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Gastrointestinal Tolerability After PI/NNRTI Substitution with Lopinavir/ritonavir

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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.[2-5]

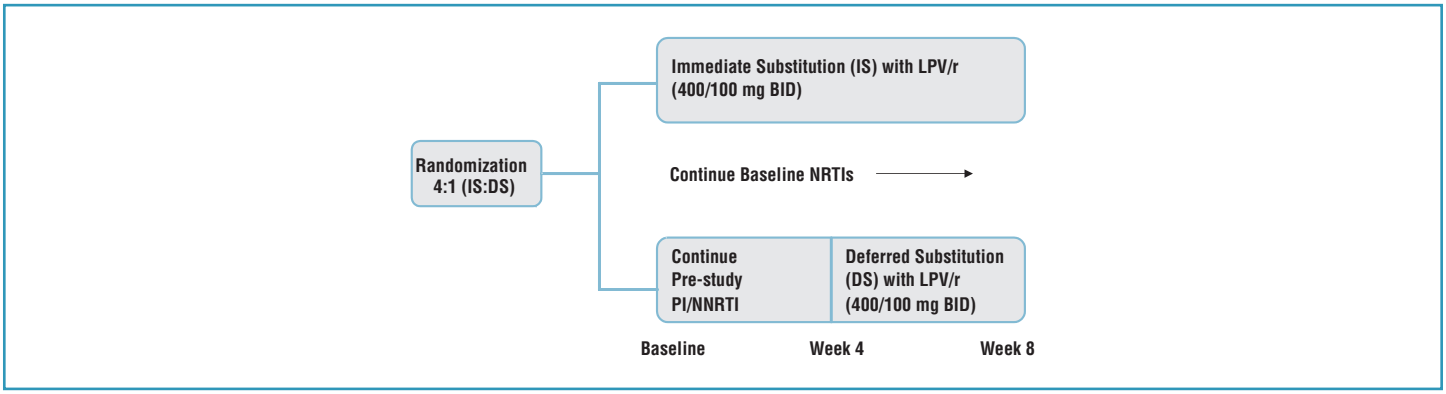
Gastrointestinal side effects are a common complication of HIV and its treatment.[6] For example, the prevalence of diarrhea was reported to be 39% in one large cross-sectional study conducted during the HAART era.[7] While diarrhea of infectious origin has decreased with the use HAART, diarrhea of non-infectious origin has increased.[8] Further, studies in ARV naïve patients have demonstrated that >10% experience diarrhea during their first year of therapy, and that diarrhea can significantly impact QOL and adherence.[9-10] 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.

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 ongoing patients received LPV/r from Week 4 to Week 8.

Figure 1. Study Design



The purpose of this analysis was to assess whether the gastrointestinal (GI) side effects experienced by patients could be improved after substitution of the PI/NNRTI with LPV/r.

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 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.[11]

Assessments

Side effects that were present at Baseline or developed during the study were assessed at each study visit. In addition, the following patient reported outcome instruments were used:

- The AIDS Clinical Trials Group (ACTG) Symptom Distress Module (ASDM),[12] supplemented with two additional questions to evaluate symptoms of nephrolithiasis,[13] 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. The ASDM was administered at each study visit.
- The Medical Outcomes Study–HIV Health Survey (MOS-HIV)[14] 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. In addition to scores for each domain, a physical health summary score (PHSS) and mental health summary score (MHSS) are computed. Higher scores indicate better QOL. 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.[15] The MOS-HIV was administered at each study visit.
- Center for Epidemiologic Studies–Depression (CES-D) is a validated self-report questionnaire containing 20 items which represent the major components of depression that have been identified in clinical and factor analysis studies. CES-D is used as a screening tool for depression.[16] The recall period for CES-D is the past week, and a CES-D score of 16 or higher indicates that the patient is experiencing depressive symptoms. The CES-D was administered at Baseline and Week 8/Study Discontinuation.
- The Global Condition Improvement Questionnaire measures the patient's overall tolerability to HIV treatment. The Global Condition Improvement Questionnaire was administered at Baseline and Week 8/Study Discontinuation.
- The Therapy Preference Questionnaire measures the patient's overall therapy preference for LPV/r or previous PI/NNRTI. The Therapy Preference Questionnaire was administered at Week 8/Study Discontinuation.

Clinical laboratory tests, including routine chemistry and hematology panels as well as plasma HIV RNA (Roche Amplicor Ultrasensitive 1.5), were evaluated at each study visit using a central laboratory.

