Poster 299

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Response to Lopinavir/ritonavir-Based HAART and Its Dependence on Prior ARV Experience: 24-Week Interim Analysis (VIHvir+ Study)

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INTRODUCTION

Since lopinavir/ritonavir (LPV/r) was approved for treatment of HIV in Spain (Aug 01) many physicians have supported its use as rescue therapy for heavily pretreated patients while others have supported its use in less ARV experienced patients. Retrospective studies have shown that the mean duration of initial antiretroviral therapy is approximately 12 months and that the duration of treatment decreased as the patients' antiretroviral experience increased.[1] The duration of LPV/r-based therapy may be related to previous antiretroviral treatment experience and viral replication status at the time of initiating therapy. In study M97-720, which assessed the effect of LPV/r-based therapy on virologic response in antiretroviral-naïve patients, development of resistance in protease was not observed over the 6 years of follow-up,[2] a predictor of the durability of virologic response.

The VIHvir+ Study is a post-marketing observational study with prospective data collection. It was designed to obtain further data on the safety and effectiveness of LPV/r and its dependence on prior ARV experience in a real life setting. It was conducted in the 61 Spanish sites shown in Table 1. The study was approved by an Ethics Committee (EC) based on local regulations.

Table 1. Investigators Participating in the VIHvir+ Study

Principal Investigator	Site/City	Principal Investigator	Site/City	Principal Investigator	Site/City
Dr. Hernandez	Ciudad de Jaen-Jaen	Dra. Barberá	Bellvitge-Barcelona	Dra. Galindo	Clínico-Valencia
Dr. Lozano	Nuestra Sra de Valme-Sevilla	Dr. Ortí	Tortosa-Tarragona	Dr.Carmena	Dr. Peset-Valencia
Dr. Gutierrez	Santa Ana de Motril-Granada	Dr. Knobel	Del Mar-Barcelona	Dr. Ortega	General-Valencia
Dra. Galvez	Torrecárdenas-Almería	Dr. Vilaró	Vic-Barcelona	Dr. Flores	Arnau Vilanova-Valencia
Dr. Jimenez	Carlos Haya-Málaga	Dr. Pedrol	Granollers-Barcelona	Dr. Pascuau	Marina Baixa-Alicante
Dr. Orihuela	Carlos Haya-Málaga	Dr. Force	Mataró-Barcelona	Dr. Portilla	General-Alicante
Dr.I Antunez	Carlos Haya-Málaga	Dra. Barrufet	Mataró-Barcelona	Dr. Gutiérrez	Elche-Alicante
Dr. Muñoz	Clínico San Cecilio de Granada	Dr. Villaverde	Reus-Tarragona	Dr. López	La Fe-Valencia
Dra. Pérez	Línea de la Concepción-Cádiz	Dr. Ribera	Val d'Hebrón-Barcelona	Dr. Roca	General-Castellón
Dr. Terrón	General de Jerez-Cádiz	Dr. Domingo	Sant Creu i Sant Pau-Barcelona	Dr. González	La Paz-Madrid
Dr. Suarez	Infanta Elena-Huelva	Dr. Ojea	Complejo H-Pontevedra	Dr. Arribas	La Paz-Madrid
Dr. Pujol	Juan Ramón Jiménez-Huelva	Dr. Prieto	Clínico de Santiago-La coruña	Dr. Peña	La Paz-Madrid
Dr. Rivero	Reina Sofía-Córdoba	Dra. Castro	Juan Canalejo-La Coruña	Dra. García	Rosell-Murcia
Dr. Kindelan	Reina Sofía-Córdoba	Dr. Juega	Juan Canalejo-La Coruña	Dr. Aguirrebengoa	Cruces-Bilbao
Dr. Pasquau	Virgen de las Nieves-Granada	Dra. López	Juan Canalejo-La Coruña	Dr. Teira	Basurto-Bilbao
Dr. López Ruz	Virgen de las Nieves-Granada	Dr. Pedreira	Juan Canalejo-La Coruña	Dr. Portu	Txagorritxu-Vitoria
Dr. Viciana	Virgen del Rocío-Sevilla	Dr. Ocampo	Xeral de Cies-Pontevedra	Dr. Arrizabalaga	Aranzazu-San Sebastián
Dr. Muniain	Virgen Macarena-Sevilla	Dra. Miralles	Xeral de Cies-Pontevedra	Dr. Rubio Caballero	Arnau Lérida-Lérida
Dr. Márquez	Virgen de la Victoria-Málaga	Dr. Labarga	San Millán-Logroño	Dra. Rosón	Bellvitge-Barcelona
Dr. Amiguet	Clínico-Zaragoza	Dr. Oteo	Provincial-Logroño	Dr. Podzamczer	Bellvitge-Barcelona
Dr. Arazo	Miguel Servet-Zaragoza	Dr. Pulido	12 de Octubre-Madrid	Dra. Ferrer	Bellvitge-Barcelona
Dr. Caro	Avilés-Avilés	Dr. Rubio	12 de Octubre-Madrid	Dr. Fumero	Bellvitge-Barcelona
Dr. Sánchez del Río	General-Oviedo	Dra. Barrios	Carlos III-Madrid	Dra. Moreno	Ramón y Cajal-Madrid
Dr. Cartón	Covadonga-Asturias	Dra. Martín	Carlos III-Madrid	Dr. Antela	Ramón y Cajal-Madrid
Dr. Maradona	Covadonga-Asturias	Dr. Soriano	Carlos III-Madrid	Dr. Dronda	Ramón y Cajal-Madrid
Dr. Asensi	Covadonga-Asturias	Dr. Martín	Puerta de Hierro-Madrid	Dr. Casado	Ramón y Cajal-Madrid
Dr. Homar	Son Llatzer-Baleares	Dr. Roca	San Carlos-Madrid	Dra. Pérez	Ramón y Cajal-Madrid
Dr. Gómez Sirvent	Universitario-Tenerife	Dra. Tellez	San Carlos-Madrid	Dr. Barros	Móstoles-Madrid
Dra. Fariñas	Valdecilla-Santander	Dr. Berenguer	Gregorio Marañón-Madrid	Dr. Torres	Severo Ochoa- Madrid
Dr. Echevarría	Valdecilla-Santander	Dr. López	Gregorio Marañón-Madrid	Dr. Sanz	La Princesa -Madrid
Dra. Martinez	General- Albacete	Dr. Cosin	Gregorio Marañón-Madrid		
Dr. Carro	Hospital de León- León	Dr. Pérez	Gregorio Marañón-Madrid		

