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Lopinavir/ritonavir (LPV/r) Safety, Tolerability and Efficacy in Hepatitis C and/or Hepatitis B-infected Patients: Review of Clinical Trials

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BACKGROUND

As concomitant Hepatitis C (HCV) and/or Hepatitis B (HepB) infection occurs commonly with HIV infection (ranging from 15-80%, depending on the risk group evaluated), efficacy, safety and tolerability of antiretroviral therapy (ARV) in this patient population compared to those without hepatitis coinfection is of interest.[1]

Analysis of the Swiss HIV Cohort suggested that patients coinfected with HCV do not have as prominent an immune recovery in response to combination antiretroviral therapy as non-coinfected patients.[2] In this study, investigators found that after one year of antiretroviral therapy, HCV coinfected patients had a 21% reduction in the likelihood of increasing CD4 cell counts by at least 50 cells/μL relative to non-coinfected patients. This finding was confirmed when investigators adjusted their evaluation for the type of antiretroviral therapy, baseline CD4 and total lymphocyte count, and in the subgroup of patients who achieved an HIV viral load <400 copies/ml. Similar results have been reported by Cowling et al. in an analysis evaluating a large observational cohort, presented here at World AIDS 2004 (poster MoPeB3300).[3]

Antiretroviral drugs, including protease inhibitors, have been shown to have a higher incidence of AST/ALT elevations in coinfected patients compared to non-coinfected patients. However, it has recently been described that some protease inhibitors, including lopinavir/ritonavir (LPV/r), have a lower incidence of these hepatotoxic events relative to other members of the class.[4]

The current analysis compares HIV/HCV and/or HepB coinfected patients to non-coinfected patients in several clinical trials of LPV/r, with respect to virologic and immunologic response, and the risk of AST/ALT elevations. The effect of HCV and/or HepB coinfection on drug discontinuation rates, hepatic adverse events, and deaths was also evaluated.

METHODS

Efficacy, safety, and tolerability data through 48 weeks from 8 clinical trials of LPV/r (n=819 adult patients) were compared in patients with HCV and/or HepB co-infection (Hepatitis+, n=132) vs. those without (Hepatitis-, n=687). HepB or HCV coinfection was determined based on baseline serologic testing for HBsAg and HCV Ab, respectively.

Similar comparisons were conducted through 5 years in a subset of ARV-naïve patients receiving LPV/r, d4T, and 3TC BID (Hepatitis+, n=11, Hepatitis-, n=89) in study M97-720.

Comparative data through 60 weeks of follow-up in study M98-863 were evaluated in a subset of ARV-naïve patients treated with a LPV/r-based regimen versus a nelfinavir-based regimen (LPV/r: Hepatitis+, n=57; Hepatitis-, n=269; nelfinavir: Hepatitis+, n=68; Hepatitis-, n=259). Both groups received d4T and 3TC BID.

The breakdown of patients by study and prior ARV treatment history is presented in Table 1.

Table 1. Summary of Clinical Trials Included in This Analysis

Study	Clinical Development Phase	Prior ARV Experience	Number of Patients		
			Total	Hepatitis+	Hepatitis–
M00-154[5]	Phase II	Naïve	44	6	38
M97-720[6]	Phase II	Naïve	100	11	89
M99-056[7]	Phase II	Naïve	38	1	37
M98-863[8]	Phase III	Naïve	326	57	269
M98-888[5]	Phase III	Experienced	148	31	117
M98-957[9]	Phase II	Experienced	57	8	49
M99-049[10]	Phase II	Experienced	36	7	29
M97-765[11]	Phase II	Experienced	70	11	59
		Total	819	132	687

Hepatitis+ patients were allowed entry into these studies; however, patients with baseline AST or ALT levels ≥3 times upper limit of normal (ULN) at screening were excluded from study entry.

ARV treatment history was a significant predictor of virologic and immunologic response, so efficacy comparisons were conducted separately among ARV-naïve and ARV-experienced patients. Safety analyses compared all coinfected patients (n=132) to all non-coinfected patients (n=687), except for the analysis of events of AST/ALT elevations. Of note, patients in studies M97-765 and M98-888 received concomitant nevirapine, an NNRTI which has been associated with liver function test elevations.