RESULTS

Of the 827 patients receiving protocol-allowed ARV regimens at the time of enrollment in PLATO, 575 reported Grade 1–2 GI side effects at Baseline. This evaluation of the 575 patients with Grade 1–2 GI side effects at Baseline provides the opportunity to assess the change in GI tolerability during this study. Demographic characteristics and patient disposition for these 575 patients are summarized in Tables 1 and 2, respectively.

Table 1. Demographic Characteristics of Patients Who Entered the Study with GI Side Effects

n=453	Immediate Substitution n=122	Deferred Substitution n=575	Overall
Sex			
Male	354 (78%)	94 (77%)	448 (78%)
Female	99 (22%)	28 (23%)	127 (22%)
Race			
White	343 (76%)	92 (75%)	435 (76%)
Black	70 (15%)	21 (17%)	91 (16%)
Other	40 (9%)	9 (7%)	49 (9%)
Ethnicity			
Hispanic	131 (29%)	35 (29%)	166 (29%)
Age			
Mean	41.5	43.4	41.9
Minimum–Maximum	23–82	25–70	23–82

Table 2. Disposition of Patients Who Entered the Study with GI Side Effects

	Immediate Substitution n=453	Deferred Substitution n=122	Overall n=575
Completed Study	417 (92%)	114 (93%)	531 (92%)
Prematurely Discontinued*	36 (8%)	8 (7%)	44 (8%)
Adverse Events/HIV Events	20 (4%)	2 (2%)	22 (4%)
Withdrawal of Consent	9 (2%)	5 (4%)	14 (2%)
Loss to Follow-up	5 (1%)	1 (1%)	6 (1%)
Other	8 (2%)	2 (2%)	10 (2%)

* Multiple reasons for discontinuation could have been reported.

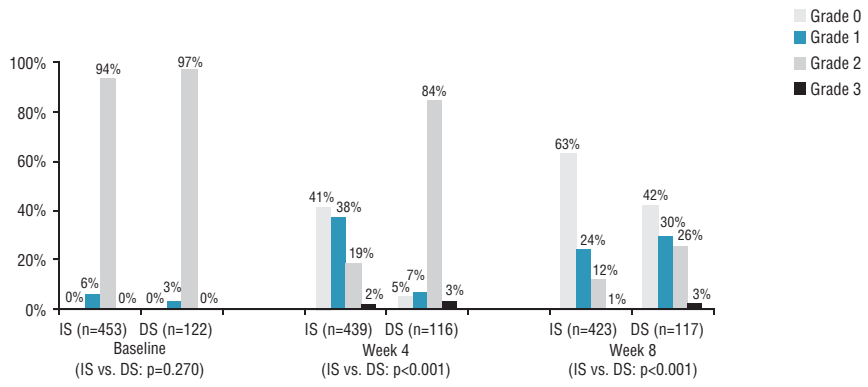
The distribution of PI/NNRTI medication used by patients with GI side effects at Baseline is summarized in Table 3. No difference was detected between the Immediate and Deferred Substitution arms with respect to the PI/NNRTI used at the time of enrollment (p=0.287).

Table 3. Pre-study PI/NNRTI for Patients Who Entered the Study with GI Side Effects

	Immediate Substitution n=453	Deferred Substitution n=122	Overall n=575
Nelfinavir	213 (47%)	67 (55%)	280 (49%)
Indinavir	96 (21%)	21 (17%)	117 (20%)
Indinavir/Ritonavir	86 (19%)	21 (17%)	107 (19%)
Efavirenz	37 (8%)	5 (4%)	42 (7%)
Other	21 (5%)	8 (7%)	29 (5%)

Of the 827 patients enrolled in the study, GI side effects were reported for 96% (280/291), 69% (117/170), 59% (107/182), 31% (42/136) and 60% (29/48) of patients previously on NFV, IDV, IDV/RTV, EFV or another regimen, respectively. The most frequently reported GI side effects at Baseline were diarrhea (70%), nausea (25%), and abdominal pain (13%). Of the 575 patients with GI side effects at Baseline, 94% (Immediate Substitution arm) to 97% (Deferred Substitution arm) had Grade 2 GI side effects at Baseline. At Week 4, improvements in GI side effects of at least one toxicity grade were reported for 77% of patients in the Immediate Substitution arm and only 10% of patients in the Deferred Substitution arm. At Week 8, GI side effects reported at Baseline in the Immediate Substitution arm continued to improve, while GI side effects reported in the Deferred Substitution arm began to improve after 4 weeks on LPV/r therapy. The pattern seen in the Deferred Substitution arm at Week 8 is consistent with the improvement seen in the Immediate Substitution arm at Week 4. In general, GI side effects resolved (58%) or improved at least one toxicity grade (23%) in 82% of patients at Week 8. The distribution of toxicity grades for GI side effects is summarized over time in Figure 2.

