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Concentration-targeted phase I trials of atevirdine mesylate in patients with HIV infection: dosage requirements and pharmacokinetic studies

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Abstract

Rationale: To determine the dosage requirements and pharmacokinetics of atevirdine, a non-nucleoside reverse transcriptase inhibitor and its *N*-dealkylated metabolite (N-ATV) during phase I studies in patients receiving atevirdine alone or in combination with zidovudine. *Design:* Two open label, phase I studies conducted by the adult AIDS Clinical Trials Group (ACTG) in which atevirdine was administered every 8 h with weekly dosage adjustments to attain targeted trough plasma atevirdine concentrations. *Setting:* Five Adult AIDS Clinical Trials Units. *Patients:* Fifty patients (ACTG 199; $n = 20$ and ACTG 187; $n = 30$) with HIV-1 infection and ≤ 500 CD4+ lymphocytes/mm^3. *Intervention:* ACTG 199: 12 weeks of therapy with atevirdine (dose-adjusted to achieve plasma trough atevirdine concentrations of 5–10 μM) and zidovudine (200 mg every 8 h). ACTG 187: 12 weeks of atevirdine monotherapy with atevirdine doses adjusted to achieve escalating, targeted trough plasma concentration ranges

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(5–13, 14–22, and 23–31 μM). *Measurements:* ACTG 199: atevirdine, N-ATV and zidovudine trough determinations weekly (all patients) and intensive pharmacokinetics (selected patients) prior to and at 6 and 12 weeks during combination therapy. ACTG 187: atevirdine and N-ATV trough concentrations over a 12 week period. Intensive pharmacokinetic studies were conducted prior to and at 4 and/or 8 weeks during atevirdine monotherapy in female patients. *Results:* Atevirdine plasma concentrations demonstrated considerable interpatient variability which was minimized by the adjustment of maintenance doses (range: 600–3900 mg/day) to achieve the desired trough concentrations. In ACTG 187, the mean number of weeks to attain the target value, and the percentage of patients who attained the target, was group I (5–11 μM): 2.7 ± 2.4 weeks (92%); group II (12–21 μM): 2.6 ± 1.8 (64%); and group III (22–31 μM): 7.0 ± 5.6 weeks (27%). In ACTG 199 it was 3.2 ± 5.2 weeks (95%) to achieve a 5–10 μM trough. Atevirdine demonstrated a mono- or bi-exponential decline among most of the patients studied after the first dose. During multiple-dosing a number of patterns of atevirdine disposition were observed including; rapid absorption with C_{max} at 0.5–1 h, delayed absorption with C_{max} at 3–4 h; minimal C_{max} to C_{min} fluctuation and C_{max} to C_{min} ratios of >4. N-ATV (an inactive metabolite) patterns were characterized on day one by rapid appearance of the metabolite which peaked at 2–3 h after the dose and declined in a mono- or bi-exponential manner. At steady-state N-ATV patterns demonstrated minimal C_{max} to C_{min} fluctuations with some of the patients having more stable plasma N-ATV concentrations, while others had greater fluctuations week to week. *Conclusions:* Considerable interpatient variability was noted in the pharmacokinetics of atevirdine. The variation in drug disposition was reflected in the range of daily doses required to attain the targeted trough concentrations. Atevirdine metabolism did not appear to reach saturation during chronic dosing in many of our patients, as reflected by the pattern of N-ATV/ATV ratios in plasma and saturation was not an explanation for the variation in dosing requirements. No apparent differences were noted between males and females, and atevirdine did not appear to influence zidovudine disposition. Published by Elsevier Science B.V.

Keywords: Concentration-targeted phase I trials; Atevirdine mesylate; Patients with HIV; Dosage studies; Pharmacokinetic studies

1. Introduction

Atevirdine (U-87201E, ATV, Pharmacia & Upjohn, Kalamazoo, MI) is a first-generation bisheteroarylpiperazine (BHAP) with in vitro activity against human immunodeficiency virus type 1 (HIV-1), including strains resistant to zidovudine (Campbell et al., 1993). BHAPs are nonnucleoside reverse transcriptase inhibitors (NNRTIs), a structurally diverse group of antiretroviral agents that also includes delavirdine, nevirapine, and efavirenz, L697-661, and the TIBO compounds among others (Merluzzi et al., 1990; Pauwels et al., 1990; Goldman et al., 1991; Romero et al., 1991; Dueweke et al., 1993).