Rates of Grade 3+ AST and ALT elevations (>5xULN) were assessed. Hepatic adverse events were defined as the following COSTART codes: hepatitis, hepatitis C, hepatitis nonspecific, hepatitis HBsAg, hepatomegaly, hepatorenal syndrome, hepatosplenomegaly, jaundice, jaundice cholestatic, liver damage, liver tenderness, liver fatty, liver failure, liver cirrhosis, increased alkaline phosphatase, bilirubinemia, bilirubinuria, ascites, acute brain syndrome, coma hepatic, and hepatic encephalopathy.

RESULTS

Baseline Characteristics

- There were no significant demographic differences between Hepatitis+ and Hepatitis- patients at baseline (Table 2).

Table 2. Demographic Characteristics by Baseline Hepatitis Status

	Hepatitis+ (N=132)	Hepatitis– (N=687)	p-value
Gender			NS
Male	85%	84%	
Female	15%	16%	
Age (years)	40	38	NS
Mean (range)	18-84	19-74	
Race*			NS
Caucasian	58%	63%	
Black	27%	23%	
Hispanic	12%	12%	
Other	5%	2%	
Hepatitis Status*			
Hepatitis B+ only	32%	—	N/A
Hepatitis C+ only	64%	—	N/A
Hepatitis B+ and C+	5%	—	N/A

* Totals may not equal 100% due to rounding

- Baseline HIV RNA levels and CD4 cell count were not significantly different between the Hepatitis+ and Hepatitis- groups. Mean hepatic transaminase values were significantly higher in the Hepatitis+ group (p<0.001, Table 3).

Table 3. Baseline Disease Characteristics

	Hepatitis+ (N=132)	Hepatitis– (N=687)	p-value
Baseline HIV RNA (log_{10} copies/mL)			
Mean (Range)	4.5 (2.6-6.3)	4.7 (2.6-7.6)	NS
Baseline HIV RNA >100,000 copies/mL	41 (31%)	258 (38%)	NS
Baseline CD4 count (cells/µL)			
Mean (Range)	289 (2-1048)	312 (3-1059)	NS
Baseline CD4 <50 cells/µL	18 (14%)	95 (14%)	NS
Baseline CD4 <200 cells/µL	45 (34%)	265 (39%)	NS
Mean Baseline ALT (U/L)	54.5	36.7	<0.001
Mean Baseline AST (U/L)	51.9	33.3	<0.001

Patient Disposition Through 48 Weeks

- A significantly higher percentage of Hepatitis+ patients discontinued by Week 48 (Table 4). This was mainly due to higher rates of discontinuation for loss to follow-up and for personal reasons/other among the coinfected patients. Rates of discontinuation for deaths, adverse events, or virologic failure did not differ between the groups.

Table 4. Patient Disposition at Week 48

	Hepatitis+	Hepatitis–	p-value
Patients Enrolled	132	687	
Patients Discontinued by Week 48	35 (27%)	111 (16%)	0.006
Death*	1 (1%)	8 (1%)	NS
Adverse Event/HIV-Related Event*	7 (5%)	35 (5%)	NS
Virologic Failure*	1 (1%)	13 (2%)	NS
Lost to Follow-up	9 (7%)	13 (2%)	0.004
Noncompliance*	5 (4%)	17 (2%)	NS
Required Prohibited Medication	2 (2%)	1 (<1%)	NS
Personal Reasons/Other*&	12 (9%)	24 (3%)	0.009
Admission Criteria Violation	0	1 (<1%)	N/A

* Patients could indicate more than one reason for discontinuation

& Reasons included withdrawal of consent, personal problems, pill burden, distance to site, and end stage disease

Efficacy Data Through 48 Weeks

- Risk of virologic failure (failure to achieve HIV RNA below 400 copies/mL or two consecutive results above 400 copies/mL after suppression) through 48 weeks was not statistically significantly different for Hepatitis+ vs. Hepatitis- patients among ARV-naïve or ARV-experienced patients (Figures 1 and 2).
- Virologic results were similar between Hepatitis+ and Hepatitis- patients when these groups were stratified based on baseline HIV RNA above or below 100,000 copies/ml.