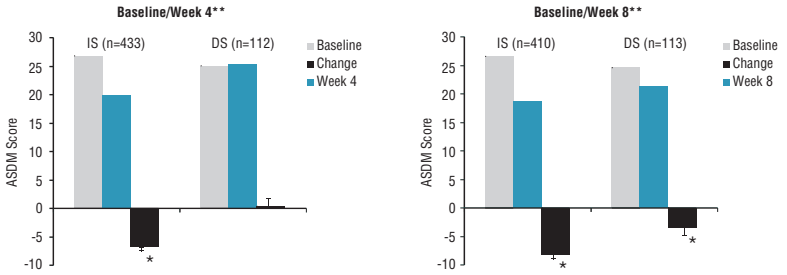
Figure 2. Toxicity Grades for GI Side Effects†



† For patients who reported GI side effects at the indicated visit. The highest toxicity grade was used for a patient when multiple GI side effects were reported for the patient at a given visit.

At Baseline, no difference was observed between the Immediate and Deferred Substitution arms with respect to ASDM total score (IS: 26.99 vs. DS: 24.82; p=0.207). At Week 4, a statistically significant improvement (mean ± SEM) from Baseline was noted in the Immediate Substitution arm (-6.86 ± 0.56; p<0.001) compared to no change in the Deferred Substitution arm (+0.38 ± 1.10; p=0.733). At Week 8, patients in the Immediate Substitution arm continued to demonstrate improvement from Baseline (-8.07 ± 0.59; p<0.001) while patients in the Deferred Substitution arm began to improve after substituting LPV/r for their PI/NNRTI (-3.36 ± 1.12; p=0.003). Results for ASDM total score are summarized in Figure 3.

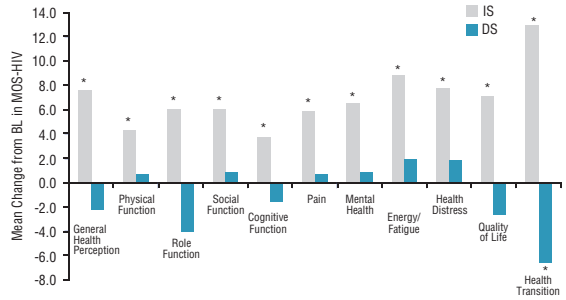
Figure 3. Augmented Symptoms Distress Module Total Scores†



† For patients who answered at least 20 of the 22 items of the ASDM questionnaire at Baseline and Week 4 (left) or Baseline and Week 8 (right).
* Statistically significant mean change from Baseline within the indicated treatment arm (p<0.01).
** Statistically significant differences between the IS and DS arms at Week 4 and at Week 8 (p<0.001).

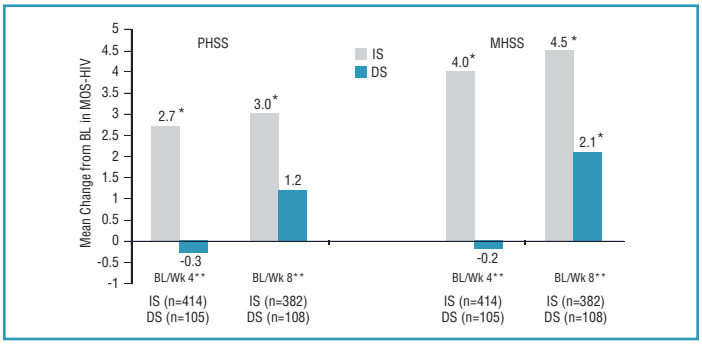
At Baseline, no statistically significant difference was observed between the Immediate and Deferred Substitution arms with respect to any of the 11 MOS-HIV domains. At Week 4, patients in the Immediate Substitution arm demonstrated statistically significant mean improvements from Baseline in all 11 MOS-HIV domains. At week 4, patients in the Immediate Substitution arm demonstrated statistically significant mean improvements from Baseline in all 11 MOS-HIV domains. In contrast, patients in the Deferred Substitution arm showed no statistically significant change from Baseline in any MOS-HIV domain with the exception of a worsening in "health transition". Similarly, statistically significant (mean ± SEM) improvements from Baseline were observed for patients in the Immediate Substitution arm with respect to PHSS (+2.7 ± 0.3 from 49.2; p<0.001) and MHSS (+4.0 ± 0.3 from 46.9; p<0.001), while no change was observed for patients in the Deferred Substitution arm with respect to either PHSS (-0.3 ± 0.7 from 49.3; p=0.673) or MHSS (-0.2 ± 0.7 from 47.4; p=0.741). At Week 8, patients in the Immediate Substitution arm continued to demonstrate improvement from Baseline in all MOS-HIV domains and with respect to PHSS (+3.0 ± 0.4; p<0.001) and MHSS (+4.5 ± 0.4; p<0.001), while patients in the Deferred Substitution arm began to improve in 6 of the 11 individual domains and with respect to PHSS (+1.2 ± 0.8; p=0.110) and MHSS (+2.1 ± 0.7; p=0.004). Mean changes from Baseline to Week 4 for the 11 MOS-HIV domains are summarized in Figure 4. Mean changes from Baseline for MOS-HIV PHSS and MHSS are summarized in Figure 5.

