Poster #106

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Evaluation of Side Effects in Patients After Substitution of Their PI/NNRTI with Lopinavir/ritonavir (LPV/r)

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BACKGROUND

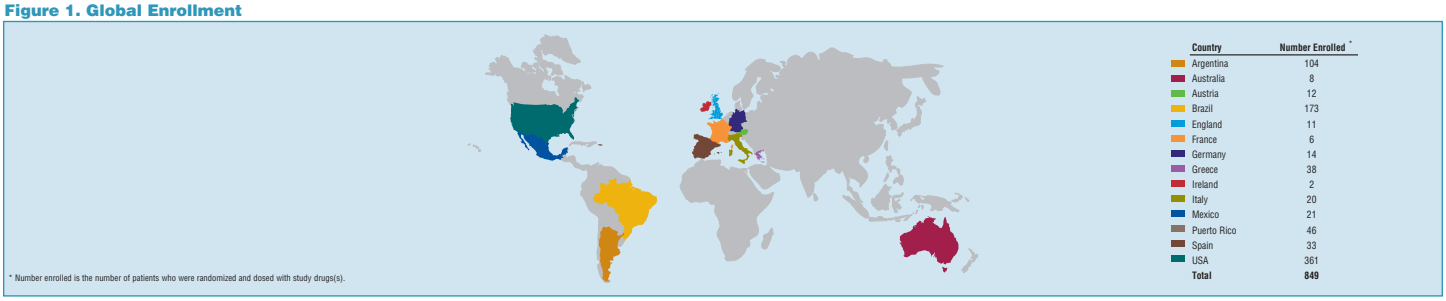
Lopinavir (LPV) is an HIV protease inhibitor that is co-formulated with ritonavir (RTV), which acts as an inhibitor of cytochrome P450 CYP3A. When used in combination, there is a substantial increase in LPV exposure, even at low RTV doses. This pharmacokinetic interaction results in mean LPV pre-dose (trough) concentrations ≥75-fold above the protein binding-adjusted EC_{50} of wild-type HIV when dosed at 400/100 mg twice a day, providing a possible barrier to the emergence of viral resistance.[1] Lopinavir/ritonavir (LPV/r; Kaletra™) has demonstrated potent antiretroviral activity in treatment-naïve patients, single PI-experienced patients, and multiple PI-experienced patients, and has been generally well tolerated in these patient populations.[2-5]

A significant number of virologically stable, HIV-infected patients experience mild-to-moderate side effects related to the protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) in their antiretroviral (ARV) regimen.[6] Treatment strategies to alleviate side effects and improve quality of life (QOL), while maintaining virologic control are needed.

METHODS

The M00-267 Study (PLATO: Performance of Lopinavir/ritonavir as an Alternative Treatment Option) is a randomized, open-label, multi-country, multi-center study of 8 weeks duration in HIV-infected patients. The purpose of this study was to assess whether the side effects experienced by patients on ARV therapy could be improved after substitution of the PI/NNRTI suspected of causing the side effects with LPV/r. In addition, other measures including the validated AIDS Clinical Trials Group (ACTG) Symptoms Distress Module,[7] with two additional questions to evaluate symptoms of nephrolithiasis (ASDM),[8] and the Medical Outcomes Study- HIV Health Survey (MOS-HIV),[9] as well as viral load, were evaluated at Baseline, Week 4 and Week 8.

Figure 1. Global Enrollment



* Number enrolled is the number of patients who were randomized and dosed with study drugs(s).

Country	Number Enrolled *
Argentina	104
Australia	8
Austria	12
Brazil	173
England	11
France	6
Germany	14
Greece	38
Ireland	2
Italy	20
Mexico	21
Puerto Rico	46
Spain	33
USA	361
Total	**849**

Key Entry Criteria

Patients were eligible for participation in this study if they met the following criteria:

- Two consecutive HIV RNA values <400 copies/mL on current ARV regimen, with the most recent within the past 3 months.
- Current ARV regimen consists of 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus nelfinavir (NFV), indinavir (IDV), IDV/RTV, nevirapine (NVP) or efavirenz (EFV).
- Intolerant to current PI/NNRTI in their ARV regimen as evidenced by a Grade 2 side effect using the Division of AIDS toxicity grading scale.[10] Primary side effect was defined as the side effect identified by the investigator which led to enrollment in this study.