Figure 1. Kaplan-Meier Estimates of Time to Loss of Virologic Response in ARV-Naïve Patients

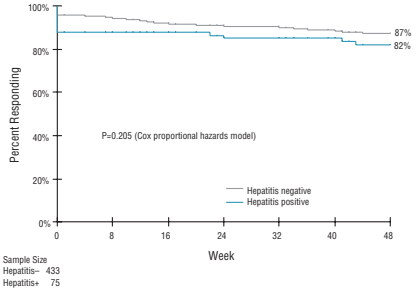
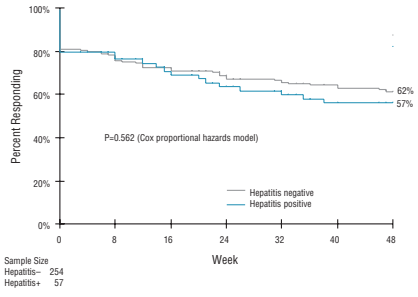


Figure 2. Kaplan-Meier Estimates of Time to Loss of Virologic Response in ARV-Experienced Patients



- There was no significant difference between Hepatitis+ vs. Hepatitis- patients in mean change in CD4 counts from baseline to 48 weeks in ARV-naïve (Hepatitis+: +211 cells/µL, Hepatitis-: +220 cells/µL, p=0.68) or ARV-experienced (Hepatitis+: +82 cells/µL, Hepatitis-: +112 cells/µL, p=0.17) patients.
- Analyses comparing Hepatitis+ patients to Hepatitis- patients within baseline CD4 subcategories yielded similar results (Figures 3 and 4). Since there was only one Hepatitis+ ARV-experienced patient with baseline CD4 <50 cells/µL, only the <200 and ≥200 cells/µL categories were plotted and analyzed for ARV-experienced patients.

Figure 3. Mean CD4 Cell Count Change from Baseline – ARV-Naïve Patients

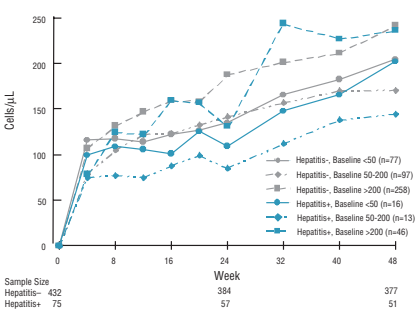
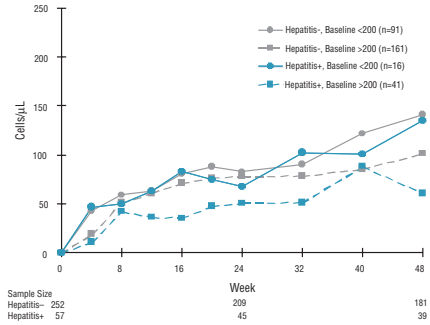


Figure 4. Mean CD4 Cell Count Change from Baseline – ARV-Experienced Patients



Safety Data

Evaluation of AST/ALT Levels

- Grade 3+ AST and ALT elevations (>5x ULN) were more common in Hepatitis+ than Hepatitis- patients (Table 5). Results were similar when analyses were conducted separately among ARV-naïve and ARV-experienced patients.

Table 5. Grade 3+ LFT Elevations (>5x ULN)

	Hepatitis+	Hepatitis–	Relative Risk	95% Confidence Interval	p-value
All Patients					
Grade 3+ AST*	13%	3%	4.1	2.2-7.5	<0.001
Grade 3+ ALT*	16%	5%	3.1	1.8-5.3	<0.001
Naïve					
Grade 3+ AST*	9%	3%	3.1	1.2-8.0	0.014
Grade 3+ ALT*	13%	4%	3.0	1.4-6.3	0.004
Experienced					
Grade 3+ AST*	19%	4%	4.7	2.1-10.8	0.001
Grade 3+ ALT*	19%	6%	3.2	1.5-6.6	0.002

* Grade 3+ elevation defined as a value >5x ULN

- Analyses were performed using an alternate definition of Grade 3+ AST and ALT elevations proposed by Sulkowski et al.[12] in which patients with elevated pre-ARV treatment serum AST/ALT levels were classified based on changes relative to baseline value rather than ULN (Table 6).
- Using this analysis, which attempts to compensate for pre-existing elevations in hepatic transaminases at baseline, Hepatitis+ ARV-naïve patients did not experience significantly more Grade 3+ AST/ALT elevations than the Hepatitis- patients (AST: 4% vs. 3%, respectively; ALT: 9% vs. 4%, respectively).

