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Comprehensive Resistance Testing in Antiretroviral-Naïve Patients Treated with Once-Daily Lopinavir/ritonavir Plus Tenofovir DF and Emtricitabine: 48-Week Results from Study 418

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BACKGROUND

Lopinavir (LPV) is an HIV protease inhibitor (PI) that is co-formulated with ritonavir (r), which functions as a pharmacokinetic enhancer. LPV/r is marketed as Kaletra®. The approved adult dose of LPV/r is 400/100 mg twice daily (BID). Antiviral activity of LPV/r has been demonstrated in antiretroviral (ARV)-naïve and PI-experienced patients. In a phase 2 study of LPV/r in combination with stavudine (d4T) and lamivudine (3TC) in ARV-naïve patients (Study 720), by intent to treat analysis, 67% of patients maintained HIV RNA <400 copies/mL through 5 years.[1]

A once-daily (QD) ARV regimen including LPV/r may offer an advantage with regard to convenience while maintaining antiviral potency in ARV-naïve patients. In a pilot study (Study 056), ARV-naïve, HIV-infected adults (N=38) received LPV/r 800/200 mg QD or 400/100 mg BID with d4T and 3TC given BID.[2,3] LPV/r 800/200 mg QD produced similar C_{max} and AUC and lower and more variable C_{trough} compared to 400/100 mg BID. However, virologic response through 72 weeks was similar.[3] Further, the Inhibitory Quotient (IQ; C_{trough}/IC_{50} for wild type HIV) achieved with once-daily LPV/r compares favorably to that of other QD PIs.[4]

Based on these pilot results, Study 418 was initiated to further assess the pharmacokinetics, antiviral activity and safety of a QD dosing regimen for LPV/r in ARV-naïve patients. In Study 418, patients received LPV/r (800 mg/200 mg QD or 400 mg/100 mg BID) with tenofovir DF (TDF) 300 mg and emtricitabine (FTC) 200 mg QD. Patients receiving LPV/r 800/200 mg QD demonstrated slightly higher lopinavir C_{max}, similar AUC, and lower C_{trough} compared to 400/100 mg BID.[5] The median IQ was 49 for QD and 94 for BID.

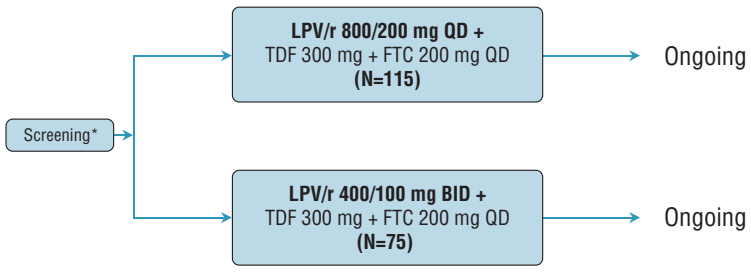
This analysis presents comprehensive resistance data obtained through 48 weeks.

METHODS

Study 418 is the first trial of an entirely once-daily LPV/r-based regimen (Figure 1).

- Randomized, open-label, multi-center, international study.
- Patients were ARV-naïve, with HIV RNA >1,000 copies/mL and any CD4 count.
- 190 patients were randomized 3:2 to LPV/r 800/200 mg QD (n=115) or 400/100 mg BID (n=75).
- All patients also received TDF 300 mg and FTC 200 mg QD.

Figure 1. Study 418 Schematic



* Patients were randomized in a 3:2 ratio to one of two study arms; baseline adherence was assessed over a 5-7 day placebo lead-in period.

Resistance

- A comprehensive approach was employed to assess resistance development. For each HIV RNA result above 500 copies/mL between Weeks 12-48, isolates were submitted for genotypic resistance testing. Corresponding baseline isolates for each patient were also submitted for testing. Genotypic changes were assessed by population sequencing (GeneSeq, Virologic).
- Resistance to LPV was defined as the emergence of any primary or active site mutation in protease (positions 8, 30, 32, 46, 47, 48, 50, 82, 84, 90) with corresponding phenotypic LPV resistance of at least 2.5-fold vs. wild-type.
- TDF resistance was defined as the emergence of the K65R mutation or any thymidine analog mutation (TAM positions 41, 67, 70, 210, 215, 219 in reverse transcriptase).
- FTC resistance was defined by the emergence of the M184V/I mutation in reverse transcriptase.

RESULTS

Demographics

- Demographics and baseline characteristics were similar between treatment groups.
- Overall, 22% were female and 46% were non-white.
- The patient population was relatively advanced, as approximately 45% of patients had baseline CD4 count below 200 cells/mm^3 and 38% had baseline HIV RNA above 100,000 copies/mL.
- Mean baseline HIV RNA and CD4 cell count were 4.8 $\log_{10}$ copies/mL and 260 cells/mm^3, respectively.

