Abstract # 962

45th Annual Meeting of the Infectious Diseases Society of America; October 4-7, 2007 San Diego, CA

Switching from Lopinavir/Ritonavir (LPV/r) Soft Gel Capsule (SGC) to Tablet Formulation improves Tolerability in Indigent AIDS Clinic

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ABSTRACT

Background: LPV/r tablets compared to SGC have no oleic acid or sorbitol, have no refrigeration/food requirements, and have less pharmacokinetic variability. It was our objective to evaluate tolerability, quality of life (QoL), and lipid differences after switching from LPV/r SGC to Tablet.

Methods: Seventy-four HIV-infected subjects on LPV/r-based regimens were enrolled prior to (n=25) or within 8wks (n=49) after switching from LPV/r SGC to Tablet. Formulation preference and satisfaction were assessed post-switch. Tolerability assessments included bowel habit (BH), global condition improvement (GCI), and ACTG symptom distress module (ASDM). Tolerability, QoL, and fasting lipids pre-switch were compared to Wk4 and Wk12. Baseline QoL and BH were recalled for those subjects enrolled post-switch.

Results: At Wk4, more patients preferred LPV/r Tablet to SGC (74% vs. 8%) and satisfaction with the Tablet formulation was expressed. Significant improvement in BH was reported at Wk4 (mean change in BH-score: -0.281, p=0.002) and maintained through Wk12 (p=0.014). Overall LPV/r tolerability improved with the switch. At Wk4, 45% of subjects felt "better", 45% felt "about the same", 5% "worse", and 5% did not respond. These GCI-improvements were maintained through Wk12 (p<0.0001). Correlation was seen between the BH-score and GCI-improvement at Wk4 (p=0.017) and waned by Wk12. ASDM and QoL were unchanged at Wk4 and Wk12. Interestingly, a mean reduction in triglycerides of 33mg/dl (18%), unrelated to lipid-lowering therapy, was observed at Wk12 (n=33, p=0.035).

Conclusions: Switching from LPV/r SGC to Tablet resulted in significant improvement in gastrointestinal tolerability with a resulting positive impact on subjects' overall well being (GCI). QoL was maintained. The observed 18% reduction in triglyceride level deserves further evaluation.

BACKGROUND

- The new LPV/r 200/50 mg tablet formulation has been well received by clinicians and patients because of its reduced daily pill burden from six SGC to four tablets, lack of special food requirements needed to achieve desired plasma drug exposure, and its stability at room temperature, eliminating the need for refrigeration [1-3].

BACKGROUND CONTINUED

- Because the new tablet formulation lacks oleic acid [4], an excipient believed to contribute to gastrointestinal (GI) intolerance with the SGC, it has been speculated that the tolerability of LPV/r would improve with the use of the tablet formulation.
- In this study, a phase IV tolerability assessment was conducted in HIV-infected subjects who were switched from the SGC to the tablet formulation of LPV/r. Self-reported daily bowel habit, quality of life (QOL), and fasting lipid profile obtained prior to the switch were compared to similar data obtained 12 weeks post-formulation change.

METHODS

- This was a prospective cohort study that enrolled clinically stable HIV-infected subjects receiving LPV/r-based antiretroviral regimen.

Screening

- HIV-subjects age ≥18 years
- Enrolled prior to, or within 8 weeks of formulation switch
- No CD4 cell count restriction
- No pregnancy/breastfeeding

Laboratory Evaluations

- Clinical labs monitored at baseline and at week 12:
  - Fasting lipid profile
  - HIV-1 RNA
  - CD4 cell count

Bowel Movement Evaluation

Daily bowel habit (BH) was assessed prior to switch and at weeks 4 & 12. The bowel habit score was assessed using the scoring system below and dividing the sum by 4.

- Stool consistency: solid =1, loose =3, watery=5
- Volume: small =1, moderate=3, large=5
- Presence of blood in stools: no=1, yes=5
- Frequency per day: 1 – 5 (>4 BM per day scored as 5)

The scale has a minimum of 1 (best BHS outcome) and a maximum of 5 (worst BHS outcome).