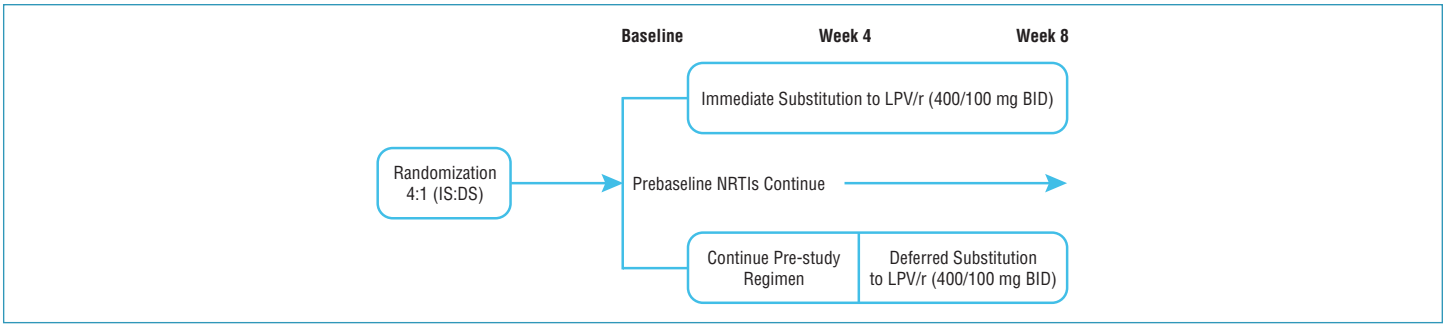
Study Design and Analysis

Patients experiencing Grade 2 PI/NNRTI-associated side effects were randomized (4:1) to Immediate Substitution at Baseline or Deferred Substitution at Week 4 of their PI/NNRTI with LPV/r. All patients remained on their baseline NRTIs for the 8-week duration of the study, and all patients received LPV/r from Week 4 to Week 8. For the purpose of this presentation the following validated QOL instruments were evaluated:

- ASDM – measures the presence and bothersomeness of side effects commonly seen with HIV and ARV treatment. Higher scores indicate the presence of more symptoms and/or a greater degree of distress related to the 22 symptoms.
- MOS-HIV – is widely used to evaluate the QOL of HIV-infected patients. It consists of 35 questions, which assess various domains of health during the past 4 weeks, including general health perception, pain, physical functioning, role functioning, social functioning, mental health, energy/fatigue, health distress, cognitive function, quality of life and health transition. Higher scores indicate better QOL. In addition to scores for each domain, a physical health summary score (PHSS) and a mental health summary score (MHSS) were also assessed and presented here. For example, a one point increase in Baseline PHSS has been associated with a 3% decrease in the likelihood of developing an AIDS-defining event (excluding death) and a 2.7% decrease in the likelihood of discontinuing treatment. In addition, a one point increase in Baseline MHSS has been associated with a 1.6% decrease in the likelihood of treatment discontinuation.[11]

Side effects that were present at Baseline or developed during the study were assessed at each study visit. The ASDM and MOS-HIV were administered at each study visit. Clinical laboratory tests, including routine hematology and chemistry panels, as well as plasma HIV RNA (Roche Amplicor Ultrasensitive 1.5) were evaluated at each study visit using a central laboratory.

Figure 2. M00-267 Study Design



RESULTS

Of the 849 patients enrolled, 827 were considered evaluable for efficacy analysis while 22 patients were considered unevaluable and have been excluded from efficacy analysis as they were not receiving the protocol-specified PI/NNRTI plus 2 NRTIs at study entry. Results have been summarized for patients who were on NFV, IDV/RTV, IDV and EFV at the time of study entry and for all efficacy evaluable patients as a whole. Demographic characteristics and patient disposition are summarized in Table 1 and Table 2, respectively.