Efficacy

- By intent-to-treat (noncompleter=failure) analysis, 70% (QD) and 64% (BID) of patients demonstrated HIV RNA <50 copies/mL at Week 48 (Figure 2), 95% CI for the difference (–7% to 20%) as shown in Figure 2.
- CD4 cell count mean increases from baseline were comparable between treatment groups (Figure 3).

Figure 2. Study 418: HIV RNA <50 copies/mL (ITT NC=F)

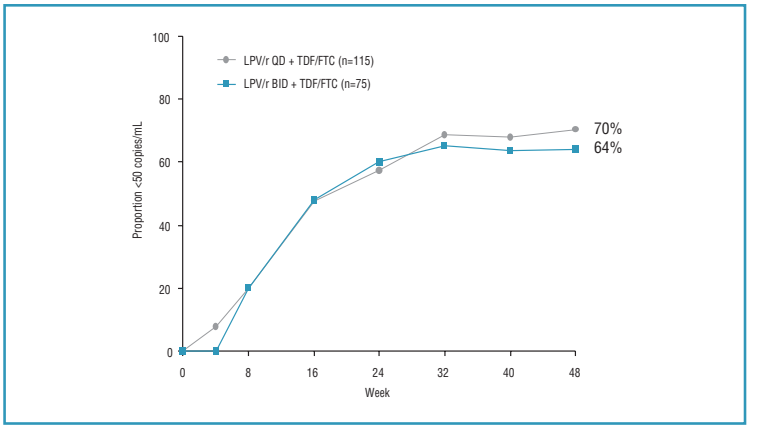
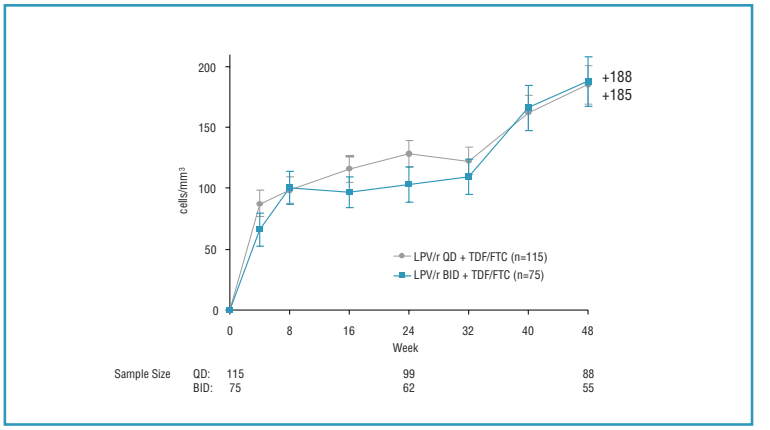


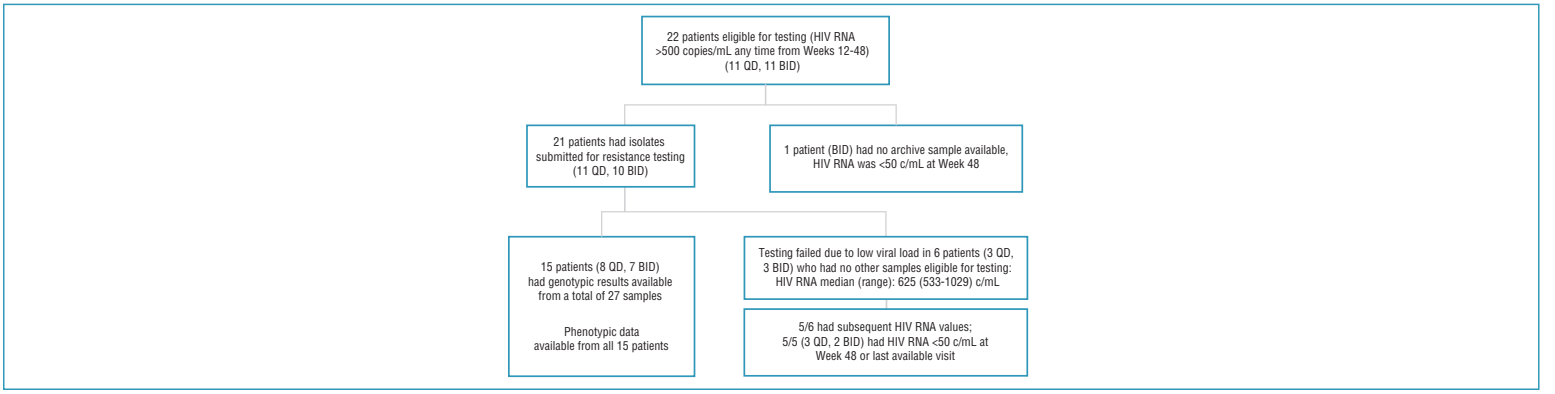
Figure 3. Study 418: CD4 Cell Count Mean (±SE) Change from Baseline



Resistance

- 22 patients (11 QD, 11 BID) had samples eligible for resistance testing (HIV RNA > 500 copies/mL at any time from Weeks 12-48) as shown in Figure 4.
- Resistance testing results were available for a total of 27 samples from 15 patients (8 QD, 7 BID).

