

ABT-378/ritonavir plus stavudine and lamivudine for the treatment of antiretroviral-naive adults with HIV-1 infection: 48-week results

Robert L. Murphy, Scott Brun^a, Charles Hicks^b, Joseph J. Eron^c, Roy Gulick^d, Martin King^a, A. Clinton White, Jr.^e, Constance Benson^f, Melanie Thompson^g, Harold A. Kessler^h, Scott Hammerⁱ, Richard Bertz^a, Ann Hsu^a, Anthony Japour^a and Eugene Sun^a

Objective: To evaluate the safety and antiviral activity of different dose levels of the HIV protease inhibitor ABT-378 combined with low-dose ritonavir, plus stavudine and lamivudine in antiretroviral-naive individuals.

Design: Prospective, randomized, double-blind, multicenter.

Methods: Eligible patients with plasma HIV-1 RNA > 5000 copies/ml received ABT-378 200 or 400 mg with ritonavir 100 mg every 12 h; after 3 weeks stavudine 40 mg and lamivudine 150 mg every 12 h were added (group I, n = 32). A second group initiated treatment with ABT-378 400 mg and ritonavir 100 or 200 mg plus stavudine and lamivudine every 12 h (group II, n = 68).

Results: Mean baseline HIV-1 RNA was 4.9 log₁₀ copies/ml in both groups and CD4 cell count was 398 × 10⁶/l and 310 × 10⁶/l in Groups I and II respectively. In the intent-to-treat (ITT; missing value = failure) analysis at 48 weeks, HIV-1 RNA was < 400 copies/ml for 91% (< 50 copies/ml, 75%) and 82% (< 50 copies/ml, 79%) of patients in groups I and II respectively. Mean steady-state ABT-378 trough concentrations exceeded the wild-type HIV-1 EC₅₀ (effective concentration to inhibit 50%) by 50–100-fold. The most common adverse events were abnormal stools, diarrhea and nausea. No patient discontinued before 48 weeks because of treatment-related toxicity or virologic rebound.

From the Department of Medicine, Northwestern University, Chicago, ^aAbbott Laboratories, Abbott Park, Illinois, ^bDuke University Medical Center, Durham, the ^cDepartment of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, the ^dDepartment of Medicine, Cornell University, New York, ^eThomas Street Clinic/Baylor College of Medicine, Houston, Texas, the ^fDepartment of Medicine, University of Colorado, Denver, Colorado, the ^gAIDS Research Consortium of Atlanta, Atlanta, Georgia, the ^hDepartments of Medicine and Immunology/Microbiology, Rush Medical College, Chicago, Illinois and the ⁱDepartment of Medicine, Columbia University, New York, USA.

Requests for reprints to: R. L. Murphy, Department of Medicine, Division of Infectious Diseases, Northwestern University, 676 North St. Clair Street, Suite 1920, Chicago, IL 60611, USA.

Note: James Thommes, Pacific Oaks Research, Los Angeles, California, Mary Albrecht, Department of Medicine, Harvard University, Boston, Massachusetts and Kathryn Real, Abbott Laboratories, Abbott Park, Illinois, USA also contributed to this work.

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Conclusions: ABT-378 is a potent, well-tolerated protease inhibitor. The activity and durable suppression of HIV-1 observed in this study is probably attributable to the observed tolerability profile and the achievement of high ABT-378 plasma concentrations.

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Introduction

Antiretroviral therapy with HIV-1 protease inhibitors is associated with dramatic and often sustained declines in plasma HIV-1 RNA levels, as well as improvement in immunologic status [1–5]. This treatment effect has resulted in a significant reduction in the incidence of opportunistic diseases and improvement in survival [5–8]. Despite these outcomes, clinical trials evaluating antiretroviral regimens containing a protease inhibitor and two nucleoside analog reverse transcriptase inhibitors have shown that plasma HIV-1 RNA is suppressed to levels below 50 copies/ml for only approximately one-half of patients by intent-to-treat (ITT) analyses after 24 or more weeks of therapy [9,10]. Although the reasons for treatment failure are multiple, currently available protease inhibitors exhibit marginal pharmacokinetics with trough plasma concentrations falling close to or below the levels required to fully inhibit replication of wild-type HIV-1 *in vitro* [11]. There is currently an unmet need for antiretroviral agents and regimens that combine marked and sustained efficacy, sufficient tolerability and ease of use.

