

Efficacy, Safety and Tolerability of Lopinavir/ritonavir (LPV/r) in HIV-Infected Women: Results of a Meta-Analysis of 7 Prospective, Randomized Clinical Trials (RCTs) Through 48 Weeks

Ashwaq Hermes, Linda Fredrick, Mary Pasley, Roger Trinh, Marisol Martinez, Michael Norton
Abbott, Abbott Park, IL

Corresponding author: Michael Norton - Abbott, 200 Abbott Park Road, Building AP30-3, Abbott Park, IL 60064

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Background

- The number of women infected with HIV has increased over the last two decades with recent World Health Organization (WHO) estimates that women comprise 50% of the HIV-infected population
- Data on efficacy, safety, and tolerability of antiretrovirals (ARVs) in women are limited
- In an FDA meta-analysis, women comprised 21% of overall participants in Phase II-IV HIV studies from 2000-06
- LPV/r has demonstrated safety and efficacy in ARV-naïve and experienced subjects in clinical trials
- In most guidelines, LPV/r is the preferred protease inhibitor in pregnancy and a choice for women of childbearing age

Study Objective

- This meta-analysis provides information regarding the efficacy, safety and tolerability of LPV/r in women as compared with men

Methods

Inclusion Criteria of Trials for Meta-analysis

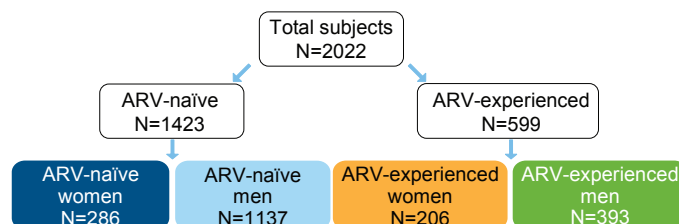
- Subjects:
 - HIV-1 infected adults*
 - ARV-naïve or ARV-experienced
 - Received standard of care ARV regimen (3 ARVs)
 - Received approved LPV/r dosage
- Prospective, randomized clinical trial from Abbott database
- Clinical trial data through 48 weeks available:
 - Proportion of subjects with HIV RNA <50 copies/mL
 - Changes in CD4⁺ T-cell count from baseline
 - Treatment-related adverse events and laboratory abnormalities

Studies That Met Criteria

- Antiretroviral-naïve: M97-720, M98-863, M99-056, M02-418, M05-730, M10-336
- Antiretroviral-experienced: M06-802

*Pregnant women were excluded from the analysis.

Figure 1. Subjects That Met Meta-analysis Criteria



Statistical Analyses

- Comparisons were made between ARV-naïve women and men and between ARV-experienced women and men using one-way ANOVA for continuous variables and Fisher's exact test for categorical variables

Results

Table 1. Baseline Demographics and HIV Disease Characteristics

Variable	ARV-naïve women N=286	ARV-naïve men N=1137	ARV-experienced women N=206	ARV-experienced men N=393
Age (years) Mean ± SD	39.2 ± 11.13	38.2 ± 9.64	38.7 ± 8.31	41.6 ± 9.08 [†]
Race				
White, n (%)	138 (48.3)	869 (76.4)*	78 (37.9)	230 (58.5)*
Black	128 (44.8)	205 (18.0)	97 (47.1)	111 (28.2)
Other	20 (7.0)	63 (5.5)	31 (15.0)	52 (13.3)
Ethnicity				
Hispanic/Latino	36 (12.6)	118 (10.4)	74 (35.9)	129 (32.8)
Non-Hispanic/Latino	250 (87.4)	1019 (89.6)	132 (64.1)	264 (67.2)
BL HIV-1 RNA, log ₁₀ copies/mL				
Mean ± SD	4.8 ± 0.77	4.9 ± 0.71 [†]	4.2 ± 0.80	4.3 ± 0.82
<100,000 copies/mL	172 (60.1)	580 (51.0)*	175 (85.0)	332 (84.5)
≥100,000 copies/mL	114 (39.9)	557 (49.0)	31 (15.0)	61 (15.5)
BL CD4 ⁺ T-cell/mm ³	(N=285)	(N=1136)	(N=189)	(N=365)
Mean ± SD	218 ± 148.2	255 ± 187.9 [†]	259 ± 165.9	251 ± 175.2
≥200	152 (53.3)	650 (57.2)	104 (55.0)	193 (52.9)
<200	133 (46.7)	486 (42.8)	85 (45.0)	172 (47.1)
<50	42 (14.7)	174 (15.3)	11 (5.8)	46 (12.6)*

[†], *Statistically significantly different compared to women (P<0.05) based on one-way ANOVA and Fisher's exact test, respectively. Black and Other combined for analyses of race.

