Poster 811

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Evaluation of HCV RNA and Liver Injury in HCV/HIV Coinfected Patients Initiating Lopinavir/r or Nelfinavir-based Therapy

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ABSTRACT

Background: Initiation of highly active antiretroviral therapy (HAART) in HCV/HIV coinfected patients (pts) has been associated with increased HCV viral load and transaminase flares. Prior studies have included mixed treatment regimens, making interpretation difficult. This study compared two HAART regimens in naïve subjects.

Methods: Seventy putatively coinfected pts (HCV EIA-positive) from a phase 3 trial in which antiretroviral-naïve pts were randomized to receive either lopinavir (LPV)/r 400/100 mg bid or nelfinavir (NFV) 750 mg tid, both dosed with stavudine and lamivudine, were retrospectively evaluated. HCV and HIV RNA viral load (VL) (Roche Amplicor Monitor) were measured at baseline (BL), weeks 24/48, and during ALT increases to >5x the upper limit of normal.

Results: 57/70 (81%) pts were positive for HCV RNA at BL. Six pts in each treatment arm discontinued the study prior to week 48. Among this subset of patients reaching 48 weeks of therapy, HIV virologic/immunologic responses were grossly similar. Mean BL HCV VL was 6.07 and 6.22 $\log_{10}$ IU/mL in LPV/r (n=22) and NFV (n=35) groups, respectively (p=0.607). HCV RNA tended to increase to a mean of 6.68/6.32 $\log_{10}$ IU/mL and 6.48 /6.44 $\log_{10}$ IU/mL for the LPV/r and NFV groups, respectively, at weeks 24/48. In pts with BL CD_4 <100 cells/mm^3, a higher proportion of pts in the NFV group vs. LPV/r group experienced a >0.5 log increase in HCV VL from BL to week 48 (5/11 [45%] vs. 0/10, respectively, p=0.035). CD_4 and HCV genotype were not associated with HCV VL changes at 48 weeks in either treatment group. Mean ALT at BL was 55 U/mL for the LPV/r group and 47 U/mL for the NFV group. There were mean increases in ALT of 38 U/L and 16 U/L for the NFV group vs. decreases of 14 U/L and 11 U/L for the LPV/r group at week 24 (p=0.006) and week 48 (p=0.101), respectively.

Conclusions: In HAART-naïve HCV/HIV-coinfected pts, initiation of LPV/r or NFV-based therapy tends to result in increased serum HCV RNA at 24 weeks that improves by 48 weeks of therapy, with significantly more >0.5 $\log_{10}$ increases from BL to week 48 in NFV-treated pts with BL CD_4 <100 cells/mm^3. An increase was observed in mean ALT levels in the NFV arm at week 24, but not in the LPV/r-treated group, although week 48 ALT values were not significantly different from BL in either group. These observations may have clinical relevance in terms of interpretation of ALT abnormalities following initiation of HAART in coinfected patients.

BACKGROUND

- 16-20% of HIV-infected patients in the US are coinfected with HCV[1]
- This proportion increases to approximately 73% for high-risk populations[1]
- Coinfection with HCV/HIV has been associated with faster progression to fibrosis[2] and end-stage liver disease (ESLD), especially in patients with low CD_4 cell counts[3]
- Mortality due to ESLD appears increased in coinfected patients versus HIV-monoinfected patients[4,5]
- Initiation of highly active antiretroviral therapy (HAART) in HCV/HIV-coinfected patients has been associated with both increased HCV viral load and transaminase flares in many, but not all, studies[6,7,8]
- Prior reports have included mixed treatment regimens, making interpretation of the effects of HAART difficult[9]
- The parent trial was a prospective, randomized, double-blind, comparative phase III trial in antiretroviral-naïve patients[10] (Abbott 863) comparing lopinavir (LPV)/r 400/100 mg bid (n=326) or nelfinavir (NFV) 750 mg tid (n=327), plus a fixed NRTI backbone (d4T + 3TC). This trial demonstrated the superior antiretroviral activity and comparable tolerability for LPV/r vs. NFV-treated patients.

