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Adherence in Antiretroviral Treatment-Naïve Subjects Treated With Once-Daily Atazanavir/Ritonavir or Twice-Daily Lopinavir/Ritonavir, Both in Combination With Tenofovir/Emtricitabine: 48 Week Results From the CASTLE Study

J. Su, J. Absalon, R. Yang, M. Mancini, U. Iloeje, D. McGrath for the BMS CASTLE Study Group
Bristol-Myers Squibb, Wallingford, CT, USA

Jun Su
Bristol-Myers Squibb
Wallingford, CT
USA
Tel: 203-677-5758
E-mail: jun.su@bms.com

ABSTRACT

Background

Adherence to an antiretroviral regimen is an important predictor of treatment success in HIV therapy. In the CASTLE study, once-daily atazanavir/ritonavir (ATV/RTV) was found noninferior to twice-daily lopinavir/ritonavir (LPV/RTV) in antiviral efficacy, with a better lipid profile and less gastrointestinal toxicity in treatment-naïve patients.

Methods

CASTLE was a 96-week, randomized, open-label study comparing ATV/RTV with LPV/RTV, both in combination with tenofovir/emtricitabine (TDF/FTC). Adherence was assessed using the Multicenter AIDS Cohort Study questionnaire. The proportion of patients with complete adherence to assigned regimen was assessed from Week 4 through Week 48 for treated patients with evaluable results.

Results

883 patients were randomized; 878 treated. For treated patients, baseline demographics and characteristics were well balanced: median age 35 years; 68% male; 9% Asian, 18% black, 23% other, 49% white; median CD4 cell count 204 cells/mm³; median plasma HIV RNA 4.98 log₁₀ copies/mL. Discontinuations prior to Week 48 were: ATV/RTV, 9% [39/441]; LPV/RTV, 13% [58/437]. Adverse event (AE)-related discontinuations were 2% [10/441] and 3% [14/437] on ATV/RTV and LPV/RTV, respectively. The most common reason for sometimes or often missing medication at Week 48 was forgetting (6% [4/71] ATV/RTV vs 11% [7/62] LPV/RTV). Other reasons (eg, depression, feeling sick, or stigma) were rarely cited.

Conclusions

Both ATV/RTV and LPV/RTV, in combination with TDF/FTC, had high rates of adherence (> 80%) in treatment-naïve HIV-infected patients throughout the first 48 weeks of the study.

INTRODUCTION

Adherence to an antiretroviral (ARV) regimen is an important predictor of treatment success in HIV therapy.

Poor adherence can lead to the acquisition of mutations conferring resistance to ARV therapy,¹ and subsequent treatment failure.²

Atazanavir (ATV) is a potent, generally well-tolerated, once-daily HIV-1 protease inhibitor extensively studied in treatment-naïve and treatment-experienced patients.

At Week 48, the CASTLE study showed that in combination with tenofovir/emtricitabine (TDF/FTC), ATV/ritonavir (RTV) is noninferior to lopinavir/ritonavir (LPV/RTV) in antiviral efficacy, with significantly less elevation of lipids and better gastrointestinal tolerability in treatment-naïve HIV-infected patients.³