Table 6. Grade 3+ LFT Elevations – Alternate Grade 3+ Definition

	Hepatitis+	Hepatitis–	Relative Risk	95% Confidence Interval	p-value
All Patients					
Grade 3+ AST*	10%	4%	2.8	1.4-5.4	0.002
Grade 3+ ALT*	11%	5%	2.3	1.3-4.3	0.006
Naïve					
Grade 3+ AST*	4%	3%	1.4	0.4-4.9	0.559
Grade 3+ ALT*	9%	4%	2.1	0.9-5.1	0.103
Experienced					
Grade 3+ AST*	17%	4%	3.9	1.7-8.9	0.001
Grade 3+ ALT*	13%	5%	2.6	1.1-6.1	0.032

*Grade 3+ elevation defined as a value >5x ULN for patients with normal baseline values and as >3.6x baseline for patients with AST/ALT values higher than ULN at baseline

- Rates of Grade 3+ AST/ALT elevations were similar for HCV coinfected-only vs. HepB coinfected-only patients (Table 7).

Table 7. Grade 3+ LFT Elevations – HCV Coinfected-Only vs. HepB Coinfected-Only Patients

	HepB Only (n=40)	HCV Only (n=76)
Grade 3+ AST*	10%	13%
Grade 3+ ALT*	15%	13%

* Grade 3 elevation defined as a value >5x ULN

Hepatic Adverse Events

- Excluding AST/ALT increases, hepatic adverse events of any severity or relationship to study drug occurred similarly in Hepatitis+ (2%) vs. Hepatitis- (2%) patients (Table 8).

Table 8. Hepatic Adverse Events (Excluding Grade 3+ LFT Elevations)

	Hepatitis+ (N=132)	Hepatitis– (N=687)	p-value
Any Hepatic Adverse Event	3 (2%)	17 (2%)	NS
Hepatitis	0	5 (1%)	NS
Hepatitis C Virus	1 (1%)	0	N/A
Hepatomegaly	1 (1%)	8 (1%)	NS
Jaundice	0	2 (<1%)	NS
Liver Damage	0	1 (<1%)	N/A
Liver Tenderness	0	2 (<1%)	NS
Alkaline Phosphatase Increased	0	2 (<1%)	NS
Bilirubinemia	0	1 (<1%)	N/A
Encephalopathy (Hepatic)	1 (1%)	0	N/A

- There was no significant difference in deaths (Hepatitis+: 2%, Hepatitis-: 1%) or adverse events leading to discontinuation (7% in each group; values are higher than those in Table 4 due to discontinuations occurring after Week 48).
- No hepatic-related events resulted in death. Five patients in the Hepatitis- group died (rhabdomyolysis, carcinoma of the lung, coronary artery disease, pancreatitis, lymphoma-like reaction with reactive TB), as did three patients in the Hepatitis+ group (pneumonia, Hodgkin's lymphoma, shock with sepsis). Other than the pancreatitis, none of the deaths were considered related to study drug.

LPV/r vs. Nelfinavir in ARV-Naïve HIV/Hepatitis+ Coinfected Patients

- As demonstrated in study M98-863, a double-blind, randomized trial, Hepatitis+ LPV/r-treated patients (n=57) demonstrated a tendency towards a lower incidence of Grade 3+ AST and ALT elevations than Hepatitis+ NFV-treated patients (n=68) through 60 weeks of treatment (AST: 4% vs. 13%, respectively; ALT: 12% vs. 17%, respectively).[13]
- Excluding AST/ALT increases, hepatic adverse events of any severity or relationship to study drug occurred similarly in LPV/r-treated (4%) vs. NFV-treated (4%) Hepatitis+ patients through 60 weeks of treatment in M98-863.
- No LPV/r-treated (or NFV-treated) Hepatitis+ patients discontinued therapy due to elevated liver enzymes through 60 weeks of treatment in M98-863.[13]
- No hepatic-related events resulted in death for Hepatitis+ patients through 60 weeks of treatment in M98-863. Two LPV/r-treated Hepatitis+ patients died (pneumonia and Hodgkin's lymphoma), as did one NFV-treated Hepatitis+ patient (AIDS and fungal infection). None of the deaths were considered related to study drug.