OBJECTIVES AND METHODS

The **primary objective** of this study is to evaluate the durability of a LPV/r-based HAART regimen according to the patient's previous antiretroviral experience. As a secondary objective, the study aims to identify primary and secondary mutations conferring resistance to lopinavir which have not been previously described in antiretroviral-naïve patients. Patients will be observed for a period of 3 years. This is an interim analysis of the first 6 months of follow-up.

The **main inclusion criteria** prior to entering the study were: to be male or female patients aged 18 years or older with proven HIV infection and have received prescription to receive antiretroviral therapy including LPV/r. The decision to treat the patient with LPV/r had to be made before the physician proposed participation in the study to the patient. Such patients also had to belong to any of the following cohorts:

A. Antiretroviral-naïve patients.
B. Protease inhibitor-naïve patients, irrespective of their immune and viral status and current antiretroviral therapy.
C. Protease inhibitor-treated patients (excluding LPV/r) with a stabilized viral load below 5,000 copies/mL in the last 6 months.

Study Procedures

Eligible patients who provided informed consent had routine visits performed at week 4, week 12 and week 24 during the first 6 months of study participation. Throughout the study, CD4, HIV-RNA, SAE and reasons for premature discontinuations were recorded. In those cases where a baseline genotype analysis was performed routinely, the data were collected. In case of virologic failure while on LPV/r-based therapy (defined as either [a] the presence of HIV RNA >400 copies/mL on two consecutive measurements and after previously having achieved an HIV RNA level at or below 400 copies/mL at any moment in the study, or [b] failure to achieve HIV RNA viral below 400 copies/mL), genotype and/or LPV plasma concentration data could be collected whenever appropriate. The data are collected in an e-CRF under highly strict control measures.