Figure 4. Mean Changes from Baseline to Week 4 for Each MOS-HIV Domain†



† For patients who answered the questions in the indicated domain of the MOS-HIV questionnaire at Baseline and Week 4.
* Statistically significant mean change from Baseline within the indicated treatment arm (p<0.05).

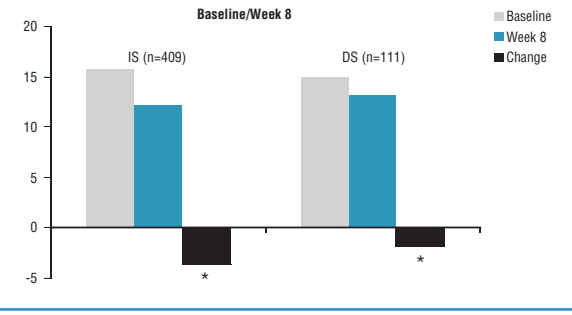
Figure 5. Mean Changes from Baseline for MOS-HIV Physical and Mental Health Summary Scores (PHSS and MHSS)†



† For patients who adequately completed the MOS-HIV questionnaire at Baseline and Week 4 (left) or Baseline and Week 8 (right).
* Statistically significant mean change from Baseline within the indicated treatment arm (p<0.01).
** Statistically significant differences between the IS and DS arms at Week 4 (p<0.001) and at Week 8 (p<0.05).

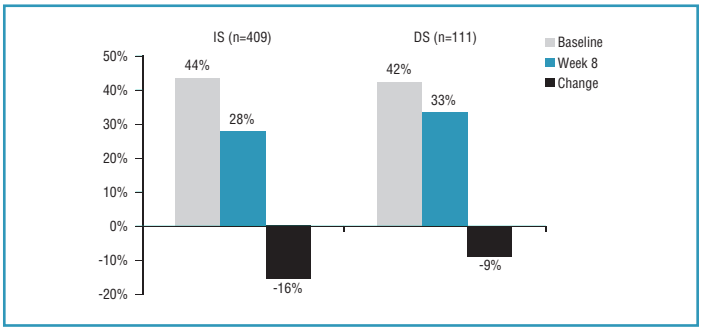
At Week 8, statistically significant reductions from Baseline (mean ± SEM) in CES-D score were observed in the Immediate Substitution arm (-3.56 ± 0.44 from 15.69; p<0.001) after 8 weeks on LPV/r therapy and the Deferred Substitution arm (-1.86 ± 0.84 from 14.92; p=0.027) after 4 weeks on LPV/r. In addition, the prevalence of depression (CES-D score ≥ 16) appeared to decrease from Baseline to Week 8 in the Immediate Substitution arm (8 weeks of LPV/r therapy, 44% to 28%; p<0.001) and the Deferred Substitution arm (4 weeks of LPV/r therapy, 42% to 33%; p=0.059). Results from CES-D questionnaire are summarized in Figure 6a (Mean CES-D Scores) and Figure 6b (Prevalence of Depression).

Figure 6a. Mean CES-D Scores†



† For patients who adequately completed the CES-D questionnaire at Baseline and Week 8.
* Statistically significant mean change from Baseline within the indicated treatment arm (p < 0.05).