Table 1. Demographic Characteristics

	Immediate Substitution	Deferred Substitution	Overall
N	686	163	849
Sex			
Male	546 (80%)	132 (81%)	678 (80%)
Female	140 (20%)	31 (19%)	171 (20%)
Race			
White	531 (77%)	127 (78%)	658 (78%)
Black	101 (15%)	24 (15%)	125 (15%)
Other	54 (8%)	12 (7%)	66 (8%)
Ethnicity			
Hispanic	186 (27%)	44 (27%)	230 (27%)
Age			
Mean	41.9	42.4	42.0
Minimum-Maximum	21-82	25-70	21-82

Table 2. Patient Disposition

	Immediate Substitution	Deferred Substitution	Overall
Patients enrolled	686	163	849
Discontinuation*	62 (9%)	14 (9%)	76 (9%)
Adverse events/HIV events	32 (5%)	4 (2%)	36 (4%)
Withdrawal of consent	14 (2%)	7 (4%)	21 (2%)
Loss to follow-up	7 (1%)	2 (1%)	9 (1%)
Other	16 (2%)	3 (2%)	19 (2%)

* Multiple reasons for discontinuation could have been reported.

Table 3 summarizes the distribution of PI/NNRTI medication used by patients at the time of enrollment in this study. No difference was detected between the Immediate and Deferred Substitution arm with respect to the PI/NNRTI used at the time of enrollment (p=0.086).

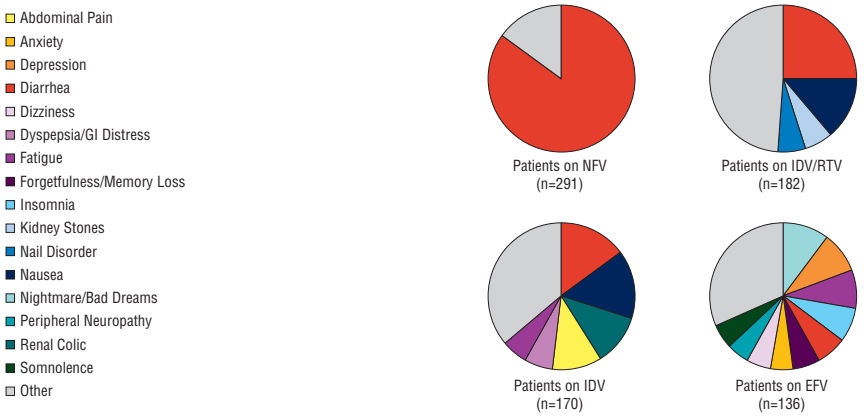
Table 3. Summary of Pre-study PI/NNRTI Regimen†

	Immediate Substitution	Deferred Substitution	Overall
N	667	160	827
Nelfinavir	223 (33%)	68 (43%)	291 (35%)
Indinavir/Ritonavir	152 (23%)	30 (19%)	182 (22%)
Indinavir	141 (21%)	29 (18%)	170 (21%)
Efavirenz	116 (17%)	20 (13%)	136 (16%)
Other	35 (5%)	13 (8%)	48 (6%)

† For patients included in efficacy analyses.

Figure 3 summarizes the primary side effects reported at Baseline for patients in the indicated pre-study PI/NNRTI therapy groups. For the 827 efficacy evalauable patients, primary side effects reported at Baseline with ≥5% prevalence included diarrhea (41%), nausea (8%), and fatigue (6%). The primary side effect was defined for this study as the side effect identified by the investigator that led to enrollment into the study.

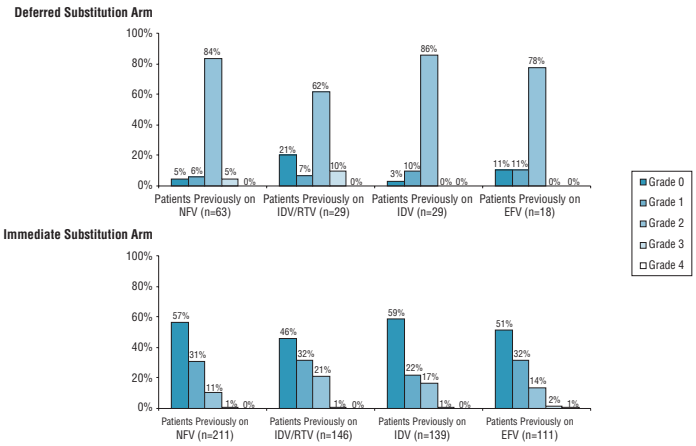
Figure 3. Primary Side Effects at Enrollment by Pre-study PI/NNRTI†



† Primary side effects reported for ≥5% of patients in the indicated pre-study PI/NNRTI therapy group at the Baseline visit are shown in the pie chart.

