Genotypic and Phenotypic Resistance Observations among Patients with Viremia while on Lopinavir/Ritonavir "Monotherapy"

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Background

- Traditional triple-agent HAART is effective, but costly, and associated with toxicities and development of multi-class resistance in patients with virologic failure
- Several retrospective and prospective studies suggest that lopinavir/ritonavir (LPV/r) monotherapy can be effective in suppressing HIV RNA to undetectable levels[1-5]
- The main concern of this approach has been the possibility of rapid development of viral resistance, which historically has been observed in patients on antiretroviral monotherapy
- The primary mutations associated with LPV resistance in PI-naïve patients have not been established
- This poster provides genotypic and phenotypic resistance observations from patients who are participating in two on-going studies and who experienced virologic failure (VF) while on LPV/r monotherapy

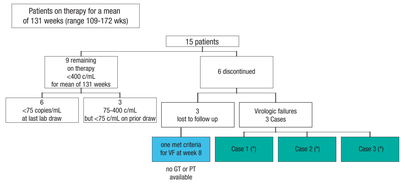
Methods

- Virologic failure (VF) defined as two consecutive HIV RNA levels above 400 copies/mL or failure to achieve HIV RNA level below 400 copies/mL.
- 33 patients were evaluated from two ongoing studies of LPV/r monotherapy. In total, eight patients experienced VF.
  - Four of 15 from a retrospective cohort*[1]
  - Four of 18 from a prospective trial of patients switched to LPV/r monotherapy from an NNRTI-based regimen[3]
- Data from eight patients who experienced VF were examined for resistance. Where available (n=5), genetic sequences and phenotypes from baseline and the time of VF were compared.

*Retrospective review of 15 patients treated with LPV/r monotherapy for greater than eight weeks. Reasons for LPV/r monotherapy were: seven for failure/intolerance to NNRTI or NRTI based regimen, two following pancreatitis on prior PI based regimen, and six with simplification of a combination Kaletra based regimen.

Results

Fig. 1: Patient disposition from retrospective cohort



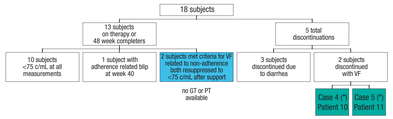
(*) Cases described in detail in Table 2

- 24 week results from the prospective study were presented previously.[3] Additional results are presented in Table 1 and updated for most subjects to week 48.

Table 1: Updated Subject Results from Prospective Study

Patient #	Sex	Age	BL CD4	Regimen	Duration prior regimen in weeks	Outcome on LPV/r
1	M	44	602	EFV, CBV	81	<75 entire 48 weeks
2	M	48	223	EFV, CBV	145	<75 entire 48 weeks
3	M	45	209	NVP, d4T, 3TC	193	<75 entire 48 weeks
4	F	31	476	NVP, d4T, 3TC	251	<75 entire 48 weeks
5	M	38	150	NVP,CBV	85	blip to 3314 week 40 (non-adherence) <75 at weeks 44 and 48
6	F	22	1174	NVP, d4T, 3TC	164	<75 entire 48 weeks
7	F	58	280	EFV, CBV	130	D/C week 4 diarrhea
8	M	53	295	NVP, TDF, 3TC	71	D/C week 2 diarrhea
9	M	54	385	NVP, CBV	209	<75 entire 48 weeks
10	M	45	264	NVP, TDF, 3TC	85	VF week 30
11	M	41	392	NVP, TDF, 3TC	113	VF week 12
12	M	49	261	NVP, TDF, 3TC	57	<75 entire 48 weeks
13	M	56	137	NVP, TDF, 3TC	182	D/C week 8 diarrhea
14	F	53	397	NVP, d4T, 3TC	257	<75 entire 48 weeks
15	M	70	73	NVP, TDF, 3TC	35	Adherence related VF week 48
16	M	65	264	EFV, TDF, 3TC	21	<75 entire 48 weeks
17	F	37	440	NVP, TDF, 3TC	217	<75 entire 48 weeks
18	M	34	170	NVP, TDF, 3TC	41	Adherence related VF week 8, <75 at week 40

Fig. 2: Patient disposition from prospective study



(*) Cases described in detail in Table 2

Resistance Results

- Genotypic and phenotypic resistance observations were available on five of eight patients experiencing VF
  - Three of five were from the retrospective cohort (mean time on LPV/r monotherapy – 111 weeks, range 83 – 132)
  - Two of five were from the prospective trial (mean time on LPV/r monotherapy – 22 weeks, range 13 – 30)

