Poster #104

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Evaluation of Diarrhea in Patients After Substitution of Nelfinavir with Lopinavir/ritonavir (LPV/r)

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BACKGROUND

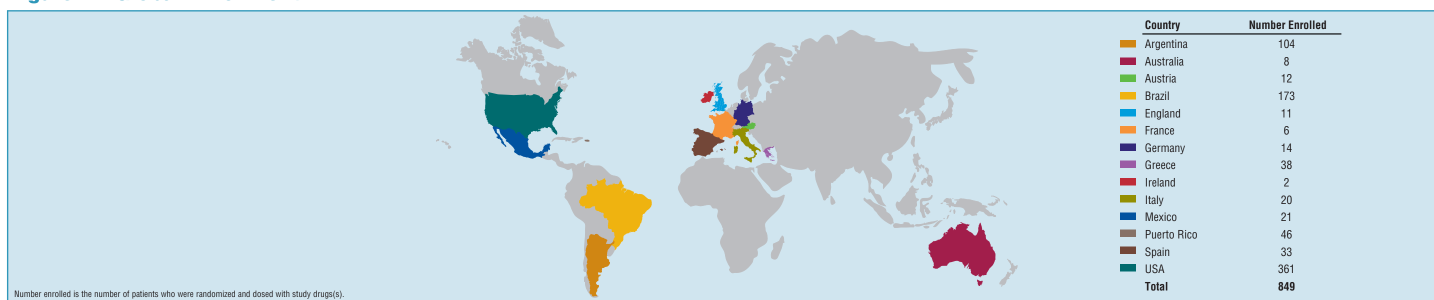
Lopinavir (LPV) is an HIV protease inhibitor that is co-formulated with ritonavir (RTV), which acts as an inhibitor of cytochrome P450 CYP3A. When used in combination, there is a substantial increase in LPV exposure, even at low RTV doses. This pharmacokinetic interaction results in mean LPV pre-dose (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. For example, diarrhea (mild-to-moderate) is the most frequently reported adverse event among patients receiving nelfinavir (NFV).[7] In addition, results from a previous study in patients receiving NFV plus stavudine (d4T) and lamivudine (3TC) indicate that the side effects of NFV-based therapy are a major contributor to ARV treatment interruptions and/or discontinuations.[8]

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,[9] with two additional questions to evaluate symptoms of nephrolithiasis (ASDM),[10] and the Medical Outcomes Study - HIV Health Survey (MOS-HIV)[11] were assessed at Baseline, Week 4 and Week 8. For the purpose of this presentation, the statistical analysis has been restricted to those patients who enrolled with side effects related to NFV.

Figure 1. Global Enrollment



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 consisted of 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus 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.[12] Primary side effect was defined as the side effect identified by the investigator which led to enrollment in this study.

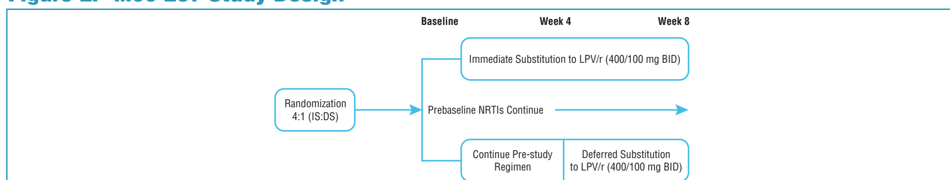
Study Design and Analysis

Patients experiencing Grade 2 PI/NNRTI-associated side effects were randomized (4:1) to Immediate Substitution (IS) at Baseline or Deferred Substitution (DS) 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 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 assesses 11 domains of health during the past 4 weeks, including general health perception, physical function, role function, social function, cognitive function, pain, mental health, energy/fatigue, health distress, quality of life and health transition. Higher scores indicate better quality of life. In addition to scores for each domain, a physical health summary score (PHSS) and a mental health summary score (MHSS) are computed. 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.[13]
- Global Condition Improvement Questionnaire – measures the patient's overall tolerability to HIV treatment.
- Therapy Preference Questionnaire – measures the patient's overall therapy preference.