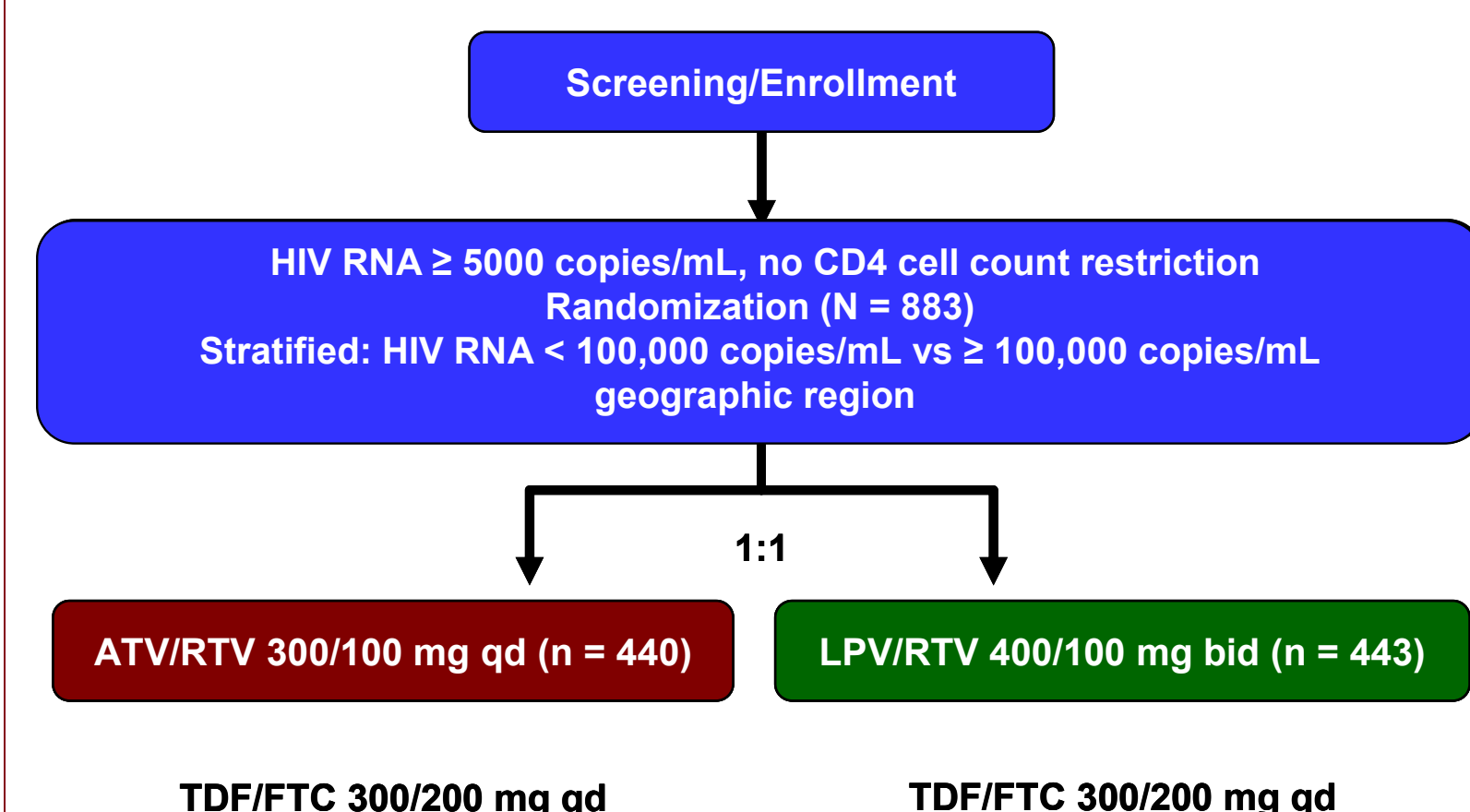
OBJECTIVE

The objective of this study was to evaluate patient-reported adherence on a once-daily ATV/RTV regimen and a twice-daily LPV/RTV regimen.

METHODS

The CASTLE study³ was a 96-week, randomized, open-label, prospective, international, multicenter study comparing once-daily ATV/RTV with twice-daily LPV/RTV, both in combination with fixed-dose TDF/FTC in 883 treatment-naïve HIV-infected patients (Figure 1).

Figure 1. The CASTLE Study Design⁴



The Multicenter AIDS Cohort Study (MACS) adherence questionnaire was used to assess patient adherence.

– The questionnaire:

- Has been validated^{5,6}
- Assesses drug use patterns during a 4-day recall period
- Was administered by an interviewer at every visit from Week 4 through Week 48.

– At each study visit during Weeks 4, 12, 24, 36, and 48, patients were asked how many medication doses they had missed during the previous day, 2 days ago, 3 days ago, and 4 days ago. Drug-specific questions included adherence with dose and frequency.

Adherence was determined by comparing actual study medications received to those reported on MACS at the same visit.

Patients' questionnaires were considered to be evaluable at a visit if they received any study medication at that visit.

Adherence was defined as taking all doses and numbers of pills as prescribed for each medication.

Patients were nonadherent if they took:

- Fewer doses of study medication in the last 4 days than prescribed
- An atypical pattern of prescribed medication in the last 4 days
- Fewer pills per dose than prescribed in the last 4 days.

Patients with partial responses to the questionnaire were also classified as nonadherent to a drug within the regimen.

Patients had to be adherent to all drugs in the treatment arm to be categorized as adherent to the regimen.

RESULTS

Baseline demographics were similar across both treatment arms (Table 1).