HYPOTHESIS AND GOALS

- Initiation of HAART is associated with ALT flares and increased HCV viral titers
- The objective of this analysis was to compare the effects of two PI-based regimens on ALT levels and HCV viral titers in HIV/HCV coinfected patients initiating antiretroviral therapy

METHODS

- A subset of 70 HCV-ELISA positive/HIV infected patients from Abbott 863 were identified and retrospectively evaluated
- HCV viral load was measured at baseline, weeks 24 and 48, and during any ALT increase to >5x the upper limit of normal
- HIV viral load (Roche Amplicor Monitor) was measured at baseline, every 4 weeks through week 24, then every 8 weeks through week 48
- HCV genotype was determined at baseline (Bayer LiPA)
- Fisher's exact test, Student's *t*-test, Cox proportional hazards model, and linear regression techniques were used as best fit the data
- A two-tailed p-value of 0.05 was used to determine significance in all cases

RESULTS

Baseline Characteristics

- Seventy patients (11%) from Study 863 were HCV-EIA positive at screening
- 57/70 (81%) were positive for HCV RNA at baseline
- Baseline demographics were comparable among the subsets of patients in both treatment groups (Table 1)
- 39/57 (68%) patients were HCV genotype 1, 1a, or 1b. The remainder included 1a/1b, 2, 2b, 3a, 4, 4c/4d; 3 patients were unable to be genotyped (Figure 1)
- There were no significant differences in baseline HCV viral load, HIV viral load, CD_4, CD_8, and ALT between the two treatment arms at baseline (Table 2)
- Six patients in each treatment arm discontinued the study prior to week 48 (Table 3)

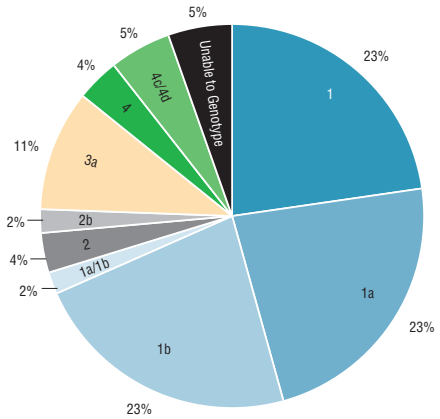
RESULTS

Table 1. Baseline Demographics

Variable	Lopinavir/r (N=29)	Nelfinavir (N=41)	p-value
Gender			NS
Male	23 (79%)	31 (76%)	
Female	6 (21%)	10 (24%)	
Age (years)			
Mean (Range)	41.9 (23-84)	37.8 (22-68)	NS
Race			NS
Caucasian	15 (52%)	26 (63%)	
Black	11 (38%)	9 (22%)	
Hispanic	2 (7%)	5 (12%)	
Other	1 (3%)	1 (2%)	
Alcohol Use			NS
Non-Drinker	5 (17%)	13 (32%)	
Drinker	14 (48%)	17 (41%)	
Ex-Drinker	9 (31%)	10 (24%)	
Unknown	1 (3%)	1 (2%)	
Risk Factors[a]			
IV Drug User	16 (55%)	23 (56%)	NS
Gay/Bisexual Male	6 (21%)	8 (20%)	NS
Sex Partner HIV Positive	4 (14%)	11 (27%)	NS

[a] Subjects may be in multiple categories

Figure 1. HCV Genotype



Note: The total of the percentages may be different than 100% due to rounding

Table 2. Baseline Disease Characteristics

Variable	Lopinavir/r (N=29)	Nelfinavir (N=41)	p-value
Baseline log_{10} HCV VL[a]			
Mean	6.07	6.22	NS
Median	6.28	6.45	
Min-Max	1.70-7.32	2.95-7.36	
Baseline log_{10} HIV VL			
Mean	4.94	4.93	NS
Median	5.12	5.02	
Min-Max	3.02-6.28	2.98-6.72	
Baseline CD_4 (cells/mm^3)			
Mean	252	253	NS
Median	205	186	
Min-Max	2.5-868	15-818	
Baseline CD_8 (cells/mm^3)			
Mean	754	801	NS
Median	578	803	
Min-Max	171-2357	257-1927	
Baseline ALT (U/L)			
Mean	55	47	NS
Median	44	39	
Min-Max	16-265	14-100	