The design of early studies for the development of ATV required consideration of the complex pharmacokinetic characteristics which this agent possesses. ATV is most soluble at a $pH < 2$, has capacity-limited hepatic metabolism via the cytochrome p450-3A system and is extensively bound to plasma proteins (primarily albumin) (Cox et al., 1992; Rosser et al., 1994; Morse et al., 1996). The primary circulating metabolite of ATV is measured in plasma as *N*-dealkylated ATV (N-ATV) and has no antiviral activity. Determination of the N-ATV/ATV ratio has been used as a measure of metabolic capacity for ATV. Preclinical studies of ATV in dogs suggested that female animals developed higher steady-state concentrations and had more toxicity (personal communication, Dr Steven Cox, Pharmacia & Upjohn). Early clinical evaluation in humans revealed that two patients developed asymptomatic hyperbilirubinemia and had concurrent ATV trough plasma concentrations exceeding 30 μM (personal communication, Dr Steven Cox, Pharmacia & Upjohn).

Therefore, we present here the results of two concentration-targeted studies, ACTG protocols 187 and 199, for which the objective was to examine the dosage requirements and disposition of ATV in male and female patient. A secondary objective was to investigate zidovudine pharmacokinetics during ATV administration.

2. Methods

2.1. Patients

Patients enrolled in ACTG 187 and 199 had acquired immunodeficiency syndrome (AIDS) according to the Center for Disease Control (CDC) criteria established prior to 1993, or had evidence of HIV infection as determined by serologic tests or HIV culture from peripheral blood. Patients were ≥ 13 years of age and were free of life-threatening opportunistic infections at study entry. Other criteria for eligibility included a CD4 + lymphocyte count ≤ 500 per mm^3, hemoglobin ≥ 9.5 gm/dl, absolute neutrophil count ≥ 1000 per mm^3, platelet count ≥ 75000 per mm^3, creatinine ≤ 1.5 mg/dl, total bilirubin ≤ 2.5 mg/dl, and measurements of AST, ALT, and alkaline phosphatase ≤ 2.5 times the upper limit of normal. Criteria for exclusion included previous therapy with other antiretroviral or immunomodulatory agents (part 2 of ACTG 199 only); a history of severe cardiovascular, CNS, or gastrointestinal disorders; hyper-cholesterolemia; active alcohol or drug abuse; cytotoxic chemotherapy within 1 month of study entry; and inability to tolerate zidovudine (part 1 of ACTG 199 only). Patients utilizing drugs metabolized by the hepatic microsomal p450 enzyme system were also excluded from study participation.

Prior to enrollment in ACTG 187 and 199 the patients underwent a complete history and physical examination. In addition, the following studies were performed: chest radiography; electrocardiography; a complete blood count with differential and platelet counts; measurements of electrolytes, glucose, BUN, creatinine, AST, ALT, LDH, alkaline phosphatase, total bilirubin, triglycerides, cholesterol; and urinalysis. Measurement of T lymphocyte subsets was performed on two occasions at least 24 h apart prior to enrollment. Physical examinations, hematology and chemistry studies, and urinalyses were repeated weekly for 12 weeks and every other week thereafter. Electrocardiography was performed every other week for 12 weeks and then monthly. T lymphocyte subsets were determined at monthly intervals throughout the study.