Study Drug Treatment

Patients meeting study eligibility criteria took LPV/r 133.3/33.3 mg capsules at a dosage of 3 capsules every 12 hours, according to approved market labelling.

Patients would remain in study if LPV/r based therapy was maintained, independently of any other antiretroviral modifications, from the original combination, done by the physician as deemed necessary.

RESULTS

As of April 20th, 2004, a total of 1,219 patients had been enrolled in this study in Spain (from June 2002 to May 2003). The distribution in the 3 study cohorts was as follows (Figure 1): A) ARV naïve (n=417), B) PI naïve (n=252) and C) PI-treated with stable VL (HIV-RNA<5,000 copies/mL) for 6 months (n=550).

Summary of Demographic and Baseline Disease Characteristics of the Study Drug Dosed Population

The majority of the enrolled patients were male (77.0%) and mean age was close to 40 years. Demographic (sex/age) and risk factor data are summarized in Table 2. A summary of baseline disease characteristics per group is presented in Table 3 (CD4, HIV RNA, previous treatments and length under ARVT).

Figure 1. Distribution of Enrolled Patients Per Group Based on ARV Experience

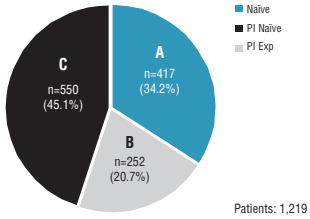


Table 2. Demographic and Baseline Characteristics

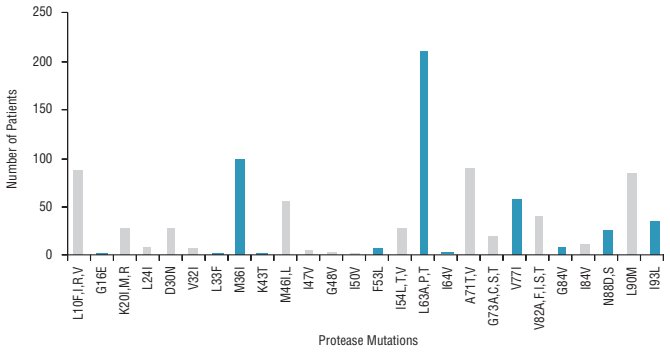
	Total (n=1,219)	Naïve (n=417)	PI Naïve (n=252)	PI Exp (n=550)
Sex (% male)	77.0	76.0	77.4	77.6
Age (years; mean ± SD)	39.7 ± 8.3	39.9 ± 9.5	38.6 ± 7.9	40.1 ± 7.5
HVC+ (%)	50.0	39.6	55.6	55.3
Risk factors (%)				
IVDU	52.4	39.8	60.7	58.2
Heterosexual	29.5	37.4	26.2	24.9
MSM	18.5	22.8	14.3	17.3
Transfusion	0.6	0.2	0.4	0.9
Unknown/Others	2.0	0.0	2.6	3.2

Table 3. Baseline Disease Characteristics

	Naïve	PI Naïve	PI Exp
HIV-RNA (log_{10} copies/mL)			
Mean ± SD	5.21 ± 0.70	4.05 ± 1.23	2.71 ± 0.80
Median (IQR)	5.31 (4.89, 5.70)	4.26 (3.25, 4.96)	2.89 (1.70, 3.46)
CD4 (cells/mm^3)			
Mean ± SD	136 ± 141	268 ± 202	421 ± 270
Median (IQR)	91 (30, 203)	232 (132, 368)	362 (219, 562)
Time since HIV diagnosis (years; mean) IQR	0.4 (0.1, 6.5)	8.6 (3.1, 12.2)	9.4 (6.1, 12.6)
Time since 1st ARV (years; mean) IQR	0.0 (0.0, 0.0)	3.2 (1.3, 6.4)	6.3 (4.7, 8.6)