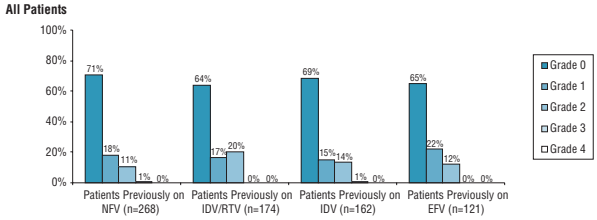
Primary side effects reported at Baseline were reassessed at Week 4 and at Week 8. Toxicity grades for the primary side effects are summarized in Figure 4 (Week 4; by treatment arm and pre-study PI/NNRTI therapy) and in Figure 5 (Week 8; by pre-study PI/NNRTI therapy for all efficacy evaluable patients). At Week 4, 83% of the efficacy evaluable patients in the Immediate Substitution arm and 16% of the efficacy evaluable patients in the Deferred Substitution arm reported an improvement from Baseline of at least one toxicity grade in their primary Grade 2 side effects. At Week 8, primary Grade 2 side effects were reported to have resolved (67%) or improved at least one toxicity grade (18%) in 85% of the efficacy evaluable patients.

Figure 4. Toxicity Grades at Week 4 for the Primary Grade 2 Side Effects Reported at Baseline†



† For all efficacy evaluable patients in the indicated pre-study PI/NNRTI therapy group with the Grade 2 primary side effect assessed at Baseline and reassessed at Week 4.

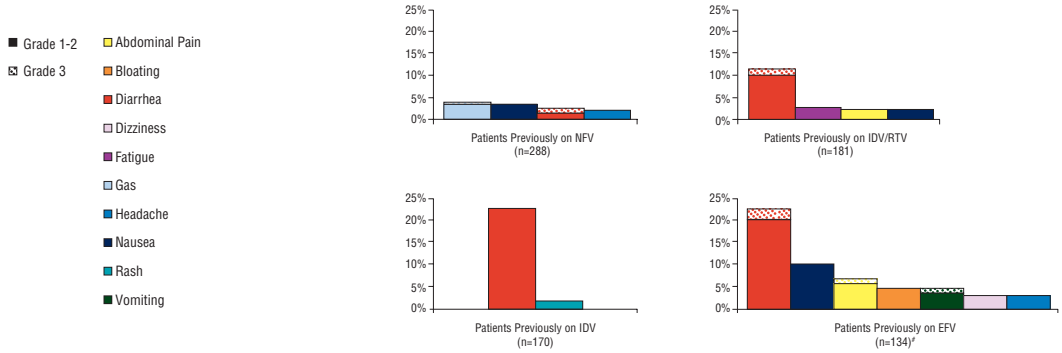
Figure 5. Toxicity Grades at Week 8 for the Primary Grade 2 Side Effects Reported at Baseline†



† For all efficacy evaluable patients in the indicated pre-study PI/NNRTI therapy group with the Grade 2 primary side effect assessed at Baseline and reassessed at Week 8.

Figure 6 summarizes the new onset side effects (Grade 1-3) reported by the >2% of patients while on LPV/r for the indicated pre-study PI/NNRTI therapy groups. For efficacy evaluable patients, new onset side effects reported by >2% of patients while on LPV/r included diarrhea (13% [Grade 1-2; 12%]), nausea (4% Grade 1-2; 4%]), abdominal pain (2% [Grade 1-2; 2%]) and gas (2% [Grade 1-2; 2%]).