2.2. Study design: ACTG 199

This trial was conducted in two parts. The principal objective of part 1 was to design a dosage regimen which would maintain plasma ATV trough levels in excess of IC_{50} values of HIV-1 isolates, and below potentially toxic levels. Most HIV-1 isolates have an ATV $IC_{50} \leq 0.1$ μM (unpublished data). In addition, initial pharmacokinetic studies in normal volunteers suggested that asymptomatic hyperbilirubinemia might occur with trough plasma concentrations ≥ 30 μM. Thus, we selected 5–10 μM as the targeted trough plasma concentration for this study. Part 1 patients were admitted to the Clinical Research Center at the University of Rochester and underwent pharmacokinetic studies. During a 1-week stay, a dose of ATV that produced plasma trough concentrations of 5–10 μM was determined for each patient. Zidovudine was administered at a dose of 200 mg orally every 8 h. A preliminary assessment of these data has been previously reported (Reichman et al., 1995). During part 1, we determined that a dose of 600 mg of ATV orally every 8 h produced desirable trough levels in the majority of patients. Therefore, this dose was administered initially to each patient in part 2. Trough levels were then monitored as outlined below, and adjustments were made when necessary to maintain ATV trough levels at concentrations of 5–10 μM for the 6 month study.

2.3. Blood sample collection and drug dosing part I

Prior to ATV dosing in patients nos. 1–5, an 8 h study of intravenous zidovudine (1.0 h infusion) was conducted. Subsequently intensive pharmacokinetics studies of the first 600 mg oral dose of ATV and the first oral ZDV dose was carried out and blood samples were collected at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, and 8 h. Subsequently the patients received ZDV 200 mg orally every 8 h and ATV 600 mg orally every 8 h. After the first week plasma trough levels were determined at weekly intervals for 2 weeks and every other week for the remainder of the study. Subsequently the dose of ATV was adjusted within 2–3 days to attain a

trough plasma concentration of 5–10 μM. Eight-hour pharmacokinetic studies were also conducted in patients nos. 1–5 from 80–88 h after the start of the study.

2.4. Part II

Patients enrolled in part II were studied on an outpatient basis. These patients were also given ATV 600 mg orally every 8 h and ZDV 200 mg orally every 8 h. Trough blood samples for ATV were collected at 48, 96, 168, 264 and 338 h. Subsequent blood sampling was at weekly intervals for 2 weeks and every other week for the remainder of the study. When possible 8 h pharmacokinetic studies, as described above, were conducted during treatment, usually after 6–12 weeks of combination therapy. All plasma specimens were stored at −70°C and shipped on dry ice to arrive at the pharmacology laboratory by the next morning. After a review of each patient's ATV concentrations and dosing history, dosage adjustments were recommended by the protocol pharmacologist in order to attain the targeted trough value.

2.5. Study design: ACTG 187

Patients were randomly assigned to one of three pre-selected targeted ATV trough concentration ranges. The targeted trough values were 5–13 μM for group I, 14–22 μM for group II, and 23–31 μM for group III. When this protocol was initiated, group I patients were to receive 600 mg tid, group II patients 1000 mg tid, and group III 1400 mg tid. However, the first five patients in group II who received 1000 mg tid had troughs which exceeded the target values and led to a protocol amendment which allowed subsequent patients in groups II and III to begin ATV at 800 mg tid. Weekly trough plasma ATV samples were collected and the ATV dosage adjusted to attain the targeted concentrations for the 6-month study. In addition to the weekly trough level monitoring, eight female patients in each group were recruited to participate in pharmacokinetic studies which were conducted after the morning dose on day 1 (24-h study), week 4 and/or week 8. The women were enrolled to complement the data from ACTG 199 which was conducted only in men. The 8-h pharmacokinetic studies were conducted as described above for the ACTG 199 study.