[a] 22 LPV/r subjects and 35 NFV subjects had baseline HCV VL data

RESULTS

Table 3. Summary of Primary Reasons for Premature Discontinuation

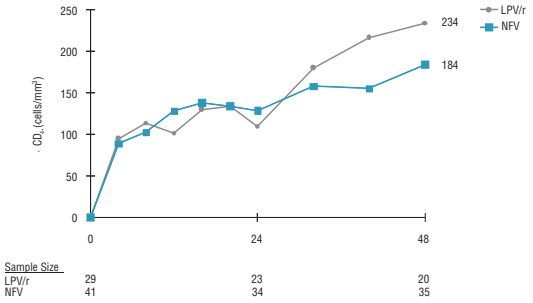
Variable	Lopinavir/r (N=29)	Nelfinavir (N=41)	p-value
Total Subjects Discontinued	6 (21%)	6(15%)	NS
Adverse Event/HIV-Related Event	2 (7%)[a]	0	NS
Lost to Follow-up	1 (3%)	4 (10%)	NS
Personal Reasons	1 (3%)	0	NS
Death	1 (3%)	1 (2%)	NS
Required Prohibited Medication	1 (3%)	0	NS
Virologic Failure	0	1 (2%)	NS
Other	1 (3%)	0	NS

[a] One subject experienced pancreatitis and pneumonia not related to study drug. The pneumonia led to death. The other subject experienced anorexia that was probably related to study drug.

Virologic Response

- Among patients reaching 48 weeks of therapy, HIV virologic and immunologic responses appeared similar. However, there was a trend toward a higher CD_4 mean change from baseline (p=0.247 at week 48, Figure 2) and a shorter time to HIV viral load suppression to <400 (p=0.274) and <50 (p=0.308) copies/mL in LPV/r-treated patients. (Figures 3a and 3b).
- HCV RNA increased to a mean of 6.68/6.32 $\log_{10}$ IU/mL and 6.48/6.44 $\log_{10}$ IU/mL for the LPV/r and NFV groups, respectively, at weeks 24/48 (Figure 4a)
- In patients with baseline CD_4 <100 cells/mm^3, HCV RNA increased to a mean of 6.75/5.95 $\log_{10}$ IU/mL and 6.28/6.49 $\log_{10}$ IU/mL for the LPV/r and NFV groups, respectively, at weeks 24/48 (Figure 4b)
- In patients with baseline CD_4 <100 cells/mm^3, a higher proportion of patients in the NFV group vs. LPV/r group experienced a >0.5 log increase in HCV viral load from baseline to week 48 (5/11 [45%] vs. 0/10, respectively, p=0.035)

Figure 2. CD_4 Mean Change from Baseline



Note: Among patients discontinuing before Week 48, a similar trend toward higher CD_4 cell count increases in the LPV/r group was observed

Figure 3a. Kaplan-Meier Estimates of Time to HIV VL <400 copies/mL

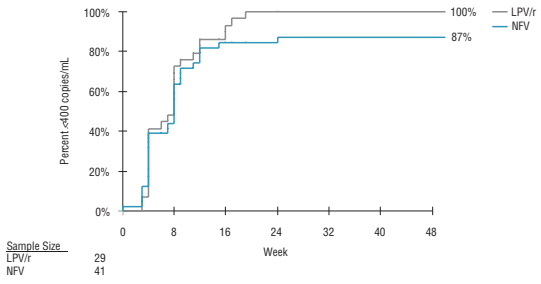
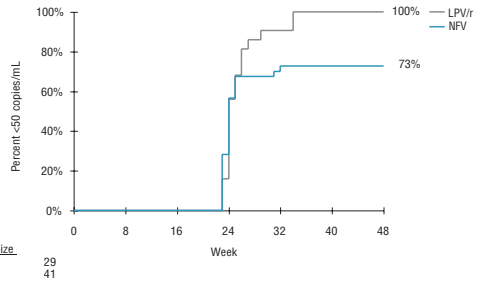