ABT-378 is a novel HIV-1 protease inhibitor that is approximately 10 times more potent than ritonavir *in vitro* [12]. ABT-378 is extremely sensitive to pharmacokinetic enhancement by low doses of ritonavir, an inhibitor of the cytochrome P450 3A isoenzyme. (*In vitro* $K_i = 0.013$ nM compared to $K_i = 0.14$ nM for indinavir) [13]. When ABT-378 was co-administered with low doses of ritonavir (ABT-378/r) in phase I trials, the resultant steady-state plasma trough concentrations of ABT-378 were 50–100-fold greater than the EC_{50} (effective concentration to inhibit 50%) for wild-type HIV, corrected for plasma protein binding [14,15]. At the doses administered with ABT-378, ritonavir is unlikely to contribute significantly to antiviral activity based on drug levels achieved in pharmacokinetic studies which are well below estimated *in vivo* inhibitory concentrations [16].

The objective of this dose-ranging study was to assess the antiviral activity and safety of ABT-378/r in combination with stavudine and lamivudine, in antiretroviral-naive HIV-infected individuals.

Methods

Study design

This study was a prospective, randomized, double-blind, multicenter clinical trial. Two groups were enrolled sequentially. Three different dose combinations of ABT-378 and ritonavir were used to evaluate safety and efficacy across a range of ABT-378 plasma concentrations achieved through ritonavir pharmacokinetic enhancement. In Group I, patients were randomized to receive either 200 mg ABT-378 with 100 mg ritonavir (ABT-378/r 200/100 mg) or 400 mg ABT-378 with 100 mg ritonavir (ABT-378/r 400/100 mg) orally every 12 h. During the first 2 weeks of therapy all doses were either directly observed by study personnel or monitored by telephone call. At week 3, stavudine 40 mg orally and lamivudine 150 mg orally every 12 h were added. Once all patients were enrolled in group I and a preliminary safety analysis had been performed, enrollment in group II began. Patients in group II were randomized to receive ABT-378/r at either 400/100 mg or 400/200 mg orally every 12 h plus standard doses of stavudine and lamivudine.

Study visits occurred at least monthly for the first 24 weeks and quarterly thereafter. Plasma HIV-1 RNA measurements were performed at all visits using the Roche Amplicor HIV-1 Monitor [Roche, Branchburg, New Jersey, USA; limit of quantitation (LOQ), 400 copies/ml] and the investigational Abbott Laboratories LCx HIV RNA quantitative assay [Abbott Laboratories, Abbott Park, Illinois, USA; LOQ, 50 copies/ml]. CD4 and CD8 cell counts, hematology and clinical chemistry evaluations were performed at each study visit. In a subset of 45 patients, plasma samples were collected for pharmacokinetic analyses of ABT-378 and ritonavir over a 12-h dosing interval following the morning dose at week 3 (group I), week 4 (group II), and week 24 (both groups).

Inclusion/exclusion criteria

Eligibility requirements included: no prior antiretroviral therapy, age ≥ 18 years, baseline plasma HIV-1 RNA > 5000 copies/ml, no acute illness, Karnofsky score ≥ 70 , no active substance abuse, and the ability to comply with study procedures. Exclusion criteria in-

cluded hemoglobin < 8.5 g/dl, absolute neutrophil count $< 1000 \times 10^6$ cells/l, platelet count $< 50\,000 \times 10^6$ /l, alanine transaminase (ALT) or aspartate transaminase (AST) > 2.5 times the upper limit of normal, creatinine > 1.5 times the upper limit of normal, and fasting triglycerides > 400 mg/dl. Women were excluded if pregnant or lactating and had to agree to use barrier birth control methods. Patients co-infected with hepatitis B and/or C virus were excluded from group I. All patients agreed to and signed an Institutional Review Board-approved informed consent form.

Statistical analysis

The sample sizes were calculated to provide power to detect uncommon adverse events. For example, the sample sizes in group I and group II provided 82% and 83% power respectively to detect at least one adverse event if the true underlying event rates were 10% and 5% respectively.

All patients who received at least one dose of study drug were included in the analyses. Baseline demographic and disease characteristics were compared using a one-way analysis of variance and Fisher's exact test. The primary efficacy variables were the proportion of patients with plasma HIV-1 RNA below the LOQ (400 copies/ml) at week 24 and the duration of virologic response through week 48. ITT and on-treatment methods were used to analyze the proportion of patients with plasma HIV-1 RNA below the LOQ. The ITT analysis [missing value = failure (M = F)] considered any patient with a missing value at a visit for any reason as a treatment failure. On-treatment analyses excluded missing values and those obtained during treatment interruption of at least 3 days. Fisher's exact test was used to test whether there was no difference between dose groups in the proportion of subjects with HIV RNA level below the LOQ at each visit. The Cox proportional hazards model was used to test for differences between dose groups in the time to loss of virologic response. Adverse events were summarized using COSTART V [17]. The relative risk of grade III/IV liver enzyme elevations based on baseline hepatitis serology was computed.