2.6. Drug assays

ATV and its N-ATV (U-89255) were measured by a high performance liquid chromatography (HPLC) method developed by Pharmacia & Upjohn (Howard and Schwende, 1993). ATV mesylate, N-ATV, and internal standard (U-88352) were provided as analytical grade powder by Pharmacia & Upjohn. All samples were heat-inactivated in a water bath at 56°C for 30 min prior to assay. To 300 μl of sample, 600 μl of a mixture of acetonitrile and 10 μg/ml U-88352 were added. The mixture was then vortexed and 5–10 μl of the upper layer was injected into the HPLC system. A standard curve in duplicate was prepared in plasma from 65.9 to 0.0851 μM for ATV and 71.1 to 0.0919 μM for N-ATV. ATV, N-ATV and the internal standard were detected with fluorescence detection at an excitation wavelength of 295 nm and an emission wavelength of 418 nm. The three compounds were eluted with a mobile phase consisting of 50% 20 mM ammonium phosphate and 50% acetonitrile. Quality control samples (high: 52.7 μM (ATV) and 56.9 μM (N-ATV); medium: 5.27 μM (ATV) and 5.69 μM (N-ATV); and low: 0.264 μM (ATV) and 0.285 μM (N-ATV)) were included with each analytical run and the data were only acceptable if two of the three quality control samples at each concentration were within 15% of their target concentration. Intraassay variation was $\leq 4\%$ and interassay variation was $\leq 7\%$ at all quality control concentrations. Standard curves were weighted with a factor of $1/x$ and the data were analyzed on a mainframe IBM computer with SAS. No interference due to ZDV or ZDV glucuronide was noted. All samples were analyzed and results reported to the clinical site within 24–48 h of receiving the sample.

All measurements for ZDV were conducted utilizing a commercially available radioimmunoassay kit from INCStar (Stillwater, MN) (Lake-Bakaar et al., 1988; ZDVTrac, 1996). Modifications from the dilutions specified by the manufacturer were

made and a 1:10 dilution of plasma was also utilized as recently reported (DeRemer et al., 1997). A spline fitting was used to assess calibration standard curves; the program utilized was the 1221-244 Ultroterm version 2 (Pharmacia/Wallac, Gaithersburg, MD). Otherwise, all methodology followed the instructions provided by the manufacturer. Intraassay variation ranged from 4.1 to 7.8% at low quality control concentrations and 3.6–4.1% at high quality control concentrations. The interday coefficient of variation was 9.6% for the low quality control and 6.6% for the high quality control.

PCNONLIN was used to evaluate the plasma concentration versus time data and to determine ATV and ZDV pharmacokinetic parameters.

3. Results

3.1. Subjects

Twenty subjects were enrolled in ACTG 199, five in part 1 and 15 in part 2. The median age was 31 years with a range 26–54. Most patients were gay/bisexual and white. Twelve patients had AIDS, and eight had asymptomatic HIV infection. All five patients enrolled in part 1 had previously received ZDV for a median of 11 weeks with a range 7–36 weeks. The median baseline CD4 count was 189 cells/mm^3 (range 9–498). Thirty patients were enrolled in ACTG 187, the clinical tolerance, immunologic and virology studies are reported in a separate paper (Demeter et al., 1998).

3.2. Dosage requirements and achievement of targeted trough concentrations

3.2.1. ACTG 187

Eleven of 12 patients in group I achieved the targeted trough ATV concentration (5–13 μM). Seven of these nine patients attained the target by week 4 of the study and the daily doses required were 1800 mg ($n=4$), 1200 mg ($n=3$) and 900 mg ($n=2$). Of the three patients who did not achieve the target, all three experienced adverse effects (all developed a rash) which required temporary dose-reduction or discontinuation of ATV.

Seven of 11 patients in group II achieved the target ATV concentration (14–22 μM). Of these five patients achieved the target by week 8 and the daily doses required were 3000 mg ($n=1$), 2400 mg ($n=1$), 2250 mg ($n=1$), 1200 mg ($n=1$) and 600 mg ($n=1$). The four patients who did not achieve the target experienced adverse effects which required temporary dose reduction or discontinuation of ATV.

Only three of 1 patients in group III achieved the targeted trough ATV concentration (23–31 μM) (Fig. 1). Of the three patients who attained the target range, two required 8 weeks, and one patient required 12 weeks to attain the target. For these three patients the daily dosage needed was 4200 mg ($n=1$), 3900 mg ($n=1$) and 1800 mg ($n=1$). Of the eight patients who did not attain the target, three had trough values ranging from 6.5 to 12.3 μM and two had trough values which exceeded the target (31.2 and 49.7 μM). Five of the eight patients who did not achieve the target experienced adverse effects which required temporary dose-reduction discontinuation of ATV.