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, while the Global Condition Improvement Questionnaire and the Therapy Preference Questionnaire were administered only at the Week 8/Discontinuation 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 in this study, 291 were on NFV-based ARV regimens at Baseline (IS: 223; DS: 68). Demographic characteristics for these 291 patients are summarized in Table 1 for the Immediate Substitution (IS), Deferred Substitution (DS) arm, and the subset as a whole. Patient disposition for this subset of patients is summarized in Table 2.

Table 1. Demographic Characteristics

	Immediate Substitution	Deferred Substitution	Overall
N	223	68	291
Sex			
Male	172 (77%)	52 (76%)	224 (77%)
Female	51 (23%)	16 (24%)	67 (23%)
Race			
White	160 (72%)	49 (72%)	209 (72%)
Black	44 (20%)	14 (21%)	58 (20%)
Other	19 (9%)	5 (7%)	24 (8%)
Ethnicity			
Hispanic	55 (25%)	19 (28%)	74 (25%)
Age			
Mean	41.8	44.2	42.3
Minimum–Maximum	23–82	25–70	23–82

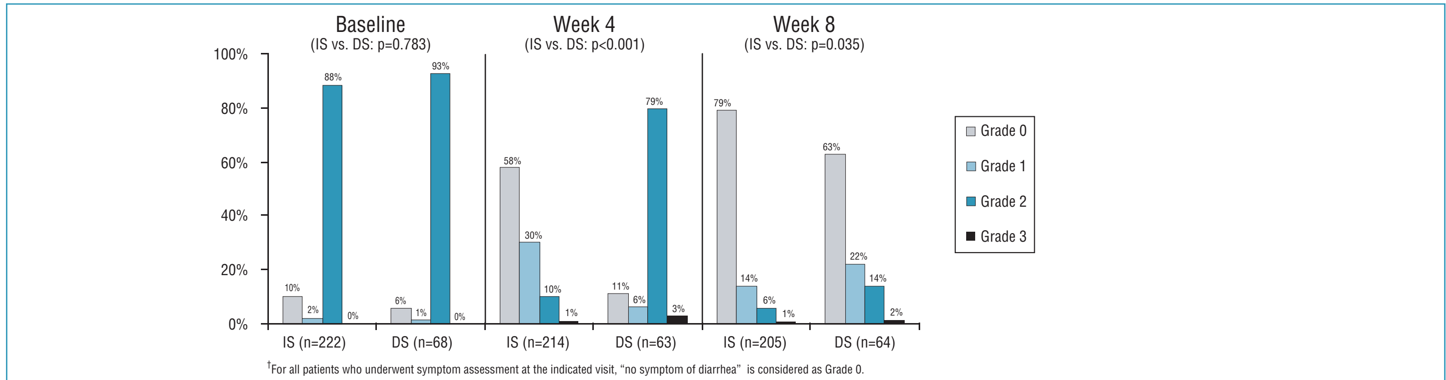
Table 2. Patient Disposition

	Immediate Substitution	Deferred Substitution	Overall
Patients enrolled	223	68	291
Discontinuation*	22 (10%)	6 (9%)	28 (10%)
Adverse events/HIV events	13 (6%)	1 (1%)	14 (5%)
Withdrawal of consent	8 (4%)	4 (6%)	12 (4%)
Loss to follow-up	1 (<1%)	1 (1%)	2 (1%)
Other	6 (3%)	2 (3%)	8 (3%)

* Multiple reasons for discontinuation could have been reported.

