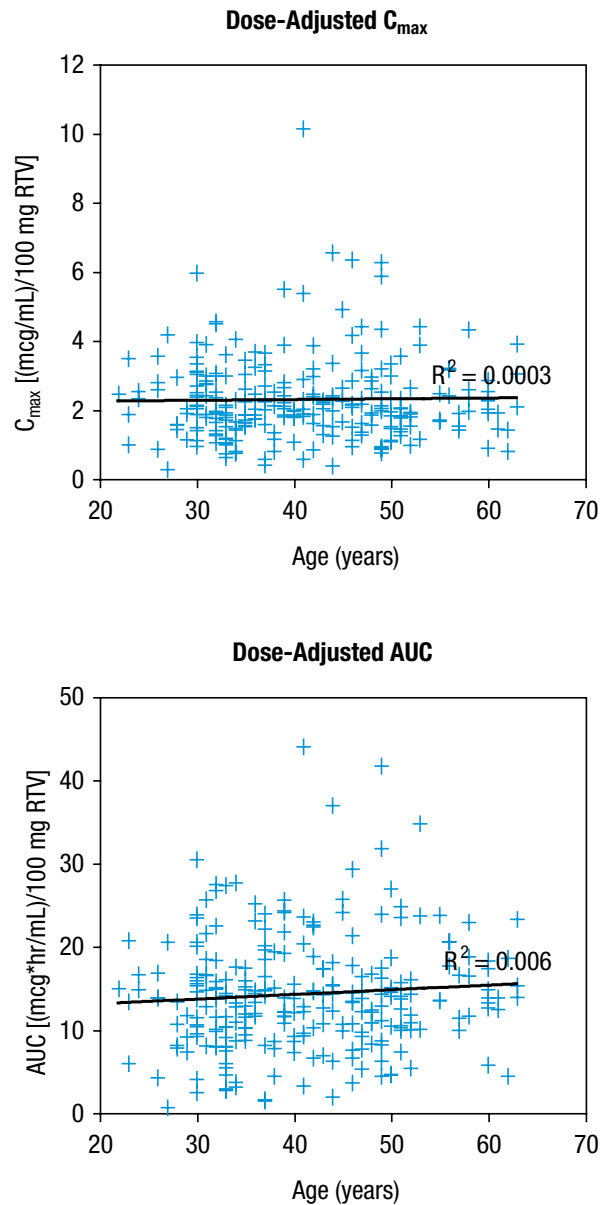
**Table 3. Ritonavir Pharmacokinetics for Doses Ranging from 200 mg TID to 600 mg BID (Studies #1–#7)**

Study	ID	Age	Regimen	Individual Values (Subjects ≥60 years old)			Regimen Mean ± SD (Subjects <60 years old)			n
				C <sub>max</sub> (µg/mL)	AUC (µg*h/mL)	C <sub>min</sub> (µg/mL)	C <sub>max</sub> (µg/mL)	AUC (µg*h/mL)	C <sub>min</sub> (µg/mL)	
#1	A1	63	RTV 500 mg BID	10.4	76.4	2.7	10.9±2.7	71.2±25.2	2.8±2.2	12
#2	A2	63	RTV 200 mg TID Days 4–12	7.8	46.5	4.2	6.6±3.8	34.0±20.2	2.3±1.9	10
			RTV 200 mg TID Days 22–29	6.1	27.7	1.4	5.2±3.1	24.0±13.4	1.4±0.9	9
#3	A3	61	RTV 600 mg BID + SQV 600 mg BID	11.5	74.3	0.73	12.5±2.7	85.9±16.0	2.7±0.8	9
#4	A4	60	RTV 400 mg BID + NFV 750 mg BID Wk 2	9.02	59.2	1.23	7.2±1.5	52.3±11.3	1.6±1.0	9
			RTV 400 mg BID + NFV 750 mg BID Wk 5	10.1	73.1	2.32	8.0±1.8	48.5±11.2	1.2±0.8	9
#5	A5	61	RTV 600 mg once	8.7	82.6	–	9.0±0.5	83.2±29.7	–	2
#6	A6	60	RTV 400 mg BID + IDV 400 mg BID	7.6	50.5	1.5	7.0 ±2.7	49.4±19.0	1.4±1.0	15
#7	A7	62	RTV 600 mg once	8.4	110.7	–	8.0±3.2	98.9±40.5	–	5
	A8	60	RTV 600 mg once	12.1	79.1	–	14.3±6.0	116.9±36.6	–	4
	A9	60	RTV 600 mg once	17.1	103.6	–	14.3±6.0	116.9±36.6	–	4

AUC – Area under the plasma concentration time curve during a dosing interval or extrapolated to infinity (single dose)

- Regression analysis of dose-adjusted AUC and  $C_{max}$  data pooled from the 7 ritonavir studies suggested there was no relationship between either parameter and age (see Figure 1).  $R^2$  values for AUC and  $C_{max}$  were 0.006 and 0.0003, respectively, and neither parameter was statistically significantly associated with age ( $p \geq 0.1987$ ).