Pharmacokinetic parameters for ABT-378 and ritonavir [C_{\max} , pre-morning dose concentration (trough level or C_{trough}), area under the plasma concentration time curve for a dosing interval (AUC_{12}), and half-life over a 12-h dosing interval ($t_{1/2}$)] were determined by non-compartmental methods. Repeated measures analyses using a mixed linear model with effects of regimen, week and their interaction were performed to examine if the pharmacokinetic parameters changed over time. All reported *P*-values are based on two-sided tests of significance.

Results

Baseline characteristics

A total of 100 patients participated, 32 in group I and 68 in group II. The groups were well-balanced for sex, age, race, ethnicity, risk factor for HIV-1 infection, and time since HIV-1 diagnosis. The mean age was 35 years, 96% were male, 70% were Caucasian and 30% were African-American. The mean time since diagnosis of HIV-1 infection was 2.3 years.

There were no significant differences in the mean baseline plasma HIV-1 RNA levels or CD4 cell counts for patients enrolled into either of the treatment arms in groups I or II. Overall, the mean baseline plasma HIV-1 RNA was $4.9 \log_{10}$ copies/ml in both groups. The mean baseline CD4 cell count was 398×10^6 /l and 310×10^6 /l for patients enrolled in groups I and II respectively (Table 1).

Antiviral activity

A rapid decline in plasma HIV-1 RNA was observed across all treatment arms and was sustained through week 48 with a mean reduction from baseline of $2.23 \log_{10}$ copies/ml. At week 3, the mean decrease from baseline in HIV-1 RNA was $-1.85 \log_{10}$ copies/ml for patients receiving ABT-378/r alone in group I. The slope of HIV-1 RNA decay from baseline to week 2 in patients who initiated ABT-378/r alone was similar to that in patients who initiated all three drugs simultaneously in group II ($-1.73 \log_{10}$ copies/ml versus $-1.68 \log_{10}$ copies/ml). The lack of a week 3 study visit for group II precluded direct comparison with group I at that time point. All patients, except one who discontinued therapy early in the study, had a decline in plasma HIV-1 RNA to < 400 copies/ml.

The median times to achieve < 400 copies/ml were 43 and 42 days for group I (200/100 mg and 400/100 mg) and 56 and 57 days for group II (400/100 mg and 400/200 mg), respectively. The corresponding values for median time to achieve < 50 copies/ml were 77 and 72 days for group I (200/100 mg and 400/100 mg) and 74 and 85 days for group II (400/100 mg and 400/200 mg) respectively. Patients with baseline plasma HIV-1 RNA $> 100\,000$ copies/ml generally took longer to achieve a viral load < 400 copies/ml than patients with baseline values $< 100\,000$ copies/ml (median time to < 400 copies/ml 12 weeks versus 4 weeks respectively). Response rates were not significantly different at week 20 and thereafter.

In the ITT M = F analysis at 48 weeks, HIV-1 RNA was < 400 copies/ml for 91% (< 50 copies/ml, 75%) and 82% (< 50 copies/ml, 79%) of patients in groups I and II, respectively. Overall at week 48, 85% of patients had HIV-1 RNA < 400 copies/ml by ITT

Table 1. Baseline characteristics of the patient population.

