Abstract P15

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# Antiretroviral Therapy in Special Populations: Response to Lopinavir/ritonavir, Tenofovir DF, and Emtricitabine in Antiretroviral-Naïve Patients by Gender, Race/Ethnicity, and Hepatitis Co-infection Status

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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). In a phase 2 study of LPV/r in combination with stavudine (d4T) and lamivudine (3TC) in antiretroviral (ARV)-naïve patients (Study 720), by intent-to-treat analysis, 62% of patients maintained HIV RNA <50 copies/mL through 6 years.[1]

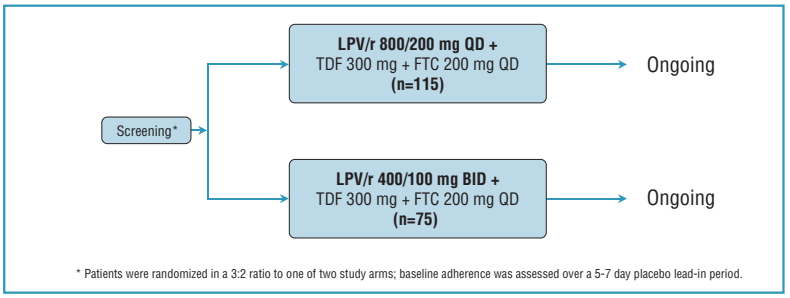
Once-daily (QD) dosing regimens may offer an advantage over BID regimens with regard to convenience. However, they must be carefully studied to ensure that a gain in convenience is not offset by a loss of antiviral potency. Study 418 is the first study of an entirely QD LPV/r-based regimen in ARV-naïve patients. Through 48 weeks, a regimen of LPV/r dosed at 800/200 mg plus tenofovir DF (TDF) 300 mg and emtricitabine (FTC) 200 mg QD was demonstrated to have non-inferior efficacy to the same regimen with LPV/r dosed BID, despite trough concentrations more than 60% lower with QD compared to BID dosing. The proportion of patients with HIV RNA <50 copies/mL by intent-to-treat, noncompleter=failure analysis was 70% for the QD arm and 64% for the BID arm (95% confidence interval for the difference, –7% to 20%).[2]

Female, non-white patients, and hepatitis B and C co-infected patients make up an increasing proportion of the HIV-infected population worldwide, but clinical trial populations have been predominantly white and male, and patients with hepatitis co-infection have often been excluded. The current analysis was conducted to assess the safety and efficacy of QD versus BID LPV/r, in combination with TDF and FTC, in different patient subgroups.

## METHODS

- Randomized, open-label, multi-center, international study (Figure 1).
- 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.
- Antiviral activity was assessed by the proportion of patients with HIV RNA <50 copies/mL at Week 48, by intent-to-treat, noncompleter=failure analysis.
- Immunologic response was assessed by the change from baseline to Week 48 in CD4 cell count.
- Cumulative incidence of adverse events through 48 weeks was summarized.
- Fasting laboratory determinations, including directly measured LDL and HDL cholesterol values, were obtained at baseline and Week 48.
- For each analysis, results were compared between females and males, between black and white patients, and between patients with hepatitis B or C infection (HBsAg or HCVAb-positive) and those without. Patients with AST or ALT >3 times the upper limit of normal at screening were not eligible for the study.
- Race/ethnicity was self-reported by patients. Categories other than white and black were combined for analysis due to small numbers of patients (Hispanic, n=16; Asian, n=11; Other, n=2).

**Figure 1. Study 418 Schematic**




## RESULTS

### Baseline Characteristics

- Demographics and baseline disease characteristics were similar between treatment groups, with approximately 20% female, 45% non-white, and 18% with baseline positive HBsAg or HCVAb serologies (Table 1).
- The patient population had relatively advanced HIV disease, 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.

## Table 1. Study 418: Baseline Characteristics

| | LPV/r 800/200 QD (N=115) | LPV/r 400/100 BID (N=75) |
|---|---|---|
| Gender | | |
| Male | 93 (81%) | 56 (75%) |
| Female | 22 (19%) | 19 (25%) |
| Race/Ethnicity | | |
| Black | 31 (27%) | 27 (36%) |
| White | 65 (57%) | 38 (51%) |
| Other | 19 (17%) | 10 (13%) |
| Baseline hepatitis serology* | | |
| Positive for HBsAg or HCVAb | 19 (17%) | 15 (20%) |
| Negative for HBsAg and HCVAb | 95 (83%) | 60 (80%) |
| HIV RNA ($log_{10}$ copies/mL) | | |
| Median (IQR) | 4.8 (4.3-5.5) | 4.6 (4.3-5.3) |
| Range | 3.5-6.4 | 2.6-6.2 |
| CD4 count (cells/mm$^3$) | | |
| Median (IQR) | 214 (116-380) | 232 (95-339) |
| Below 200 cells/mm$^3$ | 44% | 47% |