Protease mutations were reported in 20%, 39% and 61% of patients with baseline genotype results available in the Naïve, PI Naïve and PI Exp. groups, respectively. Figure 2 represents the presence per protease mutation in the global study population at baseline with available genotypic assessment (a 64.6 % of the study patients). Primary LPV mutations per group are specified on the right. Table 4 shows the number of patients per group with 0, 1, 2, …, 9, ≥10 protease mutations (primary and secondary) at baseline. Only 10 PI Exp patients show ≥8 mutations, while Naïve and PI Naïve have less than 8. Regarding primary protease mutations the percentages for those with available genotype per ARV-experience group were 1.8%, 1.7% and 43.0%, respectively. Of note, 55 of the 280 naïve patients (19.6%) with baseline genotype results were infected with HIV harbouring at least one protease mutation.

Figure 2. Baseline Presence Per Protease Mutation In Global Population (with baseline genotypic assessment*)



LPV defined protease mutations.

Table below shows prevalence of LPV Primary Mutations per group

	30	32	46	47	48	50	82	84	90
Naïve	1	0	1	1	0	0	3	2	0
PI Naïve	0	0	2	0	0	0	1	0	2
PI Exp	27	7	54	4	3	2	36	18	83

* Patients with available genotypic assessment at baseline (N) per group: 280 (Naïve), 180 (PI naïve) and 328 (PI Exp)

Table 4. Number of Patients Per Group Showing Protease Mutations

	# Mutations											
	0	1	2	3	4	5	6	7	8	9	≥10	Total
Total	462	107	67	49	33	26	24	10	7	1	2	788
Naïve[1]	225	35	9	10	1	0	0	0	0	0	0	280
PI Naïve	110	39	18	10	3	0	0	0	0	0	0	180
PI Exp	127	33	40	29	29	26	24	10	7	1	2	328

Primary Protease Mutations at baseline per group were [N (%)]:

Naïve	5	(1.8)
PI Naïve	3	(1.7)
PI Exp	141	(42.98)

[1]This would mean that 19.6% of naïve patients were infected with HIV harbouring protease mutations at baseline

The main combinations of nucleoside reverse transcriptase inhibitors (NRTI) prescribed together with LPV/r at baseline are summarized in Table 5.

Table 5. NRTI Backbone Used with LPV/r in at Least 2% of Patients

ARV Backbone	Total	Naïve	PI Naïve	PI Exp
3TC + AZT	28.6%	52.6%	23.3%	13.0%
3TC + d4T	12.3%	14.8%	9.2%	11.7%
d4T + ddI	9.4%	4.4%	13. 3%	11.4%
ddI + TFV	9.0%	5.1%	10.4%	11.4%
3TC + TFV	6.7%	5.6%	8.4%	6.8%
d4T + TFV	5.9%	0.5%	8.4%	8.8%
3TC + ddI	5.4%	7.5%	8.0%	2.6%
ABV + TFV	4.0%	4.1%	2.0%	4.8%

Efficacy and Safety of the Study Drug Dosed Population

Of the 1,219 patients dosed, a total of 113 (9.3%) have been prematurely discontinued from the study. Patient disposition through Week 24 is summarized in Table 6.