The mean number of weeks required to attain the targeted trough values were 2.7 ± 2.4 weeks (5–11 μM), 2.6 ± 1.8 weeks (12–21 μM) and 7.0 ± 5.6 weeks (22–31 μM). The percent of patients in each group who achieved the target range was 92, 64 and 27%, respectively (Table 1). Certain patients who required dose-reduction early in the study due to development of a rash were eventually able to attain the target concentration. The ratio of N-ATV/ATV at the time the target was reached was 1.35 ± 1.19, 1.18 ± 0.39, and 1.07 ± 0.65, respectively.

3.2.2. ACTG 199

The mean number of weeks to attain the target range (5–10 μM) was 3.2 ± 5.2 weeks. The mean dose required was 568 ± 120 mg three times daily and the N-ATV/ATV ratio the week the target was reached was 1.10 ± 0.57. Fifteen patients required no dose adjustment, one an increased dose, and four patients a dose reduction to attain the 5–10 μM trough. Of those patients who had a dose reduction, three had a trough concentration by week 2 of >12 μM and one of these patients had values >28 μM. Examination of the N-

Table 1
Summary of the factors involved in implementing a trough-targeted, concentration-escalation phase I trial of ATV (ACTG 187) or a single trough range targeted trial (ACTG 199)

	No. of patients attaining targeted trough concentration	No. of weeks required to reach the targeted concentration	Range of ATV daily doses required to attain the targeted trough concentration	Range of dose adjustments to maintain the targeted trough concentration
ACTG 187				
Group I (5–13μM)	11/12 (92)[a]	2.7 ± 2.4	900–1800	0–4
Group II (14–22)	7/11 (64)	2.6 ± 1.8	600–3000	0–6
Group III (23–31μM)	3/11 (29)	7.0 ± 5.6	1800–4200	0–5
ACTG 199				
Group I (5–10μM)	19/20 (95)	3.2 ± 5.2	600–2400	0–1

[a] Values in parentheses are percent.

ATV/ATV trough ratio did not explain the need for dosage increases or decreases based on variable hepatic metabolism profiles.

3.3. ATV: male versus female first dose pharmacokinetics

The male patients ($n = 8$) undergoing intensive pharmacokinetics (8-h study) in ACTG 199 all received a 600 mg dose initially. The mean ATV C_{max} ranged from 1.43 to 6.55 μM and the T_{max} from 0.5 to 5 h. Only two out of eight patients had ATV plasma concentrations above the lower limit of quantitation longer than 4 h after the dose. Three of eight patients had measurable N-ATV at 8 h after the dose. ATV Cl_{oral} ranged from 27.7 to 82.3 l/h in the three patients with sufficient data for analysis.

The female patients ($n = 7$) in ACTG 187 received from 600 to 1000 mg doses, but also had low ATV concentrations with only three patients having measurable concentrations 4 h after the first dose. However, in contrast to the males, five out of seven female patients had measurable N-ATV 12 h after the dose, and three were still detectable at 24 h. ATV Cl_{oral} ranged from 39.5 to 121.2 l/h, with one patient who had very low ATV plasma concentrations excluded from the analysis (Cl_{oral} of 654.2 l/h).

3.4. ATV: male versus female multiple-dose pharmacokinetics

The male patients ($n = 7$; 2 on day 4, 5 at weeks 6–14) undergoing intensive steady-state pharmacokinetics in ACTG 199 all received ATV doses ranging from 400 to 700 mg plus ZDV. The mean ATV C_{max} ranged from 6.85 to 24.4 μM and the T_{max} from 0.5 to 6 h. ATV Cl_{oral} ranged from 8.87 to 44.0 l/h.