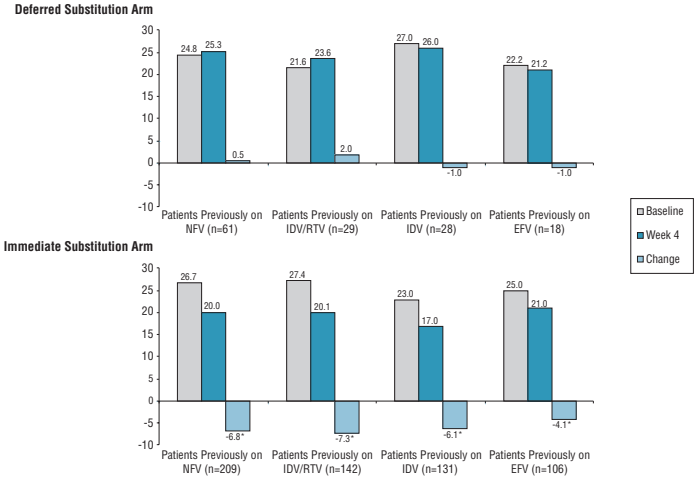
Figure 6. New Onset Side Effects Reported by Patients While on LPV/r*



* Patients could have reported more than one new onset side effect.
# For patients previously on EFV, results are presented for events experienced by at least 4 patients.

Figure 7 summarizes the results from the ASDM at Baseline and Week 4 for patients in the indicated pre-study PI/NNRTI therapy groups. Overall, the ASDM total score (mean ± SEM) at Baseline was 26.0 ± 0.7 for the Immediate Substitution arm and 24.1 ± 1.3 for the Deferred Substitution arm (between-arm p=0.205). At Week 4, a statistically significant improvement was noted in patients who substituted LPV/r for their PI/NNRTI at Baseline (-6.2 ± 0.5; p<0.001), while no change was observed in patients who deferred substitution with LPV/r until Week 4 (+0.5 ± 1.0; p=0.581). After all patients substituted LPV/r for the PI/NNRTI in their pre-study regimen, continued improvement in the ASDM total score was observed at Week 8 (-6.3 ± 0.5; p<0.001).

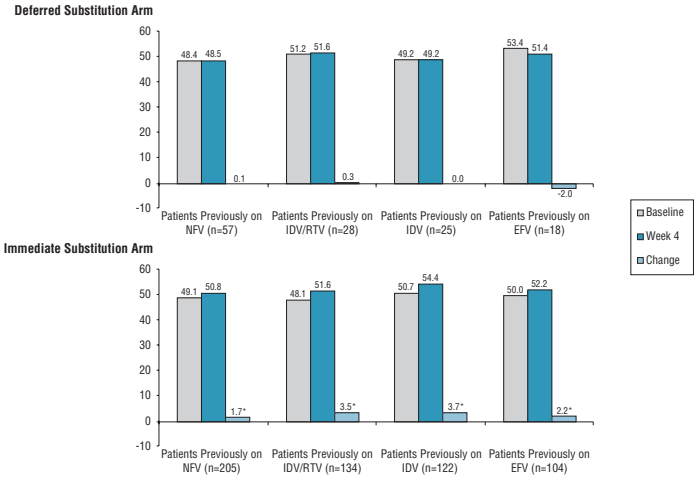
Figure 7. Mean Change in ASDM Total Score from Baseline to Week 4†



† For all efficacy evaluable patients in the indicated pre-study PI/NNRTI therapy group who answered at least 20 of the 22 items from the ASDM at Baseline and Week 4.
* Statistically significant change from baseline (p<0.001).