Figure 3b. Kaplan-Meier Estimates of Time to HIV VL <50 copies/mL



Note: The Ultrasensitive assay was not performed until Week 24

Figure 4a. Mean HCV Viral Loads All Patients

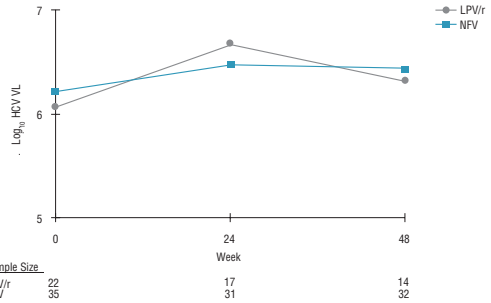
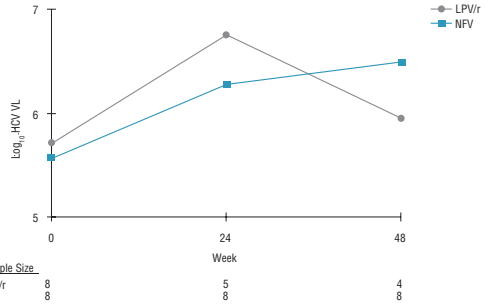


Figure 4b. Mean HCV Viral Loads Baseline CD_4 <100 cells/mm^3



ALT Response

- Mean ALT at baseline was 55 U/L for the LPV/r group and 47 U/L for the NFV group
- There were mean increases in ALT of 38 U/L and 16 U/L for the NFV group vs. decreases of 14 U/L and 11 U/L for the LPV/r group at week 24 (p=0.006) and week 48 (p=0.101), respectively (Figure 5)
- There were 8 subjects on the nelfinavir arm and 2 subjects on the LPV/r arm who experienced grade 3+ elevations in ALT. The two subjects on LPV/r had brief elevations in ALT that returned to normal by week 48. The subjects on nelfinavir had more persistent elevations over the 48 weeks (Figure 6).

Figure 5. Mean ALT

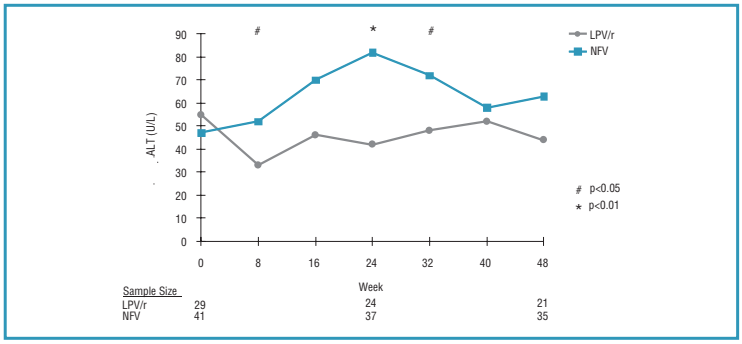
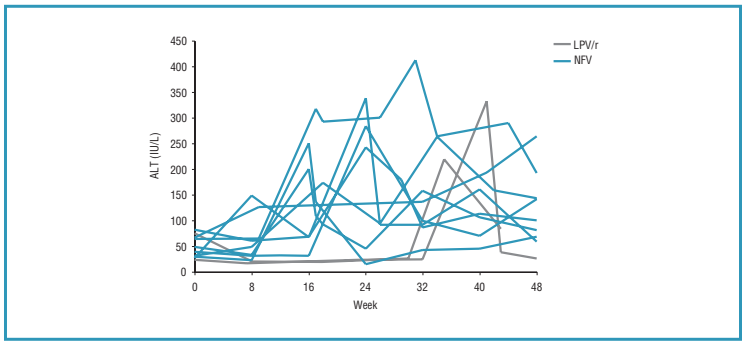


Figure 6. ALT for HIV/HCV Subjects with Grade 3/4 Elevations



SUMMARY

- In HAART-naïve HCV/HIV-coinfected pts, initiation of LPV/r or NFV-based therapy may result in increased serum HCV RNA at 24 weeks that improves by 48 weeks of therapy, with significantly more >0.5 $\log_{10}$ increases from baseline to week 48 in NFV-treated patients with baseline CD_4 <100 cells/mm^3
- An increase was observed in mean ALT levels in the NFV arm at week 24, but not in the LPV/r-treated group, although week 48 ALT values were not significantly different from baseline in either group
- This analysis suggests LPV/r appears to differentially affect HCV among coinfected patients compared to NFV

CONCLUSIONS

- Initiation of HAART is associated with HCV viral load increase and ALT flares
- Low baseline CD_4 is associated with persistent HCV RNA increases in nelfinavir-treated patients
- Patients treated with lopinavir/r-based therapy are less likely to have grade 3+ toxicity (ALT flares) associated with HCV RNA increases than those treated with nelfinavir-based therapy

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