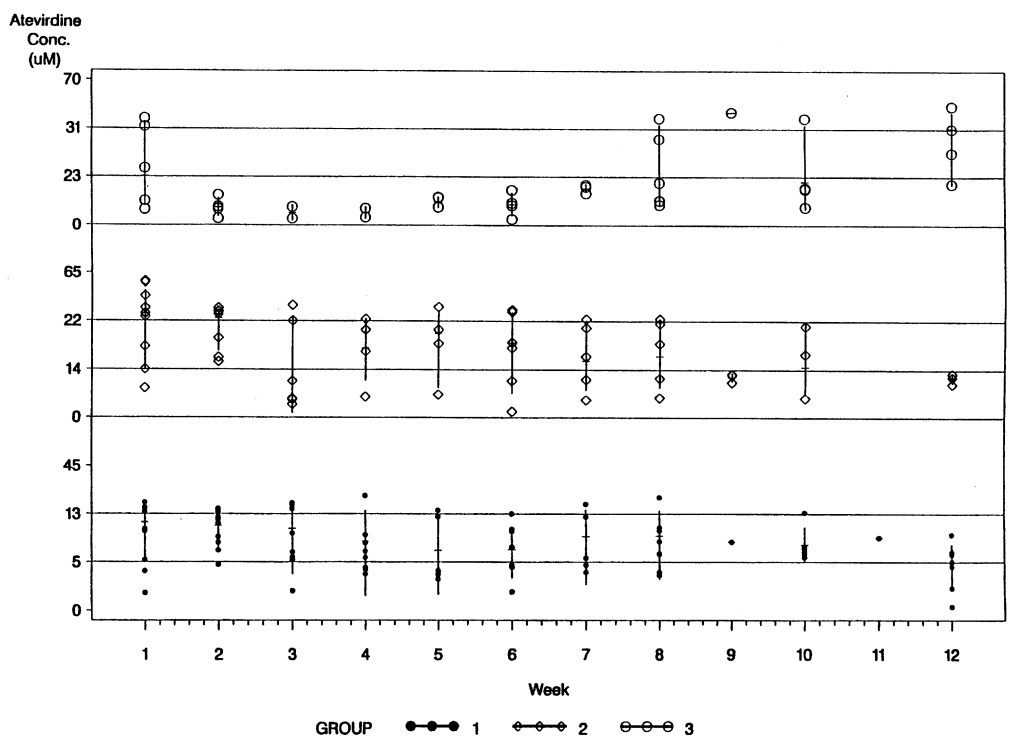

Fig. 1. A summary of the patients enrolled in ACTG 187 who attained the designated target trough ATV plasma concentration over the study period. The patients were randomized to three groups (group I: ATV concentration of 5–13 μM; group II: 14–21 μM; and group III: 22–31 μM).

At week 4 ($n = 7$) the female patients in ACTG 187 (8 h study) received from 300 to 1000 mg doses. The C_{max} ranged from 6.69 to 44.2 μM and the T_{max} ranged from 0.5 to 4 h. N-ATV was measurable in all patients with a C_{max} that ranged from 8.17 to 89.8 μM and the T_{max} ranged from 0.5 to 4 h. ATV Cl_{oral} ranged from 5.78 to 107.5 l/h.

At week 8 ($n = 6$) the female patients in ACTG 187 received from 300 to 800 mg doses. The ATV C_{max} ranged from 4.54 to 13.1 μM and the T_{max} ranged from 0.5 to 1 h. N-ATV was measurable in all patients with a C_{max} that ranged from 8.17 to 89.8 μM and the T_{max} ranged from 0.5 to 4 h. ATV Cl_{oral} ranged from 13.4 to 76.8 l/h. Table 2 summarizes the ATV and obtained from the intensive pharmacokinetic studies in ACTG 199 and 187.

3.5. Zidovudine: intraindividual pharmacokinetics

Following the first dose of ZDV ($n = 8$), the mean ZDV C_{max} was 989 ± 703 ng/ml and the median T_{max} was 0.75 h. The mean CL_{oral} was 139 ± 42.7 l/h and the plasma half-life was 1.87 ± 0.308 h. Evaluation of steady-state ZDV pharmacokinetics ($n = 8$) yielded a mean ZDV C_{max} of 795 ± 360 ng/ml and a median T_{max} of 1.0 h. The mean Cl_{oral} was 182.6 ± 21.3 l/h and the plasma half-life was 2.12 ± 1.43 h.