The toxicity grades for diarrhea used in this sutdy are as follows: Grade 1 – mild or transient, 3-4 loose stools/day or lasting <1 week; Grade 2 – moderate or persistent, 5-7 loose stools/day or lasting >1 week; Grade 3 – bloody stools or >7 loose stools/day causing orthostatic hypotension or requiring intravenous fluids.[11] At Baseline, 91% (264/291) of the patients receiving NFV-based ARV therapy were reported to have Grade 1-2 diarrhea. At Week 4, improvement of diarrhea by at least one toxicity grade was reported for 88% of patients in the Immediate Substitution arm who reported having diarrhea at the Baseline visit. In contrast, improvement in diarrhea of at least one toxicity grade was reported for only 10% of patients in the Deferred Substitution arm. At Week 8, patients in the Immediate Substitution arm continued to demonstrate improvement, while patients in the Deferred Substitution arm began to improve, after 4 weeks on LPV/r therapy. In general, diarrhea resolved (73%) or improved at least one toxicity grade (17%) in 90% of patients at Week 8. The distribution of toxicity grades for diarrhea is summarized over time in Figure 3.

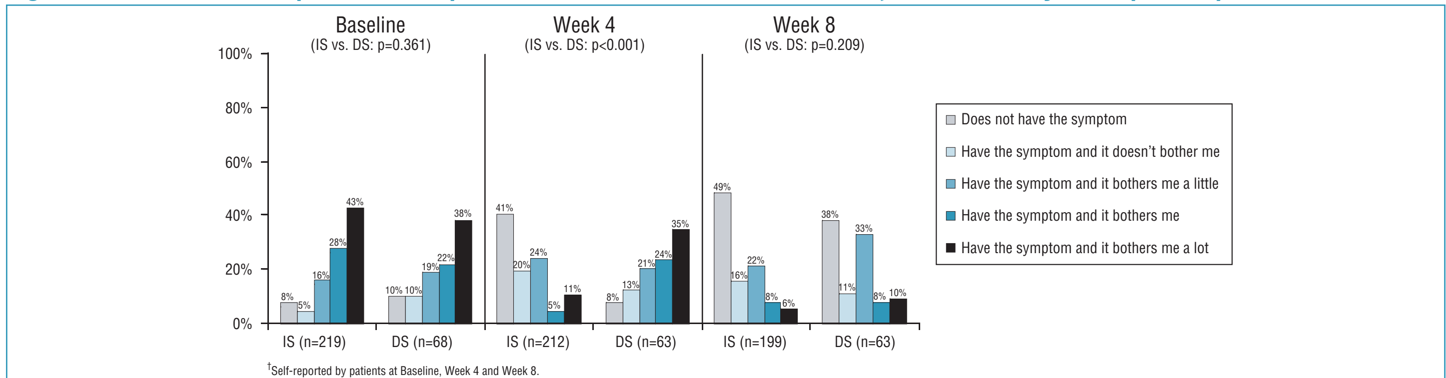
Figure 3. Toxicity Grades for Diarrhea†



†For all patients who underwent symptom assessment at the indicated visit, "no symptom of diarrhea" is considered as Grade 0.

At Baseline, 42% (120/287) of patients on NFV said the side effect of diarrhea "bothers me a lot" (ASDM score = 4 on a 0-4 scale). Improvement in the bothersomeness of diarrhea was observed in the Immediate Substitution arm from Baseline to Week 4, while patients in the Deferred Substitution arm had a similar pattern of bothersomeness scores at Baseline and Week 4. At Week 8, patients in the Immediate Substitution arm continued to demonstrate improvement compared to Baseline, while patients in the Deferred Substitution arm began to experience a reduction in the bothersomeness of diarrhea, consistent with the improvement seen in the Immediate Substitution arm at Week 4. The bothersomeness of diarrhea is summarized over time in Figure 4.