Figure 4. Study 418 Resistance Sample Selection and Testing



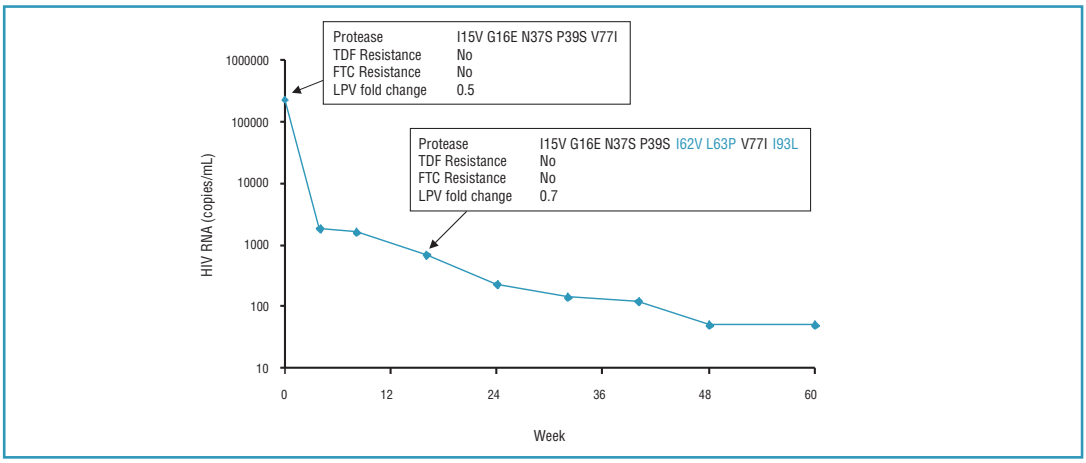
- No patient demonstrated confirmed LPV or TDF resistance (Table 1).
- 3 patients (2 QD, 1 BID) demonstrated FTC resistance.

Table 1. Incidence of Confirmed Drug Resistance

Drug	QD	BID
Lopinavir	0/8 (0%)	0/7 (0%)
Tenofovir DF	0/8 (0%)	0/7 (0%)
Emtricitabine	2/8 (25%)	1/7 (14%)

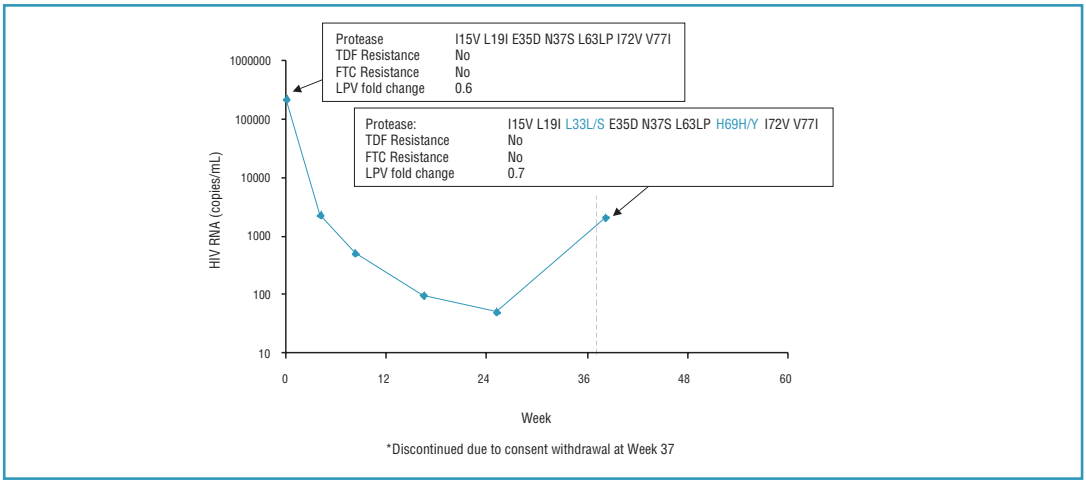
- 3 patients (1 QD, 2 BID) demonstrated any substitution in protease, but none of the changes appeared to have an impact on phenotypic resistance, as phenotypic susceptibility to LPV and other PIs remained below baseline or wild-type levels (1.0 fold).
- Figures 5-7 display HIV RNA levels over time and corresponding resistance data for these three patients.