Table 2: Summary of 5 Cases with Genotypic and Phenotypic Observations

Case	BL GT	BL PT (LPV FC)	Week of VF	Weeks on therapy with on-going viremia	Last GT (Week from 1st viremia)	Last PT (LPV FC)	Last RC	Current status (*)
1	I13V, R41K, L63A, V77I	0.5	N/A (failed to achieve VL <400)	118	(Week 100) I13V, R41K, L63A/S, I64I/M, V77I	0.92 (actual)	148%	LTFU Week 118
2	M36I, L63P	Virtual (PI sensitive)	114	28	(Week 14) V3I,* M36I, S37N,* L63P	0.8 (virtual)	ND	Added TDF Week 131
3	L19V, R41K, L63C, I93L	ND	21	69	(Week 68) **V3I,* S37N,* R41K, I54V/I, L63C, A71V, L76V, I93L**	5.7 (actual)	1.4%	Added ATV Week 83, VL <400 Week 113, See Figures 3 and 4
4	ND	ND	12	3	(Week 3) M36I	0.8 (virtual)	ND	Resuppressed on original therapy
5	M36I, L63P	ND	30	4	(Week 4) I13V N37S,* R41K, K55R, I62V, L63P, V77I, I93L	0.57 (actual)	90%	LTFU Week 32

*May not reflect evolution or changes from baseline, but be due to methodologies of various resistance assays (Virologic vs. Virco) used at different times throughout the study.

- Case 1 – Patient had baseline mutations at I13V, R41K, L63A, V77I. After ongoing viremia for 100 weeks, genotype showed new mixtures at L63A/S, I64I/M. Actual Phenotypic susceptibility to LPV was 0.92.
- Case 2 – Patient had baseline mutations at M36I, L63P. After ongoing viremia for 14 weeks, genotype showed presence of new mutations at V03I and S37N. Virtual Phenotypic susceptibility to LPV was 0.8.
- Case 3 – Patient had baseline mutations at L19V, R41K, L63C, I93L. Patient in retrospective cohort had prolonged exposure to LPV/r monotherapy for 67 weeks before demonstrating changes in genotype. After ongoing viremia (a median of 5,576 c/mL), new PI mutations developed at A71V, L76V, I54V in conjunction with an actual 5.7 fold phenotypic increase to LPV. Replication capacity was 1.4%. Details are provided in Figures 3 and 4.
- Case 4 – After ongoing viremia for three weeks, genotype showed the presence of M36I. Virtual phenotypic susceptibility for LPV was 0.8. Subject resuppressed on original therapy.
- Case 5 – Patient had baseline mutations at M36I, L63P. After ongoing viremia for four weeks, genotype showed presence of new mutations at V03I and S37N. Actual phenotypic susceptibility for LPV was 0.57.

Figure 3: LPV/r Case # 3

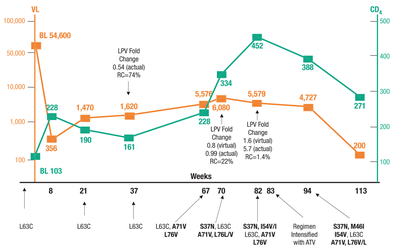
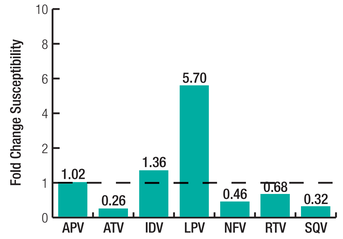


Figure 4: Phenotypic Susceptibility to PIs: Case #3 at Week 82



Discussion

- In these two small studies, the rate of virologic failure has been similar to that reported in larger trials employing LPV/r as part of triple antiretroviral therapy, although small sample sizes do not allow for definitive conclusions.
- When virologic failure occurred, rapid selection of resistance to LPV/r was not observed.
- In one case, where there was prolonged exposure to LPV/r monotherapy, in the presence of ongoing viremia (~68 weeks), we observed a moderate loss in susceptibility to LPV. That change in phenotype was associated with the selection of a primary protease mutation mixture at I54I/V, in addition to secondary mutations (S37N?, A71V, L76V).
- LPV/r monotherapy and Virologic Failures

  In most of our cases, documented or presumed non-adherence was associated with the development of viremia. The use of random PK samples to assess the presence of drug may be useful for identifying patients who are not adherent.

  Adequate drug distribution needs to be confirmed. LPV is a highly protein bound protease inhibitor. There is a possibility that certain compartments may be sequestered from drug. Cellular efflux pumps and/or individual P-glycoprotein differences may have a role.

  We have not identified a clear explanation for the delay in selection of resistance mutations in the protease enzyme for Case 3. This subject experienced ongoing viral replication for >1 year. The presence of adequate plasma LPV levels was confirmed at multiple times throughout the year. One possible factor in the development of protease resistance could have been preceding changes in gag/pol.[6]

Conclusion

- Among patients with virologic failure on LPV/r, there is no evidence of rapid evolution of resistance to LPV/r or to other protease inhibitors.
- Larger clinical trials are required to establish a prevalence of the development of resistance to LPV/r as a result of viral replication in the context of LPV/r monotherapy.
- No clear pathway for the development of LPV/r resistance was elucidated from these two small cohort studies.

References

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