Table 1. Baseline Demographics (As-treated Week 48 Evaluable Patients)

Characteristic	ATV/RTV n = 401	LPV/RTV n = 378
Median age (range), y	34 (19-72)	36 (19-71)
Male gender, n (%)	280 (70)	264 (70)
Ethnicity/race, n (%)		
White	188 (47)	189 (50)
Black	71 (18)	64 (17)
Asian	40 (10)	36 (10)
Other (Hispanic/Latino, Mestizo, and Mixed race)	102 (25)	89 (24)
Median HIV RNA (min, max), log ₁₀ copies/mL	5.01 (2.60, 5.88)	4.97 (3.32, 5.88)
Median CD4 cell count (min, max), cells/mm ³	206 (2, 760)	210 (4, 810)

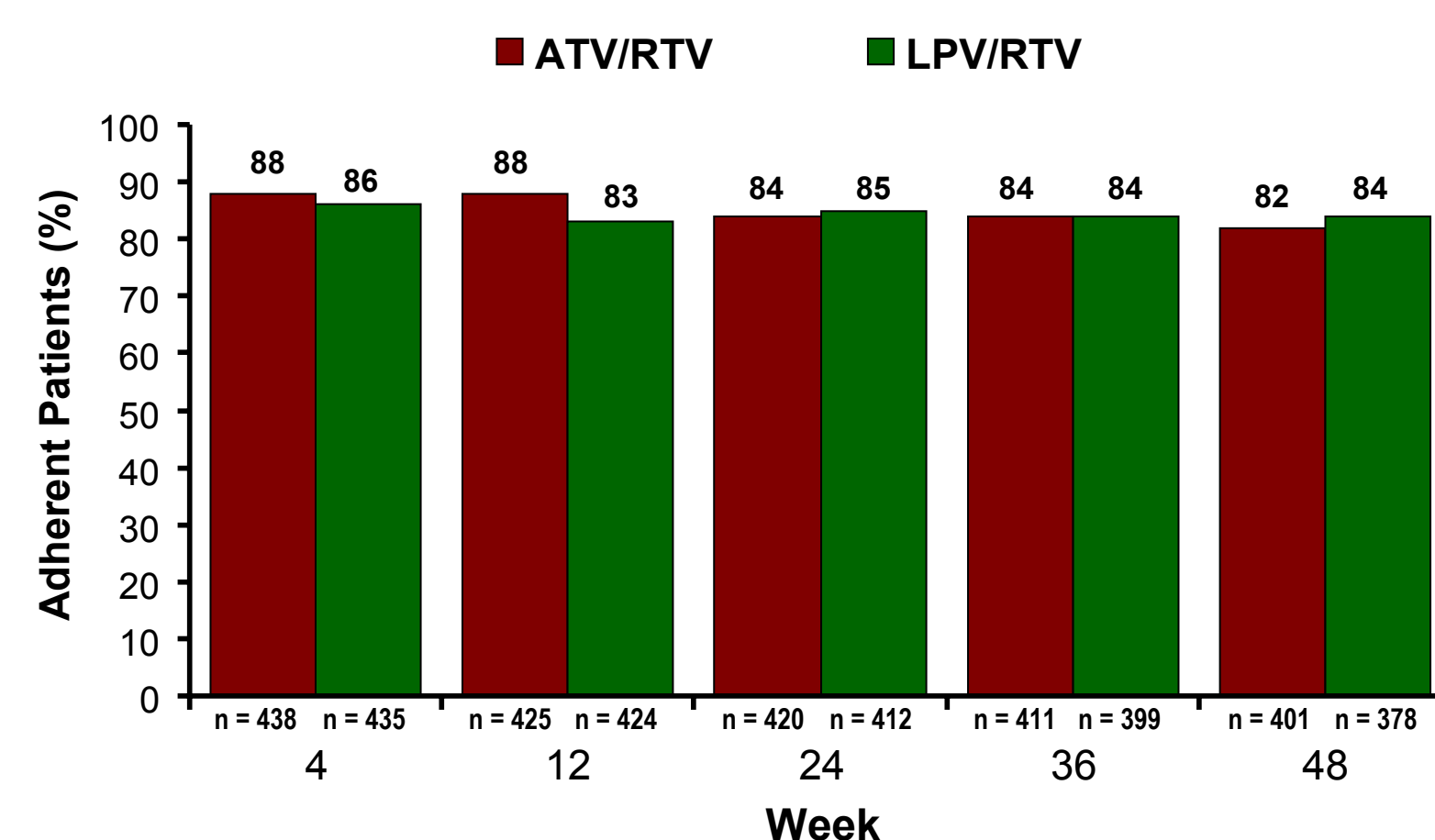
At Week 4 the MACS questionnaire was administered to 97% of patients in both treatment arms (428/439 and 420/434 patients in the ATV/RTV and LPV/RTV treatment arms, respectively).

At Week 48, the questionnaire was administered to 394/439 (90%) and 373/434 patients (86%) in the ATV/RTV and LPV/RTV treatment groups, respectively.

For both regimens the predominant reason that the MACS questionnaire was not completed from Week 12 through Week 48 was discontinuation of study medication (37/439 patients [8%] on ATV/RTV and 53/434 patients [12%] on LPV/RTV at Week 48).

