P197 Safety, Tolerability, and Efficacy of Lopinavir/ritonavir (LPV/r) in HIV-Infected Women: Results of a Meta-Analysis of 7 Prospective, Randomized Clinical Trials (RCTs) Through 48 Weeks

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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

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

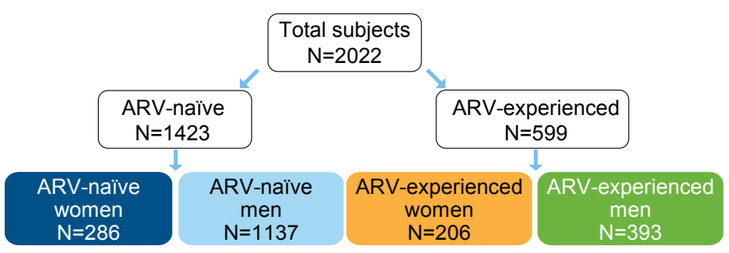
- Subjects:
  - HIV-1 infected adults*
  - ARV-naïve or ARV-experienced
  - Received standard of care ARV regimen (3 ARVs)
  - Received approved LPV/r dosage
- Prospective, randomized clinical trial from Abbott database
- Clinical trial data through 48 weeks available:
  - Proportion of subjects with 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-naive 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/mm³	(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, cont.

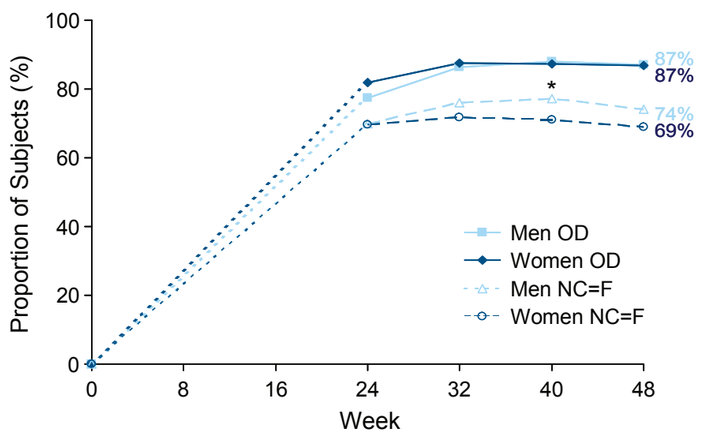
Table 2. Subject Disposition at Week 48

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.

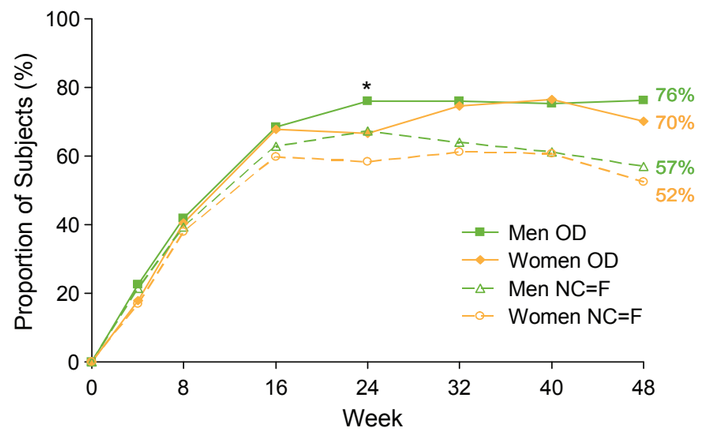
- The number of subjects that discontinued and the reasons for discontinuation are listed in Table 2
- For the ARV-naïve subjects, greater proportions of the female subjects discontinued for any reason and for the reason of loss to follow-up
- For the ARV-experienced subjects, there were no significant 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.

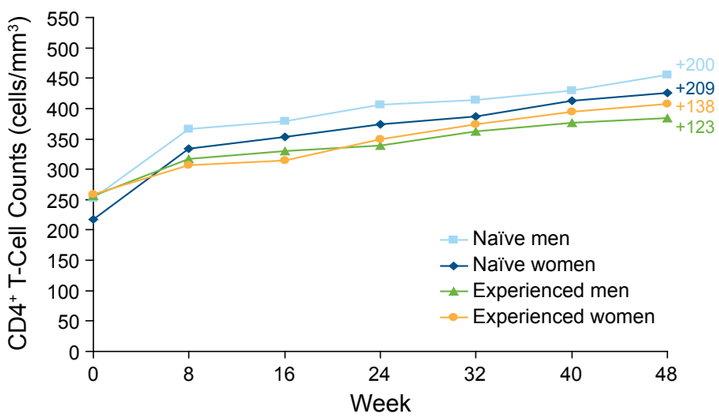
Figure 2B. Proportion of ARV-Experienced Subjects with HIV-1 RNA <50 Copies/mL through Week 48 by Gender (ITT NC=F and OD)



*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% or 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

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



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

- 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)

Results, cont.

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 > 300 mg/dL (7.8 mmol/L)	19 (6.7)	64 (5.7)	19 (9.3)	22 (5.7)
Triglycerides > 750 mg/dL (8.475 mmol/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 (>750 mg/dL) and ARV-experienced men compared to women had higher incidences of elevated CPK (>10X ULN) and elevated triglyceride levels.

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
- Compared with ARV-naive women, ARV-naïve men had higher mean baseline levels of total cholesterol:high-density lipoprotein (TC:HDL) ratio, low-density lipoprotein (LDL):HDL ratio, and triglycerides (TG), and lower TC and HDL
- Compared with ARV-experienced women, ARV-experienced men had higher mean baseline levels of TC:HDL ratio and TG, and lower TC and HDL
- For both the ARV-naive 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

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