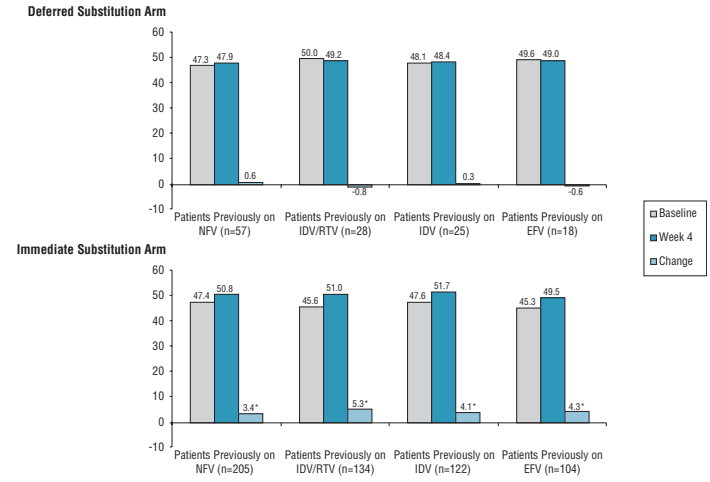
Figure 8a (Physical Health Summary Score [PHSS]) and Figure 8b (Mental Health Summary Score [MHSS]) summarize results from the MOS-HIV questionnaire at Baseline and Week 4 for patients in the indicated pre-study PI/NNRTI therapy groups. Statistically significant improvements in PHSS were noted at Week 4 in the Immediate Substitution arm (+2.6 ± 0.3 from 49.4; p<0.001) while no change was observed in the Deferred Substitution arm (-0.6 ± 0.6 from 50.0; p=0.311). Similarly, statistically significant improvements in MHSS were noted at Week 4 in the Immediate Substitution arm (+4.1 ± 0.3 from 46.6; p<0.001) and no change was observed in the Deferred Substitution arm (-0.2 ± 0.7 from 48.4; p=0.739). After all patients substituted LPV/r for the PI/NNRTI in their pre-study regimen, continued improvements were noted at Week 8 with respect to PHSS (+2.5 ± 0.3; p<0.001) and MHSS (+4.1 ± 0.3; p<0.001).

Figure 8a. Mean Change in MOS-HIV Physical Health Summary Score from Baseline to Week 4†



† For all efficacy evaluable patients in the indicated pre-study PI/NNRTI therapy group who adequately answered the MOS-HIV questionnaire at Baseline and Week 4.
* Statistically significant change from baseline (p<0.002).

Figure 8b. Mean Change in MOS-HIV Mental Health Summary Score from Baseline to Week 4†



† For all efficacy evaluable patients in the indicated PI/NNRTI therapy group who adequately answered the MOS-HIV questionnaire at Baseline and Week 4.
* Statistically significant change from baseline (p<0.001).

At Baseline, 91% of patients had plasma HIV RNA below 400 copies/mL. Plasma HIV RNA results obtained at Week 8 suggest that patients who substituted LPV/r for their pre-study PI/NNRTI appeared to maintain (intent-to-treat; Baseline [91%] vs. Week 8 [89%]) or improve (on-study; Baseline [91%] vs. Week 8 [96%]) virologic control during this study.

Of the 849 patients included in this safety analysis, 4 (<1%) experienced treatment-emergent serious adverse events with possible or probable relationship to LPV/r: diabetes mellitus (N=1), anaphylactoid reaction (N=1), hepatitis in a patient with chronic hepatitis B (N=1) and acute renal failure secondary to dehydration in a patient with an acute viral infection, diarrhea and concomitant diuretic therapy (N=1). No specific adverse event (serious or non-serious) leading to discontinuation of study drug was reported in >2% of patients. Clinical abnormalities occurring in >2% of patients after substitution of their PI/NNRTI with LPV/r included elevated triglycerides (>8.25 mmol/L; 11.4%) and elevated cholesterol (>7.77 mmol/L; 8.0%); however, it should be noted that clinical laboratory samples were obtained without regard to fasting.

CONCLUSIONS

Substitution of LPV/r for the PI/NNRTI suspected of causing the Grade 2 side effects reported at study entry resulted in:

- Resolution or improvement of at least one toxicity grade in the Primary Grade 2 side effects for approximately 85% of all patients at Week 8;
- Significant improvements in tolerability as measured by the ASDM;
- Significant improvements in quality of life as measured by the MOS-HIV (PHSS, MHSS);
- New onset diarrhea in >5% of patients, with the majority representing Grade 1 toxicities in patients having previously received either IDV or EFV; and
- Maintained or improved virologic control.

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