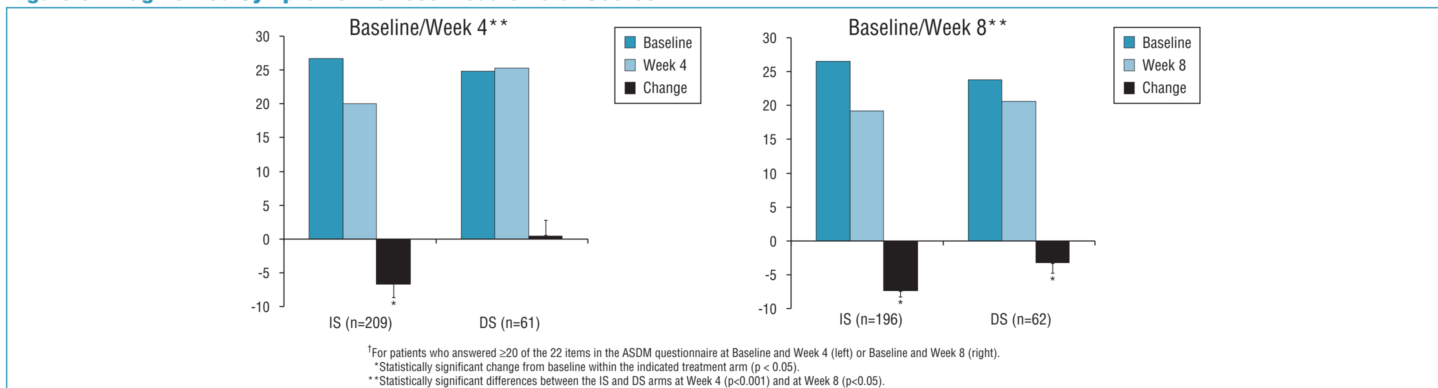
Figure 4. Bothersomeness (Distress Level) for Diarrhea or Loose Bowel Movements; as Measured by ASDM (Item #7)†



†Self-reported by patients at Baseline, Week 4 and Week 8.

At Baseline, no difference was observed between the Immediate and Deferred Substitution arms with respect to ASDM total score (IS: 26.75 vs. DS: 24.21; p=0.239). At Week 4, a statistically significant improvement from Baseline was noted in the Immediate Substitution arm (-6.75; p<0.001) compared to no change in the Deferred Substitution arm (+0.48; p=0.765). At Week 8, patients in the Immediate Substitution arm continued to demonstrate improvement (-7.33; p<0.001), while patients in the Deferred Substitution arm began to improve (-3.24; p=0.041). Results for ASDM total scores are summarized in Figure 5.

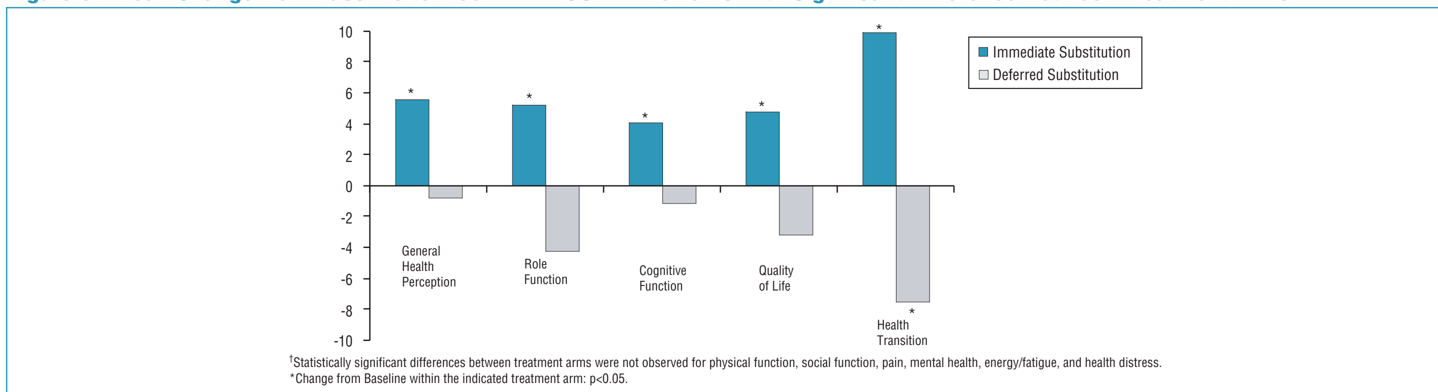
Figure 5. Augmented Symptoms Distress Module Total Scores†