In two patients in ACTG 199 additional intravenous studies (attained prior to starting ATV) yielded ZDV bioavailability data after the first dose and after 4 days of combination therapy. Patient no. 4 had an AUC_{oral}/AUC_{iv} of 0.56 (bioavailability = 56%) and 0.45 (bioavailability = 45%), respectively. Patient #5 had an AUC_{oral}/AUC_{iv} of 0.83 (bioavailability = 83%) and 0.46 (bioavailability = 46%), respectively. Patient #5 also had an AUC determination after 6 weeks which yielded an AUC_{oral}/AUC_{iv} of 0.65 (bioavailability = 65%).

4. Discussion

The pharmacokinetic data from ACTG 187 and 199 provide valuable insight into the appropriate dosage for chronic therapy with ATV. These trials employed an innovative approach to the phase I study design in order to minimize the overlap in drug exposure (i.e. AUC) among groups which is commonly observed when traditional dose-escalation is employed (Peck et al., 1993). The fact that we experienced certain difficulties while implementing this type of study design in a phase I trial was most likely related to our selection of the initial dosage regimens that were selected based upon pre-clinical pharmacokinetic data, as well as data from healthy volunteers. In some of our patients the inability to attain the targeted ATV concentrations was due to the development of an adverse effect, primarily a rash, which required either a dose-reduction or discontinuation. Another factor, which may have contributed to low ATV concentrations in selected patients, was noncompliance. One patient who was obese required the highest dose of ATV to attain the target trough value, although the exact relationship between weight and dosage requirements in this patient remains unclear. The N-ATV/ATV ratio in this subject suggested that enhanced metabolic capacity was not the primary factor leading to low ATV concentrations. The fact that this patient did eventually reach the target range suggests that reduced absorption was a more likely cause.

Previous studies of ATV in healthy adult volunteers (doses of 50–1200 mg) indicated that this compound displayed nonlinear pharmacokinetics (Cox et al., 1992), as evidenced by the observation that increasing doses yielded area under the curve values that were not dose-proportional. The disposition profile for ATV we observed during chronic dosing was similar to previous studies in healthy volunteers and HIV-infected patients (Cox et al., 1992). While a concern in designing our study was the avoidance of excessive ATV plasma concentrations (which were thought to be a result of the capacity-limited nature of this agent's hepatic metabolism) a number of patients demonstrated pharmacokinetic characteristics that led to a difficult time attaining the desired target trough plasma concentration. Similar to the obese patient mentioned above, it is difficult to determine if these patients had low absorption or

Table 2
Pharmacokinetic parameters for ATV in male (ACTG 199) and female (ACTG 187) patients

Patient no.	Week 1 Dose (mg/dose given TID)	AUC (μM/h)	Cl_{oral} (l/h)	Week 4 Dose (mg/dose given TID)	AUC (μM/h)	Cl_{oral} (l/h)	Week 8 Dose (mg/dose given TID)	AUC (μM/h)	Cl_{oral} (l/h)
ACTG 187									
1	800	260.9	12.10	800	20.88	101.2	ND[a]	ND	ND
2	600	40.06	128.5	ND	ND	ND	300	58.86	13.43
3	600	17.44	237.2	300	44.70	17.69	300	31.35	25.22
4	1000	30.07	119.6	600	161.6	9.783	400	60.36	17.46
5	1000	21.74	139.0	ND	ND	ND	ND	ND	ND
6	ND	ND	ND	800	33.55	62.84	800	26.15	80.63
7	600	148.8	26.56	400	44.0	23.96	400	28.34	37.20
8	800	3.222	746.3	ND	ND	ND	ND	ND	ND
ACTG 199									
1	ND	ND	ND	600	35.92	44.02	700	100.6	18.33
2	600	5.95	265.7	ND	ND	ND	600	46.32	34.14
3	600	1.345	1175	ND	ND	ND	600	118.8	13.31
4	600	5.055	312.8	ND	ND	ND	400	65.42	16.11
5	600	0.715	2211	ND	ND	ND	ND	ND	ND
6	600	12.56	125.9	ND	ND	ND	ND	ND	ND
7	600	15.85	99.74	ND	ND	ND	300 (week 40)	96.13	8.225

