Simplification to Lopinavir/Ritonavir Monotherapy from NNRTI-Based HAART in HIV-Infected Patients With Complete Viral Suppression; 24-Week Interim Analysis

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Background

- Traditional triple-agent HAART is quite effective, but costly, and associated with toxicities.
- One retrospective study suggested that lopinavir/ritonavir (LPV/r) monotherapy was effective for treatment of HIV infection in salvage and simplification.[1,3]
- A prospective pilot study of LPV/r monotherapy in 30 treatment-naïve patients showed that 21 (70%) had HIV RNA <400 copies/mL at week 24 by intention to treat (ITT) analysis and 21/22 (95%) using as treated (AT) analysis.[2]
- In another prospective pilot study, 12 subjects underwent simplification from indinavir/ritonavir (IND/r) + 2 NRTI to IND/r 'mono'-therapy. Viral blips were observed, but no instances of virologic failure.[4]
- We sought to determine if patients with complete viral suppression on a traditional triple drug NNRTI-based regimen could have antiretroviral therapy successfully simplified/switched to LPV/r monotherapy.

Methods

Entry Criteria

- On NNRTI-based HAART for at least 16 weeks
- HIV RNA <75 copies/mL on two consecutive occasions
- No previous PI exposure

Study Design

- Prospective single-center pilot study
- At BL subjects discontinued NNRTI and started LPV/r 400/100 bid while continuing NRTIs.
- 2 weeks post the NNRTI to LPV/r switch, subjects discontinued concomitant NRTIs and remained on LPV/r monotherapy.
- Primary endpoint is the percentage of subjects who retain a HIV RNA <75 copies/mL at 48 weeks. This poster represents a planned 24-week safety and efficacy analysis.

Virologic Evaluation

- Subjects were monitored for HIV RNA at BL, week 2, 4, and then q 4 weeks for the duration of the study.
- Adherence was assessed with pill counts, telephone contact between office visits, and by a standardized adherence questionnaire at each visit.
- Virologic failure was defined by two consecutive HIV RNA levels >400 copies/mL.
- Genotypic resistance testing was performed on subjects with virologic failure.

Table 1: Subject Baseline Demographics

Subject #	Sex	Age	BL CD4	Regimen	Duration on prior regimen in weeks	Lipid Lowering Meds
1	M	44	602	EFV, CBV	81	atorvastatin 20 mg fenofibrate 160 mg
2	M	48	223	EFV, CBV	145	
3	M	45	209	NVP, d4T, 3TC	193	atorvastatin 10 mg
4	F	31	476	NVP, d4T, 3TC	251	
5	M	38	150	NVP, CBV	85	atorvastatin 10 mg
6	F	22	1174	NVP, d4T, 3TC	164	
7	F	58	280	EFV, CBV	130	atorvastatin 10 mg
8	M	53	295	NVP, TDF, 3TC	71	
9	M	54	385	NVP, CBV	209	atorvastatin 20 mg
10	M	45	264	NVP, TDF, 3TC	85	
11	M	41	392	NVP, TDF, 3TC	113	
12	M	49	261	NVP, TDF, 3TC	57	
13	M	56	137	NVP, TDF, 3TC	182	atorvastatin 80 mg fenofibrate 160 mg
14	F	53	397	NVP, d4T, 3TC	257	
15	M	70	73	NVP, TDF, 3TC	35	
16	M	65	264	EFV, TDF, 3TC	21	
17	F	37	440	NVP, TDF, 3TC	217	
18	M	34	170	NVP, TDF, 3TC	41	

Table 2: Subjects Completing 24 Weeks With Measurable Viremia at Any Time Point

Subject #	Screen	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
10	<75	<75	<75	<75	<75	<75	<75	<75	165
15	<75	<75	<75	<75	167	<75	704	<75	<75
18	<75	<75	<75	128	10068	94	<75	118	<75

Safety Results

- Baseline and week 24 fasting lipid levels are available for all 14 subjects that completed week 24.
- Two subjects with baseline hyperglycemia developed mild diabetes mellitus.
  - In both subjects diabetes mellitus is well-controlled with diet and oral agents.
  - Both continue on study.
- Three subjects added lipid lowering therapy after the start of LPV/r therapy.
- Two subjects entered the study on lipid lowering agents and required an increase in dosage.
- In 9 subjects requiring no lipid lowering therapy:
  - Baseline mean total cholesterol 167 mg/dL triglycerides 109 mg/dL
  - Week 24 mean total cholesterol 176 mg/dL triglycerides 159 mg/dL
  - Change over 24 weeks: Total Cholesterol + 9 mg/dL Trigs + 50 mg/dL
- In 5 subjects who required a lipid lowering agent or an increase in their LLA:
  - Baseline mean total cholesterol 194 mg/dL triglycerides 204 mg/dL
  - Week 24 mean total cholesterol 175 mg/dL triglycerides 218 mg/dL
  - Change over 24 weeks: Total Cholesterol -19 mg/dL Trigs +14 mg/dL