5-Year Evaluation of LPV/r-based Therapy in ARV-Naïve HIV/Hepatitis+ Coinfected Patients

- Through five years of follow-up in M97-720 (n=100), there was no significant difference in time to virologic failure between Hepatitis+ and Hepatitis- patients (Kaplan-Meier estimates of proportion responding were 100% and 79% at five years for Hepatitis+ and Hepatitis- patients, respectively, p=0.138). None of the 11 Hepatitis+ patients experienced virologic failure.
- There was also no significant difference in mean change from baseline to 252 weeks in CD4 cell count between the Hepatitis+ and Hepatitis- patients (Hepatitis+: +613 cells/μL, Hepatitis-: +493 cells/μL, p=0.26).
- Similar safety results were observed through five years, with a higher risk of Grade 3+ AST/ALT elevations in Hepatitis+ patients (RR:10.1 and 6.5 for AST and ALT, respectively), but no significant differences in hepatic adverse events (Hepatitis+: 0%, Hepatitis-:8%, p>0.99), deaths (Hepatitis+: 0%, Hepatitis-:1%), or discontinuations (Hepatitis+: 27%, Hepatitis-:10%, p=0.13).
- There were no hepatic-related events leading to death in either subgroup.

Multivariate Analysis Evaluating Predictors of Grade 3 or 4 AST/ALT Elevations

- In a multiple logistic regression analysis using stepwise regression, baseline and demographic characteristics were evaluated to assess the risk of Grade 3+ ALT elevations among Hepatitis+ patients.
- Higher baseline ALT and alcohol use were associated with higher risk of Grade 3+ ALT elevations (Table 9). Interestingly, lower baseline AST was associated with higher risk of Grade 3+ ALT elevations, suggesting that a patient with elevated baseline ALT without elevated AST was at higher risk for further ALT elevations than a patient with concurrently elevated ALT and AST at baseline.
- Age, gender, baseline HIV RNA, baseline CD4 count, and prior ARV experience were not associated with Grade 3+ ALT elevations.

Table 9. Multivariable Logistic Regression Results for Grade 3+ ALT Elevations

Variable	Odds Ratio	95% CI	P-value
Baseline ALT (per 10 U/L increase)	1.71	1.24-2.34	<0.001
Baseline AST (per 10 U/L increase)	0.60	0.40-0.89	0.011
Current Alcohol Use	3.22	0.91-11.34	0.069

DISCUSSION

- No statistically significant difference in the risk of virologic failure or mean change in CD4 cell count from baseline was observed through 48 weeks between Hepatitis+ and Hepatitis- patients using Kaletra-based regimens regardless of prior ARV experience.
- This result is in contrast to data that has previously been presented suggesting attenuated CD4 cell count increases in HCV coinfected patients.[2] These observations suggest that specific protease inhibitors may have differential effects on immune recovery in hepatitis coinfected patients.
- There was an increased risk of Grade 3+ AST or ALT increase in those patients who were Hepatitis+ versus Hepatitis-. These increases may be attributable to higher baseline hepatic transaminase levels in coinfected patients. In fact, in an analysis designed to compensate for these baseline elevations, no significant increased risk of LFT elevations was seen in ARV-naïve patients with hepatitis coinfection. Increased risk in ARV-experienced patients may be attributable, in part, to the use of nevirapine, which has been associated with LFT elevations.
- There was no difference in hepatic adverse events, ARV discontinuation, or deaths due to adverse events between patients with and without hepatitis coinfection.
- There was a tendency towards a lower incidence of Grade 3+ AST/ALT elevations in ARV-naïve coinfected patients using a Kaletra-based regimen compared to a nelfinavir-based regimen. There was a similar rate of hepatic adverse events in patients treated with a Kaletra-based or a nelfinavir-based regimen. There were no discontinuations due to elevated liver enzymes or deaths in either treatment arm.

CONCLUSIONS

- A LPV/r-based regimen is as effective in patients with Hepatitis B and/or C coinfection compared to those with only HIV infection.
- ARV therapy with a LPV/r-based regimen provides a similar degree of immunologic recovery through 48 weeks in hepatitis coinfected patients, in contrast to previously published data evaluating other PI-based ARV regimens.
- Although higher rates of Grade 3+ AST or ALT elevations were observed in Hepatitis+ versus Hepatitis- LPV/r-treated patients, this did not result in differential rates of ARV drug discontinuations, other hepatic adverse events, or fatal outcomes. These higher rates of Grade 3+ AST/ALT elevations may be attributable to elevated baseline transaminase levels.
- Rates of AST/ALT elevations tended to be lower in ARV-naïve coinfected patients receiving a Kaletra-based regimen versus a nelfinavir-based regimen
- Results in a subset of ARV-naïve patients treated with LPV/r through 5 years were consistent with the overall analysis.
- Increased baseline ALT and current alcohol use were associated with Grade 3+ ALT elevations among Hepatitis+ patients.

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