†For patients who answered ≥20 of the 22 items in the ASDM questionnaire at Baseline and Week 4 (left) or Baseline and Week 8 (right).
*Statistically significant change from baseline within the indicated treatment arm (p < 0.05).
**Statistically significant differences between the IS and DS arms at Week 4 (p<0.001) and at Week 8 (p<0.05).

At Baseline, no statistically significant difference was observed between the Immediate and Deferred Substitution arms in any of the 11 MOS-HIV domains. At Week 4, patients in the Immediate Substitution arm demonstrated statistically significant improvement from Baseline in all MOS-HIV domains with the exception of "pain", while patients in the Deferred Substitution arm showed no statistically significant change from Baseline in any domains except for a worsening in "health transition". Similarly, statistically significant improvements from Baseline were observed for patients in the Immediate Substitution arm with respect to PHSS (+1.7 ± 0.5; p<0.001) and MHSS (+3.4 ± 0.5; p<0.001), while no change was observed for patients in the Deferred Substitution arm with respect to either PHSS (+0.1 ± 1.0; p=0.904) or MHSS (+0.6 ± 0.9; p=0.512). Statistically significant differences between the Immediate and Deferred Substitution arms were seen at Week 4 in the general health perception, role function, cognitive function, quality of life, and health transition domains; however, no significant differences were observed with respect to the physical function, social function, pain, mental health, energy/fatigue, and health distress domains. Mean changes from Baseline to Week 4 for domains in which significant difference was observed between the Immediate and Deferred Substitution arms are summarized in Figure 6.

Figure 6. Mean Change from Baseline to Week 4 in MOS-HIV Domains with Significant Difference Between Treatment Arms†

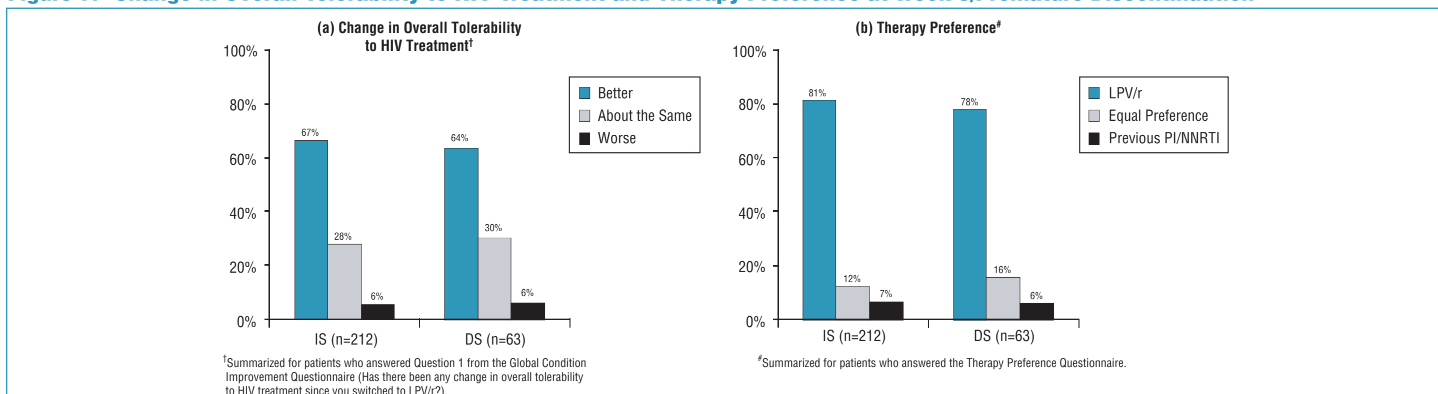


†Statistically significant differences between treatment arms were not observed for physical function, social function, pain, mental health, energy/fatigue, and health distress.
*Change from Baseline within the indicated treatment arm: p<0.05.