Table 3: Timing of Addition or Increase in Lipid Lowering Medications

Subject #	Visit	Change
5	At Screen	atorvastatin 20 mg, fenofibrate 160 mg
6	At Week 8	atorvastatin 10 mg
9	At Week 8	atorvastatin 30 mg
12	At Week 8	fenofibrate 160 mg
14	At Week 4	atorvastatin 10 mg

Discussion

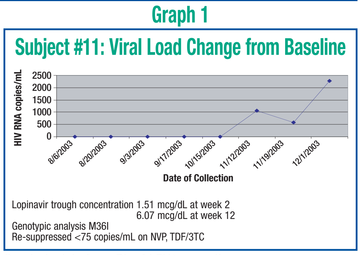
- Triple drug therapy is considered the standard for management of HIV infection. The decision to use three medications was based on studies done early in the era of HAART before the availability of boosted protease inhibitors.
- LPV/r is a potent agent with an inhibitory quotient greater than 75 for wild type virus.[5] LPV/r's intrinsic potency along with favorable pharmacokinetics may allow for <3 drug HAART.
- Several subjects had transient viremia that was associated with poor adherence and breakthrough that appeared to be linked to nonadherence.
- No short-term risk of resistance to LPV/r was observed.
- The cost of antiretroviral therapy was lower after switching to LPV/r monotherapy than the NNRTI-based HAART.
  - The average yearly discount cost of NNRTI-based triple therapy was $12,204[1] (based on the midpoint cost of original NNRTI therapy in this study).
  - The average yearly discount cost of LPV/r was $7,344.*
  - This represents an approximate 40% reduction in medication acquisition costs. If larger long-term studies validate the LPV/r monotherapy pilot studies, there exists the potential to lower costs and expand access to antiretroviral therapy.

* Medication prices accessed at the body plus – http://www.bodyplus.com on June 22, 2004.

Results

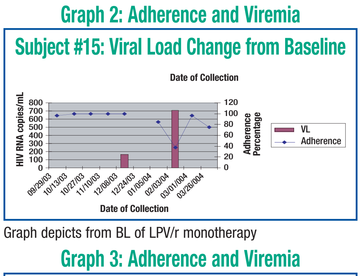
- 18 subjects enrolled.
  - 14 of 18 subjects (78%) have completed 24 weeks of treatment.
- Three subjects discontinued due to adverse events (diarrhea).
  - Subject #7 discontinued week 4.
  - Subject #8 discontinued week 2.
  - Subject #13 discontinued week 8.
    - All 3 discontinuations left study with VL <75 copies/mL.
- One subject discontinued with virologic failure at week 12 (see graph 1).
  - Genotype showed PI gene mutation M36I.
  - Subject re-suppressed after changing back to original NVP-based therapy.
- All 14 subjects (100%) had HIV RNA <400 copies/mL at week 24.
- 13 subjects (93%) had HIV RNA determinations <75 copies/mL at week 24.
- Of the 14 subjects that completed week 24, 3 had measurable viremia at some time point (refer to table 2).
  - Subject #10 at week 24 had VL of 165 copies/mL.
  - Subject #15 had VL of 167 at week 8 and VL of 704 at week 16 (see graph 2).
  - Subject #18 experienced VF at week 8, but re-suppressed to <75 copies/mL with adherence support. This subject remains on LPV/r monotherapy (see graph 3).
- 11 subjects have maintained HIV RNA <75 copies/mL at every time point.

Graph 1



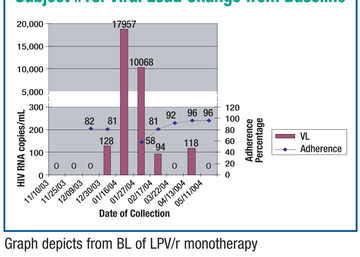
Graph depicts from BL of LPV/r monotherapy

Graph 2: Adherence and Viremia



Graph depicts from BL of LPV/r monotherapy

Graph 3: Adherence and Viremia



Graph depicts from BL of LPV/r monotherapy

Summary and Conclusions

- The majority of patients in this study remained undetectable despite the replacement of triple NNRTI-based HAART with LPV/r monotherapy.
- Simplification to LPV/r monotherapy from NNRTI-based therapy led to continued virologic control (HIV RNA <75 c/mL) in 13/18 (72%) subjects at week 24 (ITT).
- Diarrhea was the most common side effect and led to discontinuation of LPV/r in 3 subjects.
- Lipid levels increased modestly. 5 of 14 subjects controlled lipids with the addition or increase of a lipid lowering agent.
- Prior studies of LPV/r monotherapy have shown promising results in the treatment-naïve and salvage setting. This current study suggests the potential usefulness of LPV/r monotherapy in a simplification/switch strategy.
- Larger prospective studies to evaluate the long-term safety and efficacy of LPV/r monotherapy are warranted.

References

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