Quality of Life Evaluations

- QOL instruments were administered prior to switch and at weeks 4 & 12:
  - MOS HIV health survey [5]
  - Global condition improvement questionnaire
  - Medication satisfaction survey
  - Therapy preference survey
  - ACTG Symptom Distress Module (ASDM) – with two questions to assess symptoms related to nephrolithiasis

RESULTS

Table 1. Subject demographic data at study entry

	Study population (n = 74)
Male sex [n (%)]	61 (82)
Race African American [n (%)] White [n (%)] Hispanic [n (%)]	 55 (74) 17 (23) 2 (3)
†On LPV/r tablet at entry No [n (%)] Yes [n (%)]	 49 (66) 25 (34)
On anti-diarrheal drug No [n (%)] Yes [n (%)]	 67 (92) 6 (8)
On lipid lowering drug No [n (%)] Yes [n (%)]	 54 (74) 19 (26)
Median age [years (IQR)]	43 (39-47)
Median weight [kg (IQR)]	80.5 (69.6-88.6)
Median HIV-1 RNA [copies/ml (IQR)]	135 (50-170)
Median CD4 T-cell counts [cell/μl (IQR)]	294 (157-455)

LPV/r, lopinavir/ritonavir; SGC, soft gel capsule; IQR, inter quartile range. †Subjects were already switched from LPV/r SGC to tablets within 8 weeks prior to enrollment; 75% percentile, 25th to 75th percentile.

Table 2a: Quality of life assessment – MOS-HIV, ASDM, CES-D

Quality of life instruments, mean ±SD	Baseline	Change from Baseline to Week 4		Change from Baseline to Week 12	
MOS-HIV Physical Health Summary Score (PHS)	48.2 ± 11.5	0.015 ± 9.00	*P* = 0.97	0.315 ± 9.20	*P* = 0.79
MOS-HIV Mental Health Summary Score (MHS)	50.7 ± 12.0	0.366 ± 9.07	*P* = 0.74	0.313 ± 10.01	*P* = 0.81
ACTG Symptoms Distress Module (ASDM)	26.7 ± 19.8	-2.99 ± 16.34	*P* = 0.14	-2.92 ± 16.48	*P* = 0.17
Center for Epidemiology Studies - Depression (CES-D)	14.5 ± 10.2	-1.12 ± 8.00	*P* = 0.25	-0.753 ± 8.47	*P* = 0.49

Table 2b: Quality of life assessment – medication satisfaction and GCI

Quality of life instruments, mean ± SD	Week 4		Week 12	
Medication satisfaction survey (MSS)	9.01 ± 2.27	NA	8.69 ± 2.25	NA
Global condition improvement (GCI)	2.24 ± 3.05	*P* <0.0001	2.46 ± 3.30	*P* <0.0001

Table 2c: Quality of life assessment – formulation preference

Quality of life instruments, n (%)	Week 4		Week 12	
Therapy preference: Prefer LPV/r Tablet Prefer LPV/r SGC No preference	55 (78) 6 (9) 9 (13)	*P* <0.0001	46 (74) 6 (10) 10 (16)	*P* <0.0001

Quality of life instruments were scored according to the published scoring algorithm [4]. SD, standard deviation; SGC, soft gel capsule; LPV/r, lopinavir/ritonavir

Table 3: Change in self-reported bowel habit

Bowel habit (BH) score*	Baseline to Week 4 (n= 70)		Baseline to Week 12 (n=62)	
Overall change, mean ± SD	-0.281 ± 0.719	0.0017	-0.227 ± 0.707	0.0141
Bowel habit improvements among those reporting a change	Baseline to Week 4		Baseline to Week 12	
	Improvement rate	P-value	Improvement rate	P-value
Decrease in stool frequency among those reporting change	18/28 (64%)	0.13	18/32 [56%)	0.48
Improved stool consistency among those reporting change	23/30 (77%)	0.0035	19/27 (70%)	0.0343
Decrease in stool volume among those reporting change	11/16 (69%)	0.13	8/13 (62%)	0.41
Resolution of blood in stool among those reporting change	5/6 (83%)	0.10	4/6 (67%)	0.41

SD, standard deviation; *BHS example, a subject with baseline responses of: solid, moderate, no blood in stool, and frequency of "2" would have a score of: (1 + 3 + 1 + 2)/4 = 1.75 for their baseline summary score.