	Group I (ABT-378/r every 12 h)		Group II (ABT-378/r every 12 h)		Total (n = 100)
	200/100 mg (n = 16)	400/100 mg (n = 16)	400/100 mg (n = 35)	400/200 mg (n = 33)	
Sex (n)					
Male	16	14	34	32	96
Female	0	2	1	1	4
Race (n)					
Black	4	5	9	12	30
Caucasian	12	11	26	21	70
Ethnicity ^a (n)					
Hispanic	0	1	2	3	6
Age (years)					
Mean \pm SD	36.1 \pm 8.3	32.9 \pm 3.6	34.7 \pm 8.5	35.3 \pm 9.2	34.8 \pm 8.1
Range	23–54	27–39	21–55	24–59	21–59
Height (cm)					
Mean \pm SD	178.7 \pm 7.7	174.6 \pm 12.8	176.3 \pm 7.9	176.5 \pm 7.1	176.5 \pm 8.7
Weight (kg)					
Mean \pm SD	81.6 \pm 19.8	77.5 \pm 14.5	74.4 \pm 10.7	76.2 \pm 12.6	76.6 \pm 13.7
HIV-1 risk factors ^b (n)					
Homosexual/bisexual male	15	12	27	27	81
Injecting drug user	2	0	0	1	3
Transfusion recipient	0	0	1	1	2
Sex partner HIV positive	6	5	6	5	22
Sex partner injecting drug user	1	1	0	0	2
Unknown	0	2	5	3	10
Other	2	1	3	1	7
Time since HIV diagnosis (years)					
Mean \pm SD	0.8 \pm 1.0	2.8 \pm 4.4	2.8 \pm 3.9	2.2 \pm 3.9	2.3 \pm 3.7
Range	0.1–4.2	0.1–12.2	0.1–12.9	0.1–15.4	0.1–15.4
Hepatitis B/C virus status					
Positive	0	0	4	7	11
Plasma HIV RNA (log ₁₀ copies/ml)					
Mean \pm SE	4.88 \pm 0.16	4.96 \pm 0.15	4.78 \pm 0.12	4.97 \pm 0.13	4.89 \pm 0.07
CD4 cell count ($\times 10^6$ /l)					
Mean \pm SE	^c 471 \pm 66 ^c	330 \pm 77	343 \pm 38	275 \pm 40	334 \pm 24

^aWhere specified as a subcategory of race. ^bSubjects may be in multiple categories. ^cData on 15 patients.

analysis, and 92% by on-treatment analysis. Using the Abbott LCx viral load assay, 78% of patients overall had HIV-1 RNA < 50 copies/ml at week 48 (ITT). Plots of antiviral activity by dose level are presented in Fig. 1.

Response rates varied minimally between dose assignments in groups I and II at time points through week 48. At week 48 only, fewer patients achieved HIV-1 RNA < 50 copies/ml in the 400/100 mg dose arm in group I than in the 200/100 mg dose arm [50% (8/16) versus 100% (16/16) by ITT analysis; $P = 0.002$]. This observed rate of antiviral activity in the 400/100 mg dose arm in group I was also lower than that observed with the same dose level in group II at week 48 [86% (30/35) with HIV-1 RNA < 50 copies/ml by ITT]. Of the eight patients in the 400/100 mg arm in group I with HIV-1 RNA > 50 copies/ml at week 48, six patients had values < 50 copies/ml at their subsequent evaluation. Results were not significantly different for the proportion of patients with HIV-1 RNA < 400 copies/ml [100% (16/16) of the patients in the 200/100 mg arm and 81% (13/16) of the patients in

the 400/100 mg arm; $P = 0.226$]. A similar result was seen between dose arms in group II at week 48 only in the on-treatment analysis of patients with HIV-1 RNA < 400 copies/ml [100% (32/32) of the patients in the 400/100 mg arm and 80% (24/30) of the patients in the 400/200 mg arm; $P = 0.01$]. This difference was not significant in the analysis of proportion of patients with HIV-1 RNA < 50 copies/ml at week 48. No significant differences between the dosing arms was noted at other times or in a time-to-virologic failure analysis through week 48.

Immunologic changes

Substantial increases in the mean CD4 cell count were observed in all treatment arms from week 4 onwards, with no significant differences between treatment arms (Fig. 2). At week 48, the mean CD4 cell count had increased from baseline values by 244×10^6 and 213×10^6 cells/l in group I and group II respectively.

Pharmacokinetics

ABT-378 and ritonavir pharmacokinetic parameters (mean \pm SD) for the three dosing regimens at weeks