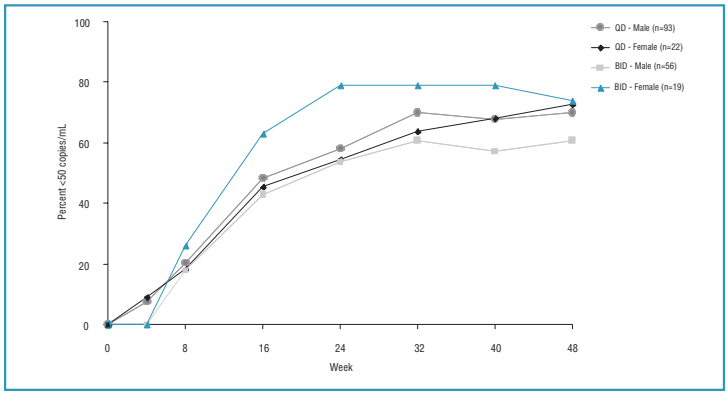
* 1 patient (QD group) did not have baseline hepatitis serology data

- No differences in baseline HIV RNA level or CD4 cell count were observed with respect to gender, race/ethnicity, or baseline hepatitis status (p>0.3 for all comparisons).

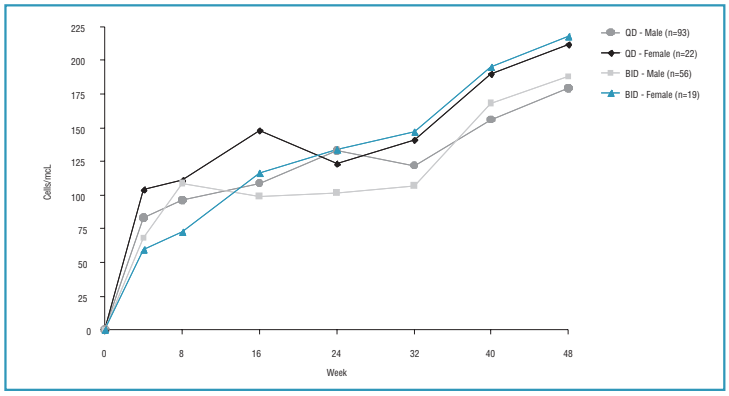
## Efficacy

- No statistically or clinically significant differences were observed between males and females in antiviral activity (Figure 2a) or CD4 cell count increases (Figure 2b) (P>0.05 for all comparisons within and between treatment groups and subgroups).

### Figure 2a. HIV RNA <50 copies/mL (ITT NC=F) by Gender

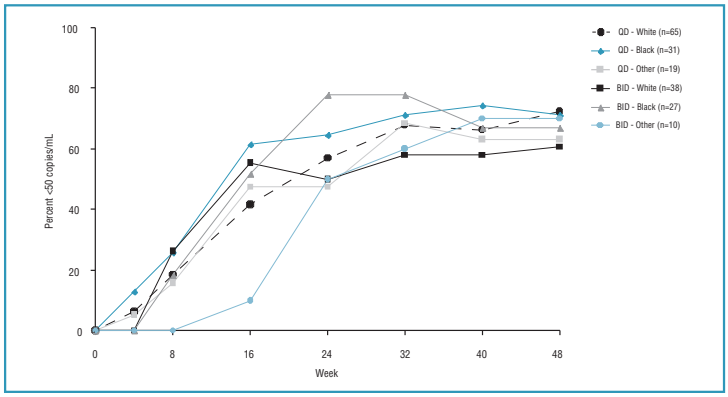



### Figure 2b. CD4 Count Mean Change from Baseline by Gender

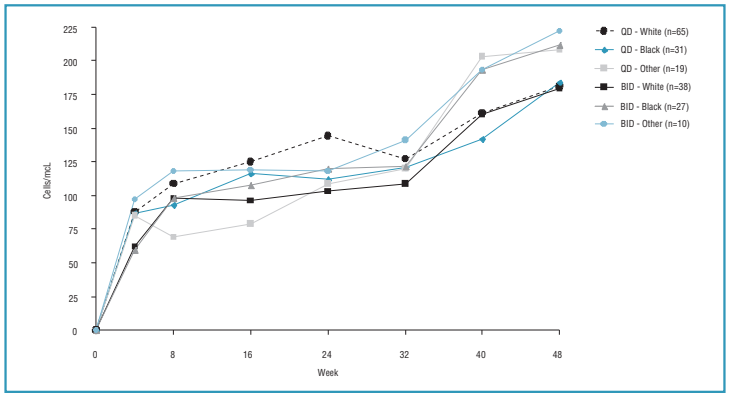



- No statistically or clinically significant differences were observed among blacks, whites, or other races/ethnicities in antiviral activity (Figure 3a) or CD4 cell count increases (Figure 3b) (P>0.05 for all comparisons within and between treatment groups and subgroups).