RESULTS CONTINUED

Table 4: Changes in Fasting Lipid Profile from Baseline to Week 12

	Lipid Lowering Drug	Baseline mean (SD)	Week 12 mean (SD)	Mean change (SD)	P-value
TC	No (n =38) Yes (n=16) Total population (n=54)	188 (35.1) 221 (66.2) 198 (48.4)	179 (34.7) 218 (55.8) 190 (45.3)	-9.20 (23.20) -2.94 (44.30) -7.33 (30.70)	0.0197* 0.795 0.0848
TRIG	No (n=33) Yes (n=14) Total population (n=47)	187 (117) 410 (410) 254 (260)	154 (111) 329 (304) 206 (203)	-33.10 (86.30) -81.20 (348.30) -47.40 (199.90)	0.035* 0.399 0.1108
HDL-C	No (n=33) Yes (n=14) Total population (n=47)	47.0 (11.3) 35.1 (15.9) 43.2 (14.0)	42.6 (11.9) 36.8 (15.8) 40.7 (13.4)	-4.50 (9.40) 1.70 (9.50) -2.49 (9.78)	0.012* 0.490 0.877
LDL-C	No (n=33) Yes (n=14) Total population (n=47)	106 (29.4) 123 (54.5) 111 (38.8)	102 (24.4) 127 (32.3) 110 (29.0)	-4.20 (21.80) 3.60 (48.60) -1.85 (31.80)	0.283 0.788 0.692

TC; total cholesterol; TRIG, triglyceride; HDL-C, high density lipoprotein; LDL-C, low density lipoprotein; SD, standard deviation, *Statistically significant (P ≤ 0.05).

DISCUSION AND CONCLUSIONS

- At Week 4, more patients preferred LPV/r Tablet to SGC (74% vs. 8%) and satisfaction with the Tablet formulation was expressed. Significant improvement in bowel habit was reported at Week 4 (mean change in BH-score: -0.281, p=0.002) and maintained through Week 12 (p=0.014).
- Switching from LPV/r SGC to Tablet resulted in significant improvement in GI tolerability with a resulting positive impact on subjects' overall well being (GCI). Overall LPV/r tolerability improved with the switch. At Week 4, 45% of subjects felt "better", 45% felt "about the same", 5% "worse", and 5% did not respond. QoL was maintained (as measured by GCI) through Week 12 (p<0.0001). Correlation was seen between the BH score and GCI at Week 4 (p=0.017) and waned by Week 12.
- No change in QOL, using MOS-HIV PHS, MOS-HIV MHS, ASDM, or CES-D, were observed with the switch in drug formulation (Table 2).
- Interestingly, a mean reduction in triglycerides of 33 mg/dL (18%), unrelated to lipid-lowering therapy, was observed at Week 12 (n=33, p=0.035). This reduction in triglyceride level deserves further evaluation.

REFERENCES

1. Schrader S, Chuck S, Rahn L, et. al. Significant improvements in self-reported gastrointestinal tolerability, quality of life, patient satisfaction, and adherence with lopinavir/ritonavir after switching from BID soft-gel capsule to BID tablets. 8th IWADRLH (San Francisco). 2006. #81.
2. Gathe JC, Lipman BA, Mayberry C, et. al. Tolerability and preference of LPV/r capsules versus tablets as single agent therapy (IMANI-2 Trial). HIV8 (Glasgow). 2006. #P104.
3. Rawlings MK, McGhee TA, Casey-Bailey S, Pasley M. A Comparison of Adverse Events and Quality of Life Before and After Switching from Kaletra Soft-gel to Kaletra Tablets in an African American Cohort. The American Conference for the Treatment of HIV (Dallas) 2007. Poster # 82.
4. Awni W,Y-L Chiu,T Zhu, et al. Significantly reduced food effect & pharmacokinetic variability with a novel LPV/r tablet formulation. Abstract WeOa0206. 3rd International AIDS Society Conference on HIV Pathogenesis & Treatment. July 24-27, 2005. Rio de Janeiro, Brazil.
5. Wu A. MOS-HIV health survey scoring guidelines. Version 2.97.

ACKNOWLEDGEMENT

- This work was supported by resources from the following:
  - An independent research grant from Abbott Laboratories
  - Emory University CFAR, Clinical and Statistical cores (NIH P30 AI050409)