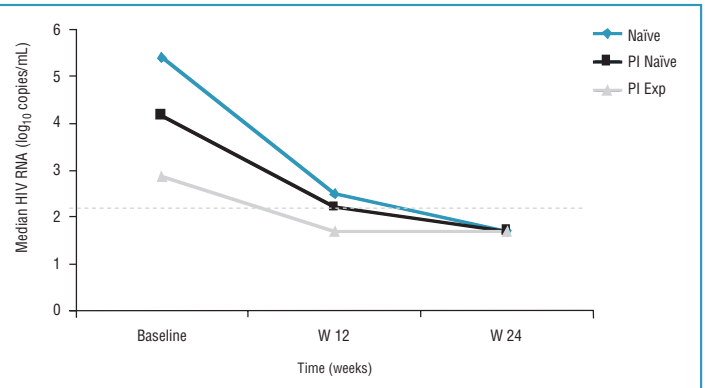
Table 6. Patient Disposition Per Group

	Total (n=1,219)	Naïve (n=417)	PI Naïve (n=252)	PI Exp (n=550)
No. of patients discontinued (%)	113 (9.3%)	49 (11.8%)	25 (9.9%)	39 (7.1%)
No. pats. discontinued per reason (%)				
Loss of adherence	21 (1.7%)	11 (2.6%)†	5 (2.0%)	5 (0.9%)
Intolerance	53 (4.3%)	17 (4.1%)	10 (4.0%)	26 (4.7%)
Virologic failure	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Death	18 (1.5%)	13 (3.1%)‡	3 (1.2%)	2 (0.4%)
Other	20 (1.6%)	8 (1.9%)	7 (2.8%)	5 (0.9%)
No. of pats. still ongoing	1,106 (90.7%)	368 (88.2%)	227 (90.1%)	511 (92.9%)

†P= 0.037; ‡P= 0.001 when comparing Naïve with PI Exp patients

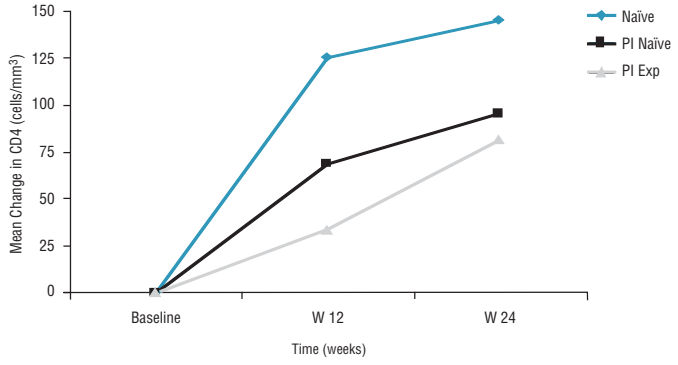
Figures 3 and 4 summarize the median HIV-RNA (copies/mL) and mean CD4 (cells/mm³) profiles at baseline, week 12 and week 24 for each ARV-experience group. The percentage of patients reaching less than 400 copies/mL during the study is shown on Figure 5. Similar VL responses were observed at week 24; however, mean CD4 count increases from baseline were significantly greater in naïve patients compared to either PI-naive or PI-experienced patients (p≤0.006).

Figure 3. Analysis of Viral Load (log_{10} copies/mL) Over Time (OT)



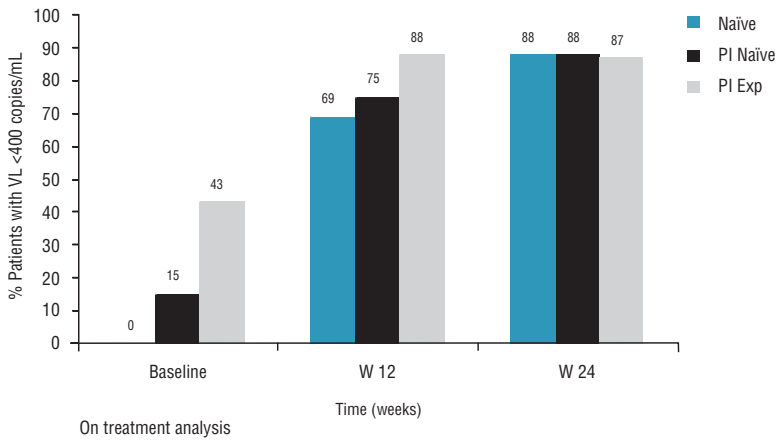
Naïve	302	233	215
PI Naïve	190	153	122
PI Exp	452	345	302

Figure 4. Mean Change in CD4+ T Lymphocytes Over Time (OT)



Naïve	310	238	224
PI Naïve	187	150	119
PI Exp	451	343	301

Figure 5. Proportion of Patients with Viral Load at or Below 400 copies/mL Over Time



On treatment analysis

A summary of SAEs that were at least moderate in severity and of possible, probable or unknown relationship to LPV/r are summarized in Table 7 and Table 8 depending on if they were reported in more or less than a 1%, respectively. Treatment based on LPV/r was generally well tolerated. Similar AE profiles (drug-related) were noted for the Naïve, PI-naïve, and PI Exp. groups respectively.