Figure 6b. Prevalence of Depression†

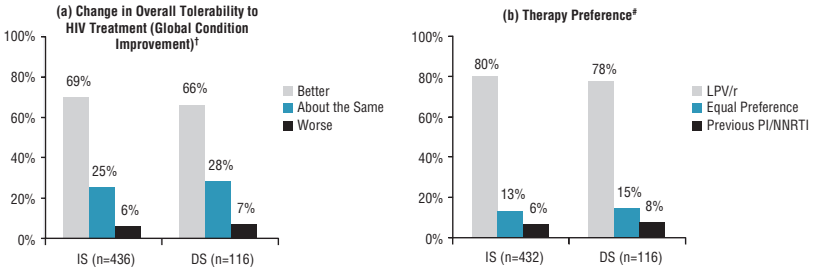


† For patients who adequately completed the CES-D questionnaire at Baseline and Week 8. A CES-D score of ≥16 indicates possible depression.

At Week 8/Premature Discontinuation, the majority of patients (68%) completing the Global Condition Improvement Questionnaire reported that their overall tolerability to HIV treatment had improved after substitution of their PI/NNRTI with LPV/r. In addition, the majority of patients (80%) completing the Therapy Preference Questionnaire preferred LPV/r to the PI/NNRTI they were taking prior to study entry. 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?) and the results from the Therapy Preference Questionnaire are summarized in Figure 7.

RESULTS *continued*

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



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

Summarized for patients who completed the Therapy Preference Questionnaire.

At Baseline, 90% of patients with GI side effects had plasma HIV RNA below 400 copies/mL. Plasma HIV RNA results obtained at Week 8 suggest that patients maintained (intent-to-treat; Baseline [90%] vs. Week 8 [90%]) or improved (on-study; Baseline [90%] vs. Week 8 [96%]) virologic control during this study. Plasma HIV RNA results are summarized in Table 4.

Table 4. Summary of the Percentage of Patients with HIV RNA <400 copies/mL†

	Baseline	Week 4**	Week 8
Intent-to-Treat			
IS	90%	95%*	89%
DS	90%	76%*	91%
On-Study			
IS	90%	96%*	96%*
DS	90%	83%*	94%

† Summarized for patients who had a Baseline and at least one post-Baseline HIV RNA measurement; missing values were considered above 400 copies/mL for the Intent-to-Treat analysis and excluded from the On-Study analysis.

* Statistically significant change from Baseline within the indicated treatment arm ($p<0.05$).

** Statistically significant difference between the IS and DS arms at Week 4 ($p<0.001$).

Of the 575 patients included in this analysis, 4 (0.7%) experienced treatment-emergent serious adverse events with possible or probable relationship to LPV/r: diabetes mellitus (in a patient with a prior history of hyperglycemia; 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 >2.0% of patients. Diarrhea (46/571; 8.1%), nausea (16/571; 2.8%) and gas (15/571; 2.6%) were the only new onset side effects reported by >2.0% of patients while they were receiving LPV/r. Clinical laboratory abnormalities occurring in >2.0% of patients after substitution of their PI/NNRTI with LPV/r included elevated triglycerides (>750 mg/dL; 11.0%)and elevated cholesterol (>300 mg/dL; 8.1%). The mean change in cholesterol through 4 weeks of LPV/r therapy (IS+DS) was +5.46 mg/dL (from 207.33 mg/dL) and through 8 weeks (IS only) was +5.17 mg/dL (from 206.83 mg/dL). Similarly, the mean change in triglycerides through 4 weeks of LPV/r therapy was +89.95 mg/dL (from 272.28 mg/dL) and through 8 weeks was +80.51 mg/dL (from 270.58 mg/dL). Results suggest that the risk of developing triglyceride levels > 750 mg/dL while on LPV/r is associated with Baseline triglyceride toxicity level and hyperlipidemia. Similarly, the risk of developing cholesterol levels > 300 mg/dL while on LPV/r appears to be associated with Baseline cholesterol toxicity level and hyperlipidemia. However, it should be noted that clinical laboratory samples were obtained without regard to fasting.

DISCUSSION/CONCLUSION

After substituting LPV/r for the PI/NNRTI in their baseline regimen, patients with PI/NNRTI-associated GI side effects demonstrated:

- Improvement in or resolution of GI side effects in 82% of patients.
- Improvement in tolerability as demonstrated by a reduction in total ASDM score.
- Improved QOL as measured by MOS-HIV.
- Decreased prevalence of depression as measured by CES-D.
- A preference for LPV/r compared to their previous PI/NNRTI as measured by the Therapy Preference Questionnaire.
- Continued or improved virologic control.

Therefore, substitution with LPV/r may be an important treatment option for patients experiencing Grade 2 gastrointestinal side effects on their current PI/NNRTI.

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