- Baseline demographics and HIV disease characteristics were compared between ARV-naïve women and men and ARV-experienced women and men (Table 1)
- For ARV-naïve subjects, a greater proportion of the male subjects were white and a greater proportion of female subjects had baseline plasma HIV-1 levels <100,000 copies/mL; male subjects had higher mean baseline plasma HIV-1 RNA levels and mean CD4⁺ T-cell counts
- For ARV-experienced subjects, greater proportions of the male subjects were white and had baseline CD4⁺ T-cell counts <50 cells/mm³

Results

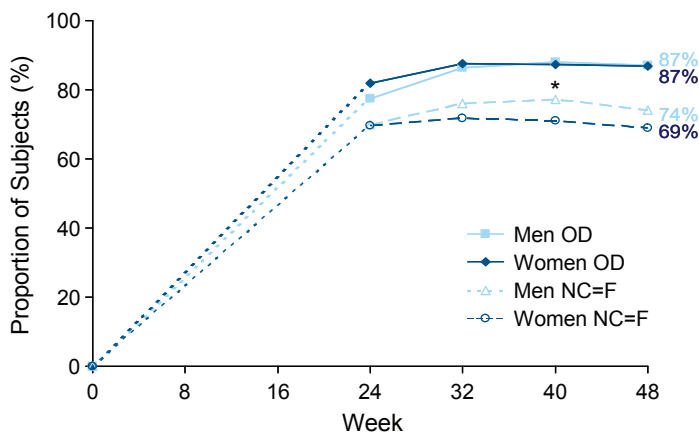
Table 2. Subject Disposition at Week 48

Variable	ARV-naïve women N=286	ARV-naïve men N=1137	ARV-experienced women N=206	ARV-experienced men N=393
Subject discontinued, n (%)				
Any reason	62 (21.7)	175 (15.4)*	49 (23.8)	86 (21.9)
Lost to follow-up	21 (7.3)	37 (3.3)*	10 (4.9)	30 (7.6)
Adverse event/HIV event	17 (5.9)	52 (4.6)	16 (7.8)	20 (5.1)
Withdrew consent	10 (3.5)	37 (3.3)	4 (1.9)	12 (3.1)
Nonadherence	8 (2.8)	29 (2.6)	13 (6.3)	17 (4.3)
Virologic failure	2 (0.7)	11 (1.0)	7 (3.4)	15 (3.8)
Death	1 (0.3)	8 (0.7)	3 (1.5)	2 (0.5)
Other	10 (3.5)	36 (3.2)	2 (1.0)	8 (2.0)

*Statistically significantly different compared to women ($P < 0.05$) based on Fisher's exact test.

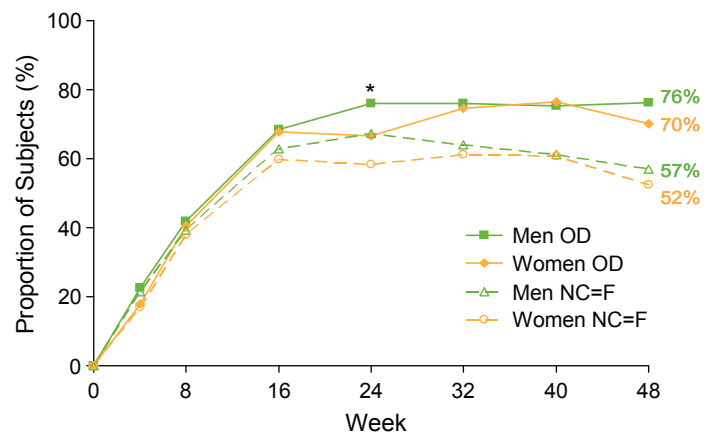
- The number of subjects that discontinued and the reasons for discontinuation are listed in Table 2
- For the ARV-naïve subjects, greater proportions of the female subjects discontinued for any reason and for the reason of loss to follow-up
- For the ARV-experienced subjects, there were no significant differences in the proportion of subjects that discontinued or in the specific reasons for discontinuation
- For both ARV-naïve and ARV-experienced subjects, regimens containing LPV/r were well tolerated by both genders as indicated by the low incidence of discontinuation due to adverse events/HIV events

Figure 2A. Proportion of ARV-naïve Subjects with HIV-1 RNA <50 Copies/mL through Week 48 by Gender (ITT NC=F and OD)



* $P < 0.05$ women vs. men comparison based on Fisher's exact test, NC=F.