**Figure 1. Dose-Adjusted Ritonavir  $C_{max}$  and AUC for Doses Ranging from 200 mg TID to 600 mg BID (Studies #1–#7)**

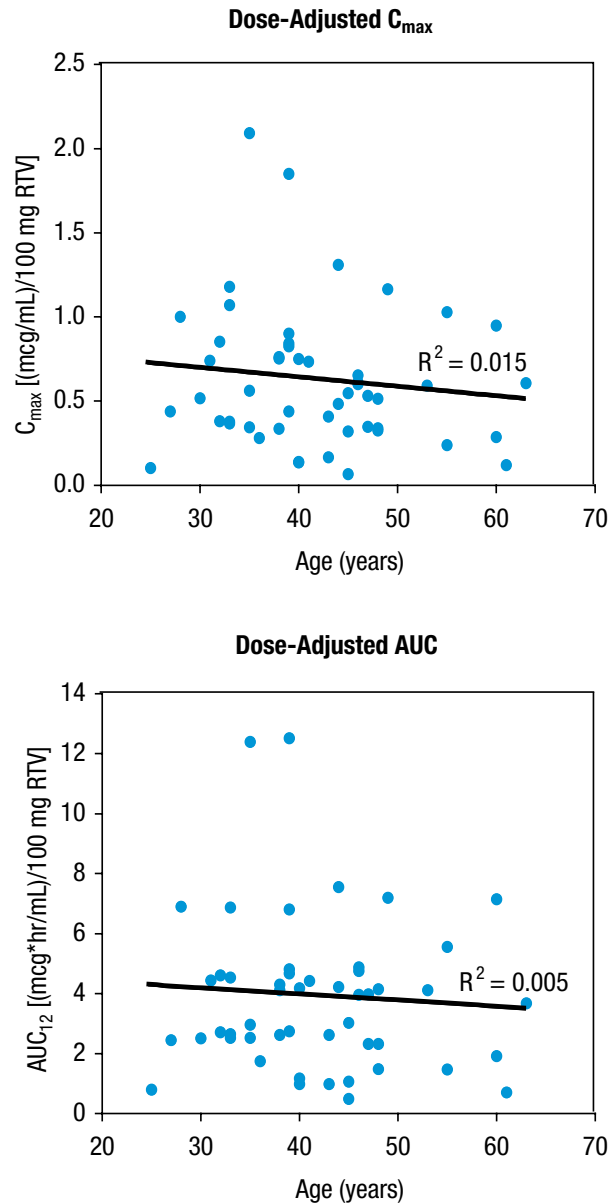


- Fifteen subjects  $\geq 60$  years of age had ritonavir trough concentrations: 8 subjects in Studies #1–#7 and 7 subjects in Studies #8 and #9. Of the 7 subjects in Studies #8 and #9, 5 received ritonavir 600 mg BID and 2 received ritonavir 600 mg BID plus AZT 200 mg TID.
- The ritonavir trough concentrations obtained from the 15 subjects  $\geq 60$  years of age were similar to the mean trough concentrations observed in each of these studies or, in the case of 600 mg BID dosing, similar to that reported in the Norvir SmPC ( $3.7 \pm 2.6 \mu\text{g/mL}$ ).
- The average trough concentration was 13.5% lower in subjects  $\geq 60$  years of age than the average trough concentration reported for each regimen and not likely of clinical significance.

## Result 2

- When ritonavir was administered as a pharmacokinetic enhancer, regression analysis of dose-adjusted AUC and  $C_{max}$  data from the lopinavir/ritonavir study suggested there was no relationship between either parameter and age (see Figure 2).  $R^2$  values for AUC and  $C_{max}$  were 0.005 and 0.015, respectively, and neither parameter was statistically significantly associated with age ( $p \geq 0.4017$ ).

Figure 2. Dose-Adjusted Ritonavir  $C_{max}$  and AUC following 400/100 mg – 533/133 mg Lopinavir/ritonavir BID Dosing (Study #10)



## Conclusions

This assessment of ritonavir in a range of dosing regimens suggests that the pharmacokinetics of ritonavir do not differ between older and younger subjects.