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Poster presentation

Impact of HIV viral diversity and baseline resistance on treatment outcomes and the emergence of resistance: the CASTLE study
48-week results

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Background

HIV viral diversity and baseline (BL) substitutions have implications for response to antiretroviral therapy, the development of resistance and disease progression. Worldwide, approximately 90% of HIV infections are non-B subtypes. The CASTLE study is a randomized, open-label, prospective study comparing once-daily ATV/r with twice-daily LPV/r, both in combination with fixed-dose tenofovir/emtricitabine in 883 treatment-naive patients from 28 countries. The impact of HIV subtypes and BL resistance on efficacy and emergence of resistance is described.

Methods

HIV subtype was determined by comparison of genotypes with a consensus B sequence. Protease substitutions were classified as major or minor according to IAS-USA (2007) and the HIV Drug Resistance Database (HIVdb). Protease polymorphisms were defined as either: 1) IAS-USA minor substitutions assigned a score of 0 by the Stanford HIV database (HIVdb Genotype Resistance Interpretation); or 2) Non-IAS-USA PI substitutions (Clade B reference). Batched genotypes were performed on BL samples, and Genotype/PhenoSense (Monogram Biosciences, South San Francisco, CA, USA) on paired samples with virologic failure (HIV-RNA = 400 c/mL) through week 48 (i.e. rebound without resuppression; never confirmed VL<400 c/mL but remained on treatment at week 48; discontinued due to lack of efficacy before week 48).

Summary of results

18 HIV subtypes were represented: B (66%), C (16%), BF (8%), and AE (6%). Response rates overall and by subtype are presented in Table 1.

Response rates by baseline substitutions are presented in Table 2.

6% of subjects in each treatment group had virologic failure. PI substitutions emerged in 10/19 ATV/r and 8/20 LPV/r VFs; all were polymorphic except in two ATV/r subjects [1(N88S, M46I); 2 (L10F, V32I, M46I, K43T, A71I, G73S, L90M)]. The subject with N88S subsequently re-suppressed to undetectable levels on same regimen (ATV

Table 1: Confirmed Virologic Response (CVR) VL<50 at Wk 48 (ITT).

	ATV/r n/N (%)	LPV/r n/N (%)
Overall*	343/440 (78)	338/443 (76)
Subtype B	230/291 (79)	210/283 (74)
Subtype Non-B	107/143 (75)	121/148 (82)
AE	23/28 (82)	25/28 (89)
BF	21/27 (78)	31/38 (82)
C	51/73 (70)	52/65 (80)
Other	12/15 (80)	13/17 (76)

* Estimated difference: 1.7 (95% CI, -3.8%, 7.1%). 18 reported HIV subtypes contain 6 subtypes, 3 sub-subtypes and 9 recombinants.

Table 2: Confirmed Virologic Response (CVR) VL<50 at Wk 48 (ITT) by Baseline Substitutions.

	ATV/r n/N (%)	LPV/r n/N (%)
PI-IAS-USA Major/Minor 0	224/290 (77)	202/257 (79)
PI-IAS-USA Major/Minor 1–2	110/138 (80)	128/170 (75)
PI-IAS-USA Major/Minor ≥ 3	3/3 (100)	1/2 (50)
PI Polymorphisms ≥ 5	191/251 (76)	173/222 (78)
NRTI (any IAS or Stanford) ≥ 1	57/73 (78)	51/64 (80)

* Estimated difference: 1.7 (95% CI, -3.8%, 7.1%). 18 reported HIV subtypes contain 6 subtypes, 3 sub-subtypes and 9 recombinants.

FC 3.71); M184V emerged in 5/19 and 4/20, and TAMs in 1/19 and 1/20, respectively. Virologic failure rates were consistent across the predominant subtypes represented in the study: ATV/r (B 5%, C 8%) and LPV/r (B 6%, C 8%).

Conclusion

Both regimens (ATV/r and LPV/r) achieved consistently high response rates regardless of HIV subtype or BL substitutions. Both regimens had infrequent emergence of non-polymorphic PI substitutions with virologic failure, and similar rates of selection of antiretroviral resistance mutations.