[a] ND, not determined.

high metabolic capacity; however the ratio of parent to metabolite was similar among both types of patients suggesting that reduced absorption may have been the more important factor. Indeed, since these trials were initiated, a greater appreciation has been developed for the impact of reduced gastric acidity among HIV-infected patients and its potential impact on BHAP NNRTIs (i.e. ATV and delavirdine) as well as other drugs that are most soluble at low gastric pH values (i.e. ketoconazole and dapsone) (Lake-Bakaar et al., 1988; Breen et al., 1994). For example, gastric hypoacidity has been reported among patients with HIV infection regardless of the CD4+ cell count (Placidi et al., 1993; Shelton et al., 1995b). The pathogenetic mechanism for the elevated gastric pH is currently unknown. Certain patients have been noted to have elevated circulating gastrin and reduced vitamin B12 absorption, suggesting a reduced functional parietal cell mass (Lake-Bakaar et al., 1988) while others have been identified with concurrent *Helicobacter pylori* infection (Shelton et al., 1995a). Two studies have reported that an elevated gastric pH secondary to didanosine administration resulted in reduced ATV and delavirdine absorption, respectively (Morse et al., 1996, 1997). While hypoacidity may have contributed to the low plasma concentrations in certain of our patients, other factors are probably contributing and need to be investigated further.

We did not observe any influence of ATV on zidovudine pharmacokinetics. The plasma concentration profiles among the patients in ACTG 199 were similar to another study which examined delavirdine and a zidovudine regimen of 200 mg every 8 h (Morse et al., 1994). Pharmacokinetic parameters such as oral clearance and half-life were also similar to other reports, which have examined a 100 mg dose (Blum et al., 1988). While some concern exists with regard to the potential for ATV to interfere with other drugs which are metabolized by the cytochrome p450 system, no data exist which suggest that drugs undergoing glucuronidation will be effected. Although a small percentage of zidovudine is metabolized via the cytochrome p450 system to aminothymidine, a potentially myelosuppressive metabolite, we did not assay this compound during this study (Placidi et al., 1993). The lack of effect on the zidovudine and zidovudine glucuronide AUC combined with the lack of observed hematologic toxicity suggests that no clinically important interaction between ATV and zidovudine occurred although no measurement of intracellular zidovudine anabolites was conducted in our studies.

Another aspect of our data was the consideration of the plasma concentration profiles, which resulted when ATV and zidovudine were taken together or alone. In addition, in vitro studies have revealed that additive antiviral activity can be attained using equimolar combinations of these two agents which range from 0.01 to 2.0 μM (Campbell et al., 1993). Furthermore, although zidovudine plasma trough concentrations are not expected to accumulate during chronic dosing, our data shows ATV to have saturable metabolism resulting in prolonged exposure to this agent yielding a long interval over which the steady-state plasma concentration for each drug are synergistic in plasma. Initial analysis of the data from ACTG 199 have been reported which indicate that combined ATV and zidovudine administration delayed the emergence of the 181 mutation compared to the time required to observe this mutational change for other NNRTIs alone (Demeter et al., 1993). Virologic and immunologic studies from ACTG 187 and examination of their relationship to ATV plasma concentrations are presented in another report (Demeter et al., 1998).

In summary, targeted ATV plasma concentrations were attained in many of the patients in both of these trials. However, individual differences in drug disposition were apparent with a wide range of dosages required to achieve the target plasma concentrations. Absorption, rather than hepatic metabolism, appears to be the main factor limiting plasma concentration. In contrast to preclinical studies, which noted different patterns of drug disposition among male and female animals, we did not observe these differences in our patients. The plasma concentrations of ATV attained in these trials provide the patient with a considerable period of exposure to drug concen-

trations which have been shown to elicit an anti-HIV effect in vitro for the majority of a 24 h period. Further clinical evaluation of ATV will help determine the future role of this agent in the armentarium of antiretroviral agents as well as the need for therapeutic drug monitoring to guide chronic therapy.

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