At study visits through Week 48, across both treatment arms, 82%-88% of patients were adherent to their treatment regimen (Figure 2).

Figure 2. Adherence to Treatment Regimen Through Week 48 (As-treated Patients)



RESULTS

Table 2. Patient-Reported Reasons for Missing Medication at Week 48 (As-treated Patients)

	ATV/RTV, n/N (%)				LPV/RTV, n/N (%)			
	Never	Rarely	Sometimes	Often	Never	Rarely	Sometimes	Often
Did not want others to notice	28/71 (39)	3/71 (4)	2/71 (3)	1/71 (1)	36/62 (58)	0/62 (0)	1/62 (2)	0/62 (0)
Do not want to take pills	31/71 (44)	2/71 (3)	1/71 (1)	0/71 (0)	35/62 (56)	0/62 (0)	1/62 (2)	1/62 (2)
Fell asleep/slept through dose time	25/71 (35)	7/71 (10)	2/71 (3)	0/71 (0)	30/62 (48)	4/62 (6)	3/62 (5)	0/62 (0)
Felt depressed or overwhelmed	30/71 (42)	1/71 (1)	3/71 (4)	0/71 (0)	35/62 (56)	0/62 (0)	2/62 (3)	0/62 (0)
Felt like drug was toxic or harmful	31/71 (44)	1/71 (1)	1/71 (1)	1/71 (1)	37/62 (60)	0/62 (0)	0/62 (0)	0/62 (0)
Felt sick or ill	29/71 (41)	2/71 (3)	2/71 (3)	1/71 (1)	33/62 (53)	2/62 (3)	2/62 (3)	0/62 (0)
Had a change in daily routine	21/71 (30)	9/71 (13)	3/71 (4)	1/71 (1)	29/62 (47)	5/62 (8)	3/62 (5)	0/62 (0)
Had problems taking the pills	31/71 (44)	3/71 (4)	0/71 (0)	0/71 (0)	33/62 (53)	4/62 (6)	0/62 (0)	0/62 (0)
Had too many pills to take	32/71 (45)	2/71 (3)	0/71 (0)	0/71 (0)	34/62 (55)	1/62 (2)	1/62 (2)	1/62 (2)
Have special instructions that conflict	32/71 (45)	0/71 (0)	2/71 (3)	0/71 (0)	36/62 (58)	1/62 (2)	0/62 (0)	0/62 (0)
Other	11/71 (15)	2/71 (3)	0/71 (0)	0/71 (0)	11/62 (18)	0/62 (0)	0/62 (0)	0/62 (0)
Ran out of pills	32/71 (45)	2/71 (3)	0/71 (0)	0/71 (0)	35/62 (56)	2/62 (3)	0/62 (0)	0/62 (0)
Simply forgot	21/71 (30)	9/71 (13)	4/71 (6)	0/71 (0)	21/62 (34)	10/62 (16)	6/62 (10)	1/62 (2)
Wanted to avoid side effects	31/71 (44)	2/71 (3)	0/71 (0)	1/71 (1)	34/62 (55)	1/62 (2)	1/62 (2)	1/62 (2)
Was away from home	21/71 (30)	7/71 (10)	6/71 (8)	0/71 (0)	27/62 (44)	6/62 (10)	4/62 (6)	0/62 (0)
Was busy with other things	22/71 (31)	7/71 (10)	4/71 (6)	1/71 (1)	34/62 (55)	1/62 (2)	2/62 (3)	0/62 (0)

Reasons for Nonadherence

At Week 48, "away from home" was the most common reason in the ATV/RTV arm (6/71, 8%) and "simply forgot" was the most common reason in the LPV/RTV arm (7/62, 11%) reported by patients for sometimes or often being nonadherent to treatment.

Adverse Events and Treatment Discontinuations

No new or unexpected safety concerns were reported.

Patient discontinuations prior to Week 48 were 9% (39/441) and 13% (58/437) in the ATV/RTV and LPV/RTV treatment arms, respectively.

Patient discontinuations due to adverse events prior to Week 48 were 2% (10/441) and 3% (14/437) in the ATV/RTV and LPV/RTV treatment arms, respectively.

CONCLUSIONS

Patients in both the ATV/RTV and LPV/RTV treatment arms had high rates of adherence (> 80%) throughout the first 48 weeks of the CASTLE study.

Adherence was comparable in both treatment arms throughout the study.

For patients who filled out the reasons for nonadherence, the most common reasons included:

- In the ATV/RTV treatment group, "away from home"
- In the LPV/RTV treatment group, "simply forgot"

Real-world adherence may not reflect the adherence in the clinical trial.⁷

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