Figure 2B. Proportion of ARV-experienced Subjects with HIV-1 RNA <50 Copies/mL through Week 48 by Gender (ITT NC=F and OD)

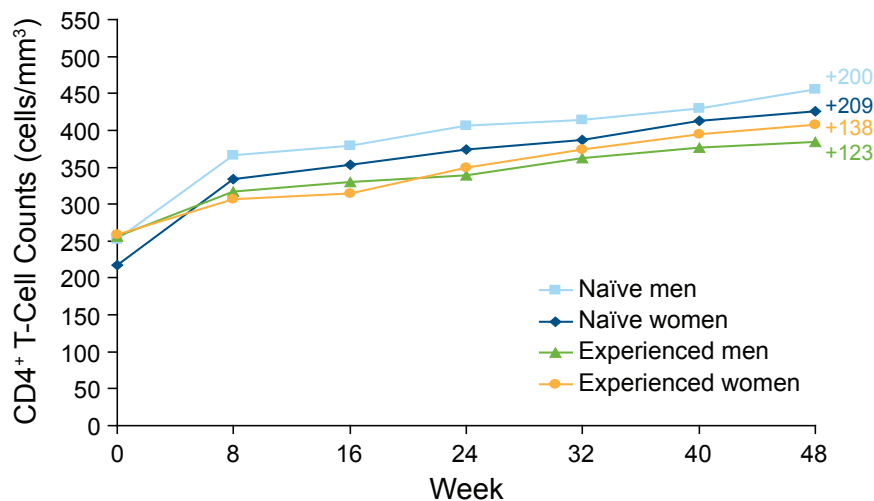


* $P < 0.05$ women vs. men comparison based on Fisher's exact test, NC=F and OD.

- At week 48 using the observed data analysis (OD), 87% of ARV-naïve men and 87% of ARV-naïve women ($P > 0.100$) were responders (plasma HIV-1 RNA <50 copies/mL) (Figure 2A). Using the non-completer equals failure analysis (NC=F), 74% of ARV-naïve men and 69% of ARV-naïve women were responders ($P > 0.05$) (Figure 2A)
- At week 48 using OD analysis, 76% of ARV-experienced men and 70% of ARV-experienced women ($P > 0.100$) were responders (Figure 2B). Using the NC=F analysis, 57% of ARV-experienced men and 52% of ARV-experienced women were responders ($P > 0.100$) (Figure 2B)
- For both ARV-naïve subjects and ARV-experienced subjects, the proportions of subjects that were responders were generally similar between men and women using the NC=F or the OD analyses

Results

Figure 3. CD4⁺ T-cell Counts Throughout 48 Weeks of Treatment with LPV/r in ARV-naïve and ARV-experienced Subjects



- The mean change from baseline in CD4⁺ T-cell counts at 48 weeks was similar between genders for ARV-naïve subjects (men=+200 cells/mm³, women=+209 cells/mm³) and ARV-experienced subjects (men=+123 cells/mm³, women=+138 cells/mm³)

Differences between women and men in mean change from baseline were tested using one-way ANOVA.

Table 3. Moderate-Severe Adverse Events Possibly Related to LPV/r with ≥ 2.0% Incidence in Any Group

Variable	ARV-naïve women N=286	ARV-naïve men N=1137	ARV-experienced women N=206	ARV-experienced men N=393
Any adverse event, n (%)	98 (34.3)	397 (34.9)	58 (28.2)	100 (25.4)
Diarrhea	34 (11.9)	182 (16.0)	26 (12.6)	49 (12.5)
Nausea	28 (9.8)	72 (6.3)	13 (6.3)	17 (4.3)
Vomiting	19 (6.6)	27 (2.4)*	6 (2.9)	8 (2.0)
Dyspepsia	6 (2.1)	8 (0.7)*	2 (1.0)	2 (0.5)
Upper abdominal pain	1 (0.3)	8 (0.7)	5 (2.4)	3 (0.8)
Fatigue	5 (1.7)	29 (2.6)	0	0
Headache	3 (1.0)	24 (2.1)	0	1 (0.3)

*Statistically significantly different compared to women ($P < 0.05$) based on Fisher's exact test.