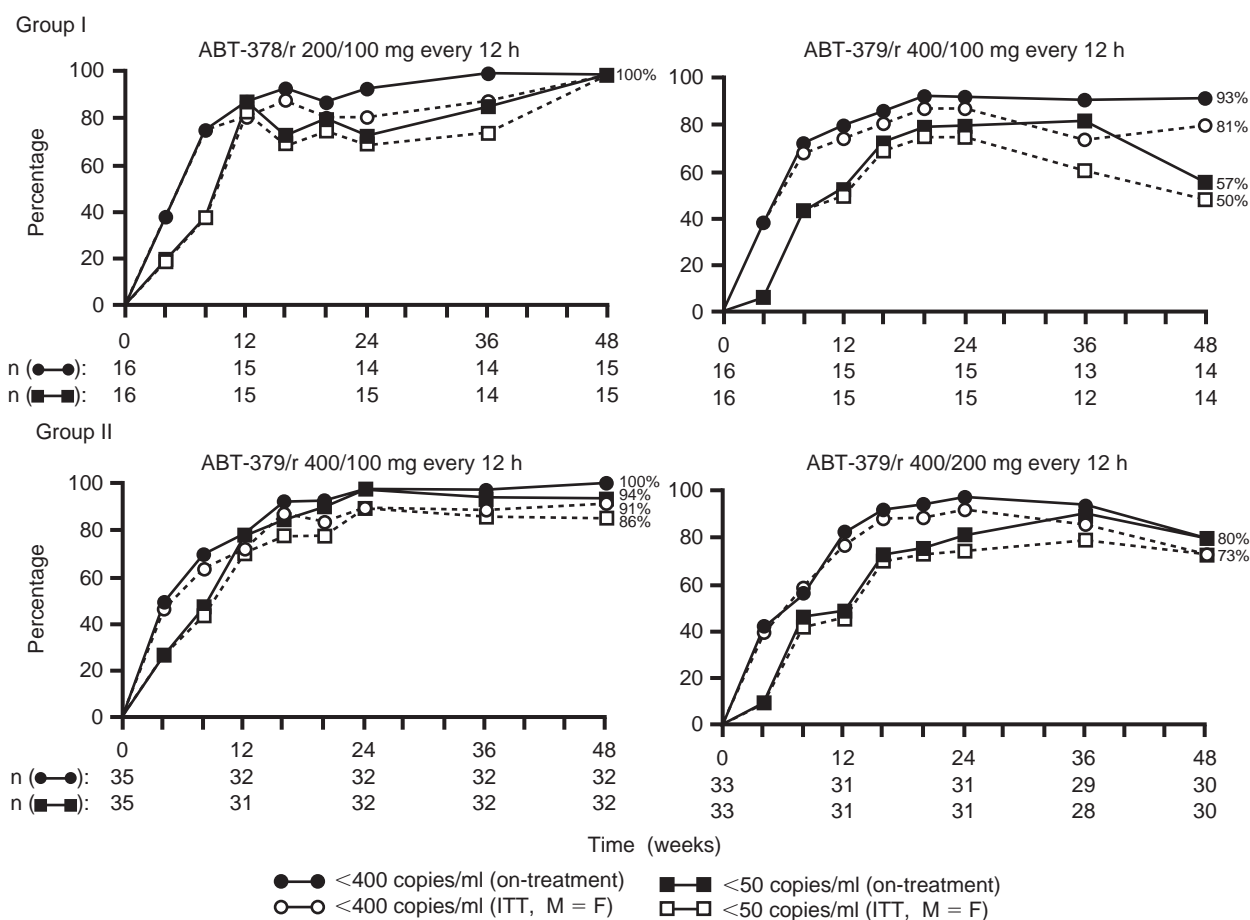


Fig. 1. Percentage of patients with plasma HIV-1 RNA below limit of quantitation, by ABT-378/r dose arm. ITT, M = F: intent-to-treat analysis with missing values considered as treatment failures.

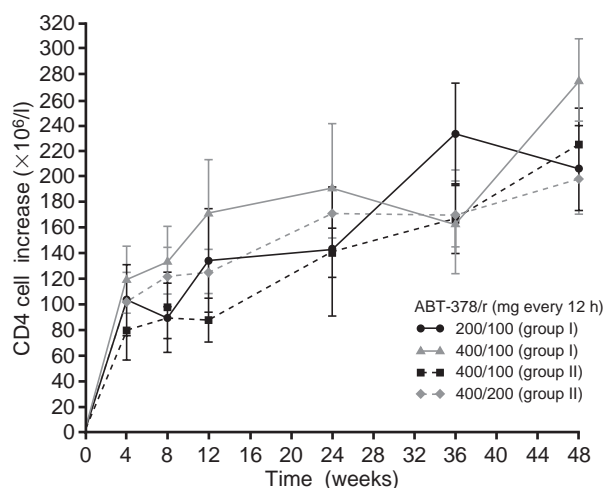


Fig. 2. Mean CD4 cell count increase from baseline (\pm SE) according to ABT-378/r dose arm.

3/4 and 24 are presented in Table 2. ABT-378 and ritonavir AUC, C_{max} , and C_{trough} did not differ significantly between week 3/4 and week 24 for any of the dosing groups ($P > 0.05$; Table 2). At week 3/4,

mean steady state ABT-378 trough concentrations were 53–103-fold more than the protein binding-adjusted EC_{50} of ABT-378 (0.07 $\mu g/ml$) for wild-type HIV-1 (Fig. 3) [18]. For the 400/100 mg regimen, mean ritonavir concentrations were below the protein binding-adjusted EC_{50} against wild-type HIV-1 for ritonavir throughout the dosing interval.