### Figure 3a. HIV RNA <50 copies/mL (ITT NC=F) by Race/Ethnicity




### Figure 3b. CD4 Count Mean Change from Baseline by Race/Ethnicity



- No statistically or clinically significant differences were observed between patients with baseline positive HBsAg or HCVAb serologies compared to patients with negative baseline HBsAg and HCVAb in antiviral activity (Figure 4a) or CD4 cell count increases (Figure 4b) (P>0.05 for all comparisons within and between treatment groups and subgroups).
- Virologic and immunologic responses were similar for patients positive for hepatitis C only (n=21) or hepatitis B only (n=12). 71% (hepatitis C) and 75% (hepatitis B) had HIV RNA <50 copies/mL at Week 48 (p=0.83, ITT NC=F analysis), and the mean increases from baseline in CD4 cell count were 235 cells/mm$^3$ (hepatitis C) and 180 cells/mm$^3$ (hepatitis B, p=0.24).

**Figure 4a. HIV RNA <50 copies/mL (ITT NC=F) by Baseline Hepatitis Serologies**

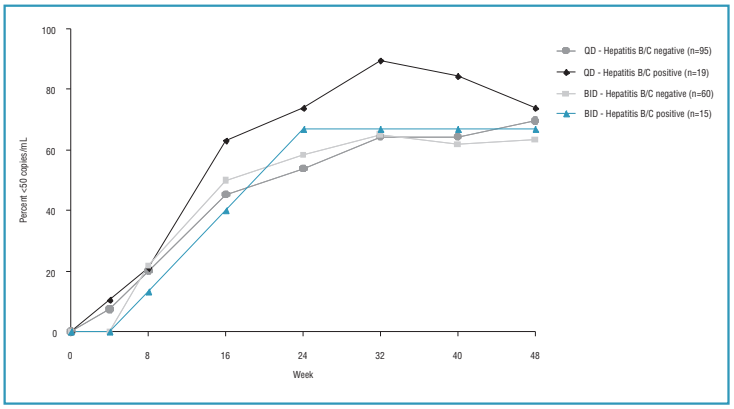
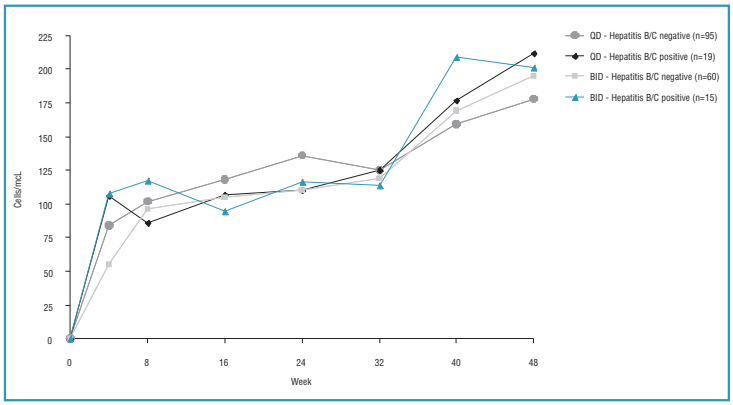



**Figure 4b. CD4 Count Mean Change from Baseline by Baseline Hepatitis Serologies**




## Safety

- No clinically significant differences in discontinuations were observed by gender, race/ethnicity, or hepatitis status. Table 2 shows results in combined treatment groups (QD and BID). Results were similar when examined in each treatment group separately.

**Table 2. Study 418: Reasons for Discontinuation Through 48 Weeks**

| Reason | Male (n=149) | Female (n=41) | White (n=103) | Black (n=58) | Other Race/ Ethnicity (n=29) | Hepatitis B/C- (n=155) | Hepatitis B/C+ (n=34) |
|---|---|---|---|---|---|---|---|
| Adverse event | 18 (12%) | 2 (5%) | 11 (11%) | 5 (9%) | 4 (14%) | 19 (12%) | 1 (3%) |
| Death | 1 (1%) | 0 | 1 (1%) | 0 | 0 | 1 (1%) | 0 |
| Lost to follow-up | 6 (4%) | 3 (7%) | 2 (2%) | 5 (9%) | 2 (7%) | 7 (5%) | 2 (6%) |
| Nonadherence | 3 (2%) | 1 (2%) | 1 (1%) | 2 (3%) | 1 (3%) | 2 (1%) | 2 (6%) |
| Virologic failure | 2 (1%) | 0 | 2 (2%) | 0 | 0 | 2 (1%) | 0 |
| Withdrew consent | 5 (3%) | 4 (10%) | 5 (5%) | 2 (3%) | 2 (7%) | 8 (5%) | 1 (3%) |
| Any reason | 35 (23%) | 10 (24%) | 22 (21%) | 14 (24%) | 9 (31%) | 39 (25%) | 6 (18%) |