- Similar proportions of ARV-naïve women and men experienced a moderate/severe treatment-related adverse event; however, greater proportions of women reported vomiting and dyspepsia
- There were no statistically significant differences in the incidences of moderate/severe treatment-related adverse events between ARV-experienced men and women

Table 4. Potentially Clinically Significant Laboratory Abnormalities with ≥2.0% Incidence in Any Group

Variable	ARV-naïve women N=284	ARV-naïve men N=1132	ARV-experienced women N=204	ARV-experienced men N=384
SGPT/ALT > 5X ULN, n (%)	5 (1.8)	30 (2.7)	2 (1.0)	10 (2.6)
SGOT/AST > 5X ULN	8 (2.8)	28 (2.5)	4 (2.0)	9 (2.3)
CPK > 10X ULN	0/19	0/85	0	11 (2.9)*
Cholesterol > 300mg/dL (7.8mmol/L)	19 (6.7)	64 (5.7)	19 (9.3)	22 (5.7)
Triglycerides > 750mg/dL (8.475mmol/L)	4 (1.4)	81/1131 (7.2)*	4 (2.0)	29 (7.6)*
Serum amylase > 2X ULN	6/124 (4.8)	18/535 (3.4)	11 (5.4)	13 (3.4)
Lipase > 2X ULN	3/163 (1.8)	29/606 (4.8)	3 (1.5)	12 (3.1)

Note that for each variable, only subjects with at least one post-baseline value were included in the analysis.

*Statistically significantly different compared to women ($P < 0.05$) based on Fisher's exact test.

- The incidence of potentially significant laboratory abnormalities was generally similar between genders. However, ARV-naïve men compared to women had a higher incidence of elevated triglyceride levels (> 750mg/dL) and ARV-experienced men compared to women had higher incidences of elevated CPK (>10X ULN) and elevated triglyceride levels

Results

Table 5. Lipid Changes From Baseline to Week 48

	ARV-naïve women N=214*	ARV-naïve men N=953†	ARV-experienced women N=159	ARV-experienced men N=305
TC:HDL ratio				
Mean BL	3.98	4.49#	3.94	4.27#
Mean change at Wk 48	-0.19	-0.12	+0.35	+0.49
Median change at Wk 48	+0.11	+0.07	+0.28	+0.29
LDL:HDL ratio				
Mean BL	2.47	2.79#	2.38	2.52
Mean change at Wk 48	-0.29	-0.30	+0.17	+0.06
Median change at Wk 48	-0.10	-0.18	+0.11	+0.04
TC mmol/L (mg/dL)				
Mean BL	4.27 (164)	4.07 (157)#	4.66 (179)	4.46 (172)#
Mean change at Wk 48	+0.94 (36)	+0.96 (37)	+0.39 (15)	+0.45 (17)
Median change at Wk 48	+0.80 (31)	+0.88 (34)	+0.36 (14)	+0.39 (15)
TG mmol/L (mg/dL)				
Mean BL	1.48 (131)	1.79 (159)#	1.54 (136)	1.92 (170)#
Mean change at Wk 48	+0.41 (37)	+0.98 (87)#	+0.40 (36)	+0.80 (71)#
Median change at Wk 48	+0.34 (30)	+0.64 (57)	+0.29 (26)	+0.54 (48)
HDL mmol/L (mg/dL)				
Mean BL	1.22 (47)	0.98 (38)#	1.26 (49)	1.10 (43)#
Mean change at Wk 48	+0.20 (8)	+0.18 (7)	-0.01 (0.2)	+0.01 (0.3)
Median change at Wk 48	+0.18 (7)	+0.16 (6)	+0.00 (0)	+0.02 (0.8)

Note that for each variable, only subjects with both baseline and week 48 values were included in the analysis.

*For ARV-naïve women, N=149 for TC:HDL ratio, LDL:HDL ratio, and HDL.

†For ARV-naïve men, N=617 for TC:HDL ratio and LDL:HDL ratio, and N=618 for HDL.

#Statistically significantly different compared to women ($P<0.05$) based on one-way ANOVA.

- Mean levels of lipids were compared at baseline and mean changes from baseline were compared at week 48. These data were not shown as part of the oral presentation, but were used as back-up slides
- Compared with ARV-naïve women, ARV-naïve men had higher mean baseline levels of total cholesterol:high-density lipoprotein (TC:HDL) ratio, low-density lipoprotein (LDL):HDL ratio, TC, triglycerides (TG), and HDL
- Compared with ARV-experienced women, ARV-experienced men had higher mean baseline levels of TC:HDL ratio, TC, TG, and HDL
- For both the ARV-naïve and ARV-experienced groups, men had a higher TG mean change from baseline at Week 48 compared to women

Conclusions

- This meta-analysis of 7 randomized clinical trials of 492 women and 1530 men on LPV/r-containing regimens, both ARV-naïve and experienced, revealed no substantial overall gender differences regarding efficacy, safety and tolerability
- Additional data from this meta-analysis are being evaluated for future presentations

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Disclosures

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