Adverse events

No discontinuations due to study drug-related clinical or laboratory adverse events occurred during the first 48 weeks of the study. The overall adherence rate was 98% based on patient-reported dose interruptions. Early termination from the study occurred in seven patients because of loss to follow up (two), non-compliance (two), personal reasons (one), development of an HIV-related event (lymphoma; one), and patient relocation (one). ABT-378/r was well tolerated with the most common adverse events of at least moderate severity related to study drug being diarrhea, nausea, and abnormal stools (Table 3).

While gastrointestinal adverse events occurred most frequently during the first 2 months of treatment, the

Table 2. Pharmacokinetic parameters (mean ± SD) for ABT-378 and ritonavir at week 3/4 and week 24.

	Ritonavir											
	ABT-378						Ritonavir					
	Group I 200/100 mg		Group II 400/200 mg		Groups I and II 400/100 mg		Group I 200/100 mg		Group II 400/200 mg		Groups I and II 400/100 mg	
	Week 3 (n = 16)	Week 24 (n = 15)	Week 4 (n = 8)	Week 24 (n = 7)	Week 3/4 (n = 21)	Week 24 (n = 18)	Week 3 (n = 16)	Week 24 (n = 15)	Week 4 (n = 8)	Week 24 (n = 7)	Week 3/4 (n = 21)	Week 24 (n = 18)
C_{max} (µg/ml)	6.65 ± 2.41	5.92 ± 1.91	11.52 ± 3.32	10.97 ± 1.75	9.58 ± 4.41	8.49 ± 2.70	0.99 ± 0.67	0.80 ± 0.46	1.75 ± 0.29	1.83 ± 0.90	0.60 ± 0.35	0.71 ± 0.62
C_{trough} (µg/ml)	3.74 ± 3.46	2.91 ± 2.92	7.23 ± 6.41	6.83 ± 6.79	5.49 ± 4.02	5.25 ± 2.92	0.29 ± 0.25	0.29 ± 0.21	0.44 ± 0.36	0.47 ± 0.50	0.21 ± 0.18	0.32 ± 0.20
AUC ₀₋₁₂ (µg · h/ml)	55.9 ± 22.1	50.6 ± 18.0	110.3 ± 31.9	105.6 ± 13.7	82.8 ± 44.5	76.5 ± 30.7	5.7 ± 3.1	5.3 ± 2.7	10.9 ± 2.3	12.6 ± 4.5	3.8 ± 1.8	4.5 ± 2.9
$t_{1/2}$ (h)	6.76 ± 2.73	6.14 ± 2.03	10.93 ± 4.34	10.80 ± 7.02	5.76 ± 2.39	5.26 ± 2.49	3.59 ± 0.83	3.52 ± 1.26	3.66 ± 1.17	3.99 ± 1.02	3.58 ± 0.58	3.40 ± 0.96

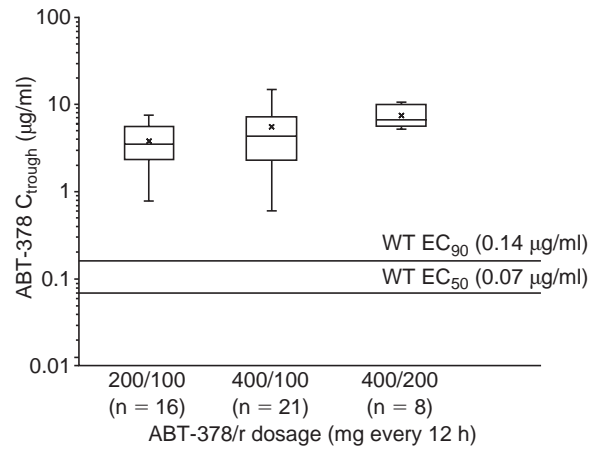


Fig. 3. Plasma ABT-378 C_{trough} values at week 3/4 by ABT-378/r dose level, relative to EC_{50} and EC_{90} for wild-type (WT) HIV-1. X represents the mean trough concentration, the upper and lower boundaries of the box mark the 75% and 25% quartiles, and the median is represented as the line dividing the box. The bars above and below extend to the highest and lowest observed trough concentrations.

prevalence of these events decreased over time with continued therapy. The incidence of adverse events was similar between treatment arms, with the exception of nausea and vomiting. In group II patients, moderate-to-severe nausea attributed to ABT-378/r occurred in 10 out of 33 (30%) patients receiving the 400/200 mg dose compared to three out of 35 (9%) receiving the 400/100 mg dose ($P = 0.031$). In addition, moderate-to-severe vomiting was more common in the 400/200 mg dose group (12%) than the 400/100 mg dose group (0%; $P = 0.05$).