Table 7. Adverse Events with Causal Relationship to LPV/R (Reported by ≥1% of Patients)

Adverse Event	Total		Naïve		PI Naïve		PI Exp	
	nº	(%)	nº	(%)	nº	(%)	nº	(%)
Diarrhea	73	(6.0)	21	(5.0)	17	(6.7)	35	(6.4)
Nausea	48	(3.9)	21	(5.0)	7	(2.8)	20	(3.6)
Vomiting	28	(2.3)	15	(3.6)	3	(1.2)	10	(1.8)
Abdominal pain	27	(2.2)	9	(2.2)	4	(1.6)	14	(2.5)

Table 8. Adverse Events with Causal Relationship to LPV/r (Reported by ≤1% of Patients)

Adverse Event	Total		Naïve		PI Naïve		PI Exp	
	nº	(%)	nº	(%)	nº	(%)	nº	(%)
Dyslipidemia	5	(0.4)	0	(0.0)	0	(0.0)	5	(0.9)
Fever	4	(0.3)	1	(0.2)	1	(0.4)	2	(0.4)
Asthenia	3	(0.2)	1	(0.2)	0	(0.0)	2	(0.4)
Drug Interaction	3	(0.2)	1	(0.2)	1	(0.4)	1	(0.2)
Migraine	3	(0.2)	2	(0.5)	0	(0.0)	1	(0.2)
Hepatotoxicity	3	(0.3)	3	(0.7)	0	(0.0)	0	(0.0)
Rash	2	(0.2)	2	(0.5)	0	(0.0)	0	(0.0)
Abdomen enlarged	1	(0.1)	0	(0.0)	0	(0.0)	1	(0.2)
Rectal hemorrhage	1	(0.1)	0	(0.0)	1	(0.4)	0	(0.0)
Seasickness	1	(0.1)	1	(0.2)	0	(0.0)	0	(0.0)
Myalgia	1	(0.1)	1	(0.2)	0	(0.0)	0	(0.0)
Thinking abnormal	1	(0.1)	0	(0.0)	1	(0.4)	0	(00)
Dyspnea	1	(0.1)	1	(0.2)	0	(0.0)	0	(0.0)
Kidney function abnormal	1	(0.1)	1	(0.2)	0	(0.0)	0	(0.0)

DISCUSSION

Results reported are from an interim analysis, conducted using data collected through the first 24 weeks, in a study designed to assess durability of response through 3 years of follow-up. Baseline characteristics of the overall population are considered a real-life reflection of the Spanish HIV population, especially as it relates to risk behavior. As expected, the ARV-experience groups themselves (naïve, PI naïve and PI Exp) exhibit different distributions on these baseline data. The prevalence of protease mutations reported at baseline was relatively low in the PI-experienced patients and may possibly explain why the virologic efficacy at Week 24, a relatively short period of follow-up, is similar between the three antiretroviral experience groups (i.e., naïve, PI-naïve, PI-experienced).

CONCLUSIONS

- On this setting that follows patients prospectively in an observational study, similar VL response was found at Week 24 between groups with different ARV experience.
- However, CD4 count improvement was greatest in ARV-naïve patients when compared to either PI-naïve or PI-experienced patients.
- AE profiles for the three ARV-experience groups were similar at Week 24.
- Long-term (3 year) follow-up will better define the safety & effectiveness of LPV/r in this real life setting.

ACKNOWLEDGMENTS

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