Figure 5. Secondary Mutations/Polymorphisms in Protease: Patient A (QD)



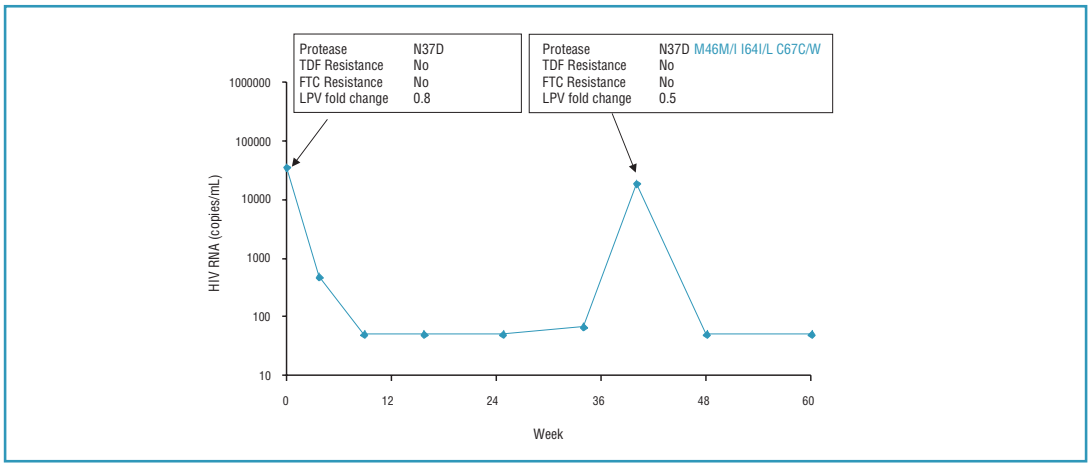
- At Week 16, Patient A (QD) demonstrated I62V, L63P, and I93L mutations that were not present at baseline (Figure 5).
- However, the L63P and I93L mutations are common polymorphisms, and the I62V mutation has not been associated with PI resistance.[6]
- No TDF or FTC resistance was observed.
- LPV phenotypic susceptibility remained below wild type.
- Subsequently, Patient A achieved HIV RNA <50 copies/mL at Weeks 48-60 with no change in therapeutic regimen.

Figure 6. Secondary Mutations/Polymorphisms in Protease: Patient B (BID)*



- Patient B (BID) discontinued at Week 37 and had genotypic data available 1 week after the last dose of study drug (Figure 6).
- While some substitutions at position 33 have been associated with PI resistance (e.g., L33F), the L33L/S substitution observed in Patient B is uncommon and has not been associated with PI resistance.[6]
- No TDF or FTC resistance was observed.
- LPV phenotypic susceptibility remained below wild type.

Figure 7. Secondary Mutations/Polymorphisms in Protease: Patient C (BID)



- Patient C (BID) demonstrated mixtures at positions 46, 64, and 67 in protease during a temporary drug interruption at Week 40 (Figure 7).
- The M46M/I mixture observed in Patient C is of unknown significance. When present with other mutations, the M46I mutation has been shown to increase resistance to various PIs,[6] but the phenotypic resistance to LPV for this subject remained below wild type.
- No TDF or FTC resistance was observed.
- If any of these changes were a manifestation of PI resistance development, FTC resistance would also be expected. Resistance generally develops first to the most fragile component of a regimen. For example, in a recent study of subjects receiving nelfinavir, stavudine and lamivudine, all subjects demonstrating a primary PI mutation (D30N or L90M) also demonstrated the M184V/I mutation in reverse transcriptase.[7]
- When study drugs were re-started, HIV RNA was re-suppressed below 50 copies/mL at Weeks 48 and 60.

CONCLUSIONS

- Through 48 weeks in antiretroviral-naïve patients, a QD regimen of LPV/r plus TDF and FTC demonstrated noninferiority to the same regimen with LPV/r dosed BID.
- A comprehensive approach to resistance testing was undertaken: for every available HIV RNA value above 500 copies/mL from Weeks 12-48, isolates were submitted for resistance testing.
- Consistent with previous trials of LPV/r-based regimens in antiretroviral-naïve patients, no patient in either group developed confirmed LPV resistance.
- Secondary protease mutations/polymorphisms in 3 patients were not associated with phenotypic or clinical LPV resistance.
- No patient in either group demonstrated TDF resistance, and only 3 patients (2 QD, 1 BID) demonstrated FTC resistance.

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