The most common grade III/IV laboratory abnormalities reported cumulatively through 48 weeks included elevations of triglycerides, cholesterol, and AST/ALT (Table 3). At week 48, total cholesterol and triglyceride levels were significantly higher than at baseline, with mean increases of 49 mg/dl and 111 mg/dl respectively. Of note, blood samples for lipid testing were collected without respect to fasting. The majority of patients with grade III/IV triglyceride (8/11) or cholesterol (6/10) levels had elevated baseline levels (> 213 mg/dl and > 200 mg/dl respectively). Only two out of ten patients with grade III/IV total cholesterol levels and two of the 11 patients with grade III/IV triglyceride levels had grade III/IV values persisting at their final measurement, including one patient with grade III/IV values for both lipids at week 48. Sixty-eight percent (56/82) of patients with baseline cholesterol values < 200 mg/dl did not develop a cholesterol value > 240 mg/dl (grade II) during ABT-378/r therapy. Similarly, 73% (66/90) of patients with baseline triglycerides < 250 mg/dl did not develop a triglyceride value > 400 mg/dl (grade II) during ABT-378/r therapy. Eight patients developed a grade III/IV

Table 3. Most common adverse events (occurring in $\geq 5\%$ of patients overall by week 48) of at least moderate severity and probable, possible, or unknown relationship to ABT-378/ritonavir, and laboratory abnormalities (reported in $\geq 5\%$ of patients overall) during 48 weeks of treatment with ABT-378/r plus stavudine and lamivudine.

	Percent ever reporting event (n)				
	Group I (ABT-378/r every 12 h)		Group II (ABT-378/r every 12 h)		Total (n = 100)
	200/100 mg (n = 16)	400/100 mg (n = 16)	400/100 mg (n = 35)	400/200 mg (n = 33)	
Nausea	13% (2)	0% (0)	9% (3)	30% (10)	15% (15)
Diarrhea ^a	13% (2)	25% (4)	17% (6)	24% (8)	20% (20)
Abnormal stools ^b	19% (3)	19% (3)	6% (2)	0% (0)	8% (8)
Vomiting	6% (1)	0% (0)	0% (0)	12% (4)	5% (5)
Asthenia	6% (1)	13% (2)	6% (2)	6% (2)	7% (7)
Headache	6% (1)	13% (2)	6% (2)	6% (2)	7% (7)
Laboratory abnormalities ^c (Grade III/IV)					
Triglycerides (> 750 mg/dl)	19% (3)	6% (1)	6% (2)	15% (5)	11% (11)
Total cholesterol (> 300 mg/dl)	13% (2)	6% (1)	6% (2)	15% (5)	10% (10)
Alanine transaminase or aspartate transaminase (> five times the upper limit of normal)	0% (0)	0% (0)	20% (7)	3% (1)	8% (8)

^aMore than three stools per day. ^bThree or fewer stools per day. ^cDetermined without respect to fasting.

elevation in AST or ALT. Four out of the eleven patients with serologic evidence of hepatitis B surface antigen or hepatitis C virus antibodies at baseline experienced grade III/IV AST or ALT elevations while on study therapy. Hepatitis B surface antigen or hepatitis C virus antibody seropositivity at baseline was associated with an eightfold increased relative risk of developing a grade III/IV AST or ALT while on study medication ($P < 0.05$). The majority of grade III/IV AST/ALT elevations returned to baseline with continued dosing and no patient discontinued ABT-378/r as a consequence of such elevations. No patients developed clinical hepatitis attributed to ABT-378/r.

Discussion

The results of this study demonstrate that ABT-378/r therapy is highly potent, durable and well tolerated when administered concomitantly with two nucleoside analog reverse transcriptase inhibitors in antiretroviral-naïve HIV-1 infected individuals. The intrinsic antiviral activity of ABT-378/r was illustrated by the magnitude of the decline in plasma HIV-1 RNA in the first 3 weeks of dosing in group I, where ABT-378/r was given as a single agent. Thus, the initial decline in HIV-1 RNA in group I patients was similar to that observed in group II patients, in whom the combination regimen of ABT-378/r, stavudine and lamivudine was initiated simultaneously. The overall efficacy and durability of the ABT-378/r dosing regimens used in this study were demonstrated by the high proportion of patients who experienced a decrease in plasma HIV-1 RNA to < 400 copies/ml at any time (99%) and after 48 weeks (85% by ITT and 92% on-treatment).