Results from Question #1 of the Global Condition Improvement Questionnaire (i.e., Has there been any change in your tolerability to HIV treatment since you switched to LPV/r?) are summarized in Figure 7a. The majority of patients (66%) from the subset of patients included in this analysis reported that their overall tolerability to HIV treatment had improved after substitution of NFV with LPV/r.

Results from the Therapy Preference Questionnaire are summarized in Figure 7b. The majority of patients (80%) from the subset of patients included in this analysis preferred LPV/r to NFV.

Figure 7. Change in Overall Tolerability to HIV Treatment and Therapy Preference at Week 8/Premature Discontinuation



†Summarized for patients who answered Question 1 from the Global Condition Improvement Questionnaire (Has there been any change in overall tolerability to HIV treatment since you switched to LPV/r?).

#Summarized for patients who answered the Therapy Preference Questionnaire.

Plasma HIV RNA results are summarized over time in Table 3. At Baseline, 92% of patients in both the Immediate Substitution and Deferred Substitution arms had plasma HIV RNA <400 copies/mL. At Week 4, 97% of patients in the Immediate Substitution arm and 86% of patients in the Deferred Substitution arm had plasma HIV RNA <400 copies/mL. At Week 8, after all patients had substituted LPV/r for NFV, 97% of patients had HIV RNA <400 copies/mL, with no difference noted between the Immediate and Deferred Substitution arms.

Table 3. Proportion of Patients with HIV RNA <400 copies/mL†

	Baseline	Week 4	Week 8‡
Immediate Substitution	92%	97%	97%
Deferred Substitution	92%	86%	97%
IS vs. DS p-value	>0.999	0.002	>0.999

† For all patients with Baseline and at least one post-Baseline viral load measurement. The data presented at Week 4 and Week 8 use an On-Study approach.
‡ All patients (Immediate and Deferred Substitution arms) were receiving LPV/r at Week 8.

Of the 291 patients included in this safety analysis, 4 (1.4%) 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 subjects. After LPV/r substitution, new onset Grade 1-3 side effects reported by >2% of patients were gas (3.8%), nausea (3.5%), diarrhea (2.4%) and headache (2.1%). Clinical laboratory abnormalities occurring in >2% of patients after substitution of NFV with LPV/r included elevated triglycerides (>8.25 mmol/L; 9.8%) and elevated cholesterol (>7.77 mmol/L; 6.5%); however, it should be noted that clinical laboratory samples were obtained without regard to fasting. Safety results for patients in this subgroup analysis are similar for the entire patient cohort. [See: D Bassetti, Y Shen, A Minguez, et al. Evaluation of Side Effects in Patients After Substitution of Their PI/NNRTI with Lopinavir/ritonavir (LPV/r). Presented at the 5th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, Paris, France, 8-11 July 2003].

CONCLUSIONS

Of the 291 patients who were receiving NFV-based ARV therapy at the time of enrollment in this study, 91% had Grade 1-2 diarrhea. Substitution of LPV/r for NFV resulted in:

- Resolution or improvement of diarrhea of at least one toxicity grade in approximately 90% of patients with Grade 1-2 diarrhea at Baseline;
- Significant improvement in tolerability as measured by the ASDM;
- Improved quality of life in several domains as measured by MOS-HIV; and
- No new onset side effect in >5% of patients.

In addition, patients appeared to maintain or improve virologic control following substitution of LPV/r for NFV. Further, over 75% of patients preferred LPV/r to NFV after 4-8 weeks of treatment with LPV/r.

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