- No clinically significant differences in the incidence of moderate or severe study-drug related adverse events were observed by gender, race/ethnicity, or hepatitis status (Table 3).
- As reported previously, diarrhea was more common among patients receiving QD compared to BID LPV/r in this study,[2] (16% vs 5%) but no other differences by treatment group were observed within subgroups defined by gender, race/ethnicity, or hepatitis status.

**Table 3. Study 418: Most Common Adverse Events**

| Event | Male (n=149) | Female (n=41) | White (n=103) | Black (n=58) | Other Race/ Ethnicity (n=29) | Hepatitis B/C- (n=155) | Hepatitis B/C+ (n=34) |
|---|---|---|---|---|---|---|---|
| Diarrhea | 18 (12%) | 4 (10%) | 13 (13%) | 5 (9%) | 4 (14%) | 19 (12%) | 3 (9%) |
| Nausea | 12 (8%) | 4 (10%) | 8 (8%) | 6 (10%) | 2 (7%) | 15 (10%) | 1 (3%) |
| Vomiting | 4 (3%) | 3 (7%) | 3 (3%) | 3 (5%) | 1 (3%) | 7 (5%) | 0 |
| Flatulence | 1 (1%) | 2 (5%) | 2 (2%) | 1 (2%) | 0 | 3 (2%) | 0 |

Includes study drug-related events of moderate or greater intensity occurring in ≥4% of patients in any subgroup

- No clinically significant differences in the incidence of grade 3 or higher laboratory abnormalities were noted by gender, race/ethnicity, or hepatitis status (Table 4). No differences between treatment groups were noted in subgroups defined by gender, race/ethnicity, or hepatitis status.

### Table 4. Study 418: Most Common Grade 3+ Laboratory Abnormalities

| Variable | Male (n=145) | Female (n=40) | White (n=101) | Black (n=57) | Other Race/ Ethnicity (n=27) | Hepatitis B/C- (n=151) | Hepatitis B/C+ (n=33) |
|---|---|---|---|---|---|---|---|
| Glucose (>250 mg/dL) | 3 (2%) | 1 (3%) | 1 (1%) | 3 (5%) | 0 | 2 (1%) | 2 (6%) |
| SGOT/AST (>5xULN) | 6 (4%) | 1 (3%) | 4 (4%) | 3 (5%) | 0 | 5 (3%) | 2 (6%) |
| SGPT/ALT (>5xULN) | 5 (3%) | 1 (3%) | 3 (3%) | 3 (5%) | 0 | 4 (3%) | 2 (6%) |
| Total cholesterol (>300 mg/dL) | 4 (3%) | 1 (3%) | 5 (5%) | 0 | 0 | 3 (2%) | 2 (6%) |
| Triglycerides (>750 mg/dL) | 6 (4%) | 2 (5%) | 6 (6%) | 0 | 2 (7%) | 8 (5%) | 0 |
| Amylase (>2xULN) | 9 (6%) | 3 (8%) | 4 (4%) | 5 (9%) | 3 (11%) | 10 (7%) | 2 (6%) |

Note: Analysis excludes patients without post-baseline laboratory data. All laboratory abnormalities occurring in ≥4% of patients in any subgroup were included.

- Mean changes from baseline to week 48 in laboratory parameters were also assessed. With the exception of lower mean increases in triglycerides among female (+42 mg/dL) vs. male (+90 mg/dL) patients (consistent with prior reports of such differences[3,4]), no clinically important differences in mean changes from baseline were noted between subgroups defined by gender, race/ethnicity, or hepatitis status.

## CONCLUSIONS

- A regimen of LPV/r dosed QD or BID with QD TDF+FTC demonstrated similar virologic and immunologic responses regardless of gender, race, or hepatitis B and C co-infection status.
- Triglycerides increases were lower in female patients compared to male patients. No other differences in safety or tolerability were observed.
- No clinically meaningful differences in antiviral activity between QD and BID dosing were observed, either overall or within subgroups defined by gender, race/ethnicity, or hepatitis B and C co-infection.

## REFERENCES

1. RM Gulick, et al., HIV7, Glasgow, November 2004, Abstract P28.
2. J Gathe, et al. 11th CROI, San Francisco, February 2004, Abstract 570.
3. P Kumar, et al., 9th CROI, Seattle, February 2002, Abstract 33.
4. P Cernohous, et al., 14th IAC, Barcelona, 2002, Abstract WePeB5972.