Although statistically significant differences were observed between dose assignments within groups I and II at the 48 week time point, these differences were not reflected at other time points nor in a time-to-virologic failure analysis through week 48. These observations are probably due to the relatively small numbers within the dosing arms rather than intrinsic differences in antiviral activity.

The results of this study compare very favorably to those obtained from other clinical trials in which treatment-naïve patients have been randomized to protease inhibitor-based treatment regimens. In a recent meta-analysis of 18 clinical trials in antiretroviral-naïve patients that included protease inhibitor-based therapies, the proportion of patients with plasma HIV-1 RNA values < 400 copies/ml or < 50 copies/ml by ITT analysis at 24 weeks was 63% and 49% respectively [9]. In reported ITT analyses of clinical trials evaluating protease inhibitor-based treatment regimens through 48 weeks, the proportion of patients with plasma HIV-1 RNA levels < 400 – 500 copies/ml or < 50 copies/ml is in the range 30–60% and 35–47% respectively [3,19–23]. As the patients in this phase II study of ABT-378/r had a high mean plasma HIV-1 RNA at baseline as well as a wide range of CD4 cell counts, these results should be applicable to a broad segment of the treatment-naïve, HIV-1 infected population.

The high proportion of subjects achieving maximal viral suppression (< 50 copies/ml) in this study probably reflects several factors: the high *in vitro* potency of ABT-378, the favorable pharmacokinetic profile achieved when it is dosed with ritonavir, and a tolerability profile that probably facilitates medication adherence. The ABT-378/r regimens evaluated used

ritonavir doses that result in low ritonavir exposures, generally below those required for antiviral activity.

The mean trough plasma concentrations of ABT-378 were 50–100-fold higher than the protein binding-corrected EC_{50} for wild-type HIV-1. These ratios of drug levels to inhibitory concentrations are substantially higher than those seen with currently available protease inhibitors administered at their approved doses and frequency, which range from one- to four-fold above the protein binding-corrected EC_{50} for wild-type virus at trough [11]. These ratios can be improved by the coadministration of ritonavir; for example, a regimen of indinavir 800 mg and ritonavir 100 mg dosed twice daily provides indinavir trough levels approximately 26-fold higher than the EC_{50} for wild-type HIV, corrected for protein binding. However, the optimal dosing, safety, and efficacy of these regimens has not been well studied [18,24]. As protease inhibitor levels have been demonstrated to correlate with the development of viral mutations and subsequent resistance and are predictive of clinical virologic response [25–27], the pharmacokinetic profile of ABT-378/r may translate into prolonged durability of response. Therefore, when selecting a dose level of ABT-378/r for further clinical development, an attempt was made to maximize trough levels while maintaining an acceptable tolerability profile.

The favorable tolerability profile of ABT-378/r is reflected by the fact that no patient discontinued ABT-378/r because of a study drug-related adverse event or laboratory abnormality through 48 weeks of treatment. Higher rates of nausea and vomiting were seen in the 400/200 mg dose arm compared to the 400/100 mg dose arm, which factored into the decision to select the 400/100 mg dose for further clinical development. Increases in either serum cholesterol and/or triglycerides to grade III/IV levels occurred in 16% of patients. Most grade III/IV lipid elevations did not persist at this level and had decreased by week 48 with continued dosing. This observation may have been secondary to multiple factors, including the use of lipid-lowering agents in two patients, diet, or fasting prior to obtaining subsequent measurement. While elevations in serum ALT and AST were observed in a minority of patients, no patient was required to discontinue study medications nor did any patient develop clinical hepatitis attributed to ABT-378/r. The majority of elevated transaminase values returned to baseline levels with continued dosing. Patients with chronic hepatitis B and/or hepatitis C were more likely to experience significant increases in hepatic transaminase levels.

In conclusion, ABT-378 is a potent HIV-1 protease inhibitor that is exquisitely sensitive to pharmacokinetic enhancement by low doses of ritonavir. This

results in ABT-378 drug levels that are well in excess of required inhibitory concentrations for wild-type HIV throughout the entire dosing interval. The drug levels achieved with ABT-378/r should create a pharmacologic barrier to viral resistance, leading to an antiviral regimen that would be expected to maintain significant durability of response beyond 48 weeks of treatment. The 400/100 mg dose level of ABT-378/r has been selected for further clinical development because this combination allows for maximization of ABT-378 plasma levels while maintaining a favorable tolerability profile.

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