

Comparative Assessment of Changes in Blood Pressure (BP) Through 48-weeks from a Phase 3 Clinical Trial of Lopinavir/ritonavir (LPV/r)

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Background

Hypertension

- Hypertension is a well-characterized risk factor for vascular mortality in the general population,^{1,2,3} and an assessment of blood pressure is likely to be an important component of cardiovascular risk in HIV-infected patients.

Hypertension in HIV-infected Subjects

- A study of 95 HIV-infected subjects described increases in systolic and diastolic blood pressure over 48 weeks of combination antiretroviral therapy,⁴ although an observational cohort study consisting of over 1500 subjects identified no meaningful difference in the prevalence of hypertension between HIV-infected individuals receiving combination antiretroviral therapy and HIV-negative individuals.⁵
- The Data Collection of Adverse Events of Anti-HIV Drugs (D:A:D) Study Group evaluated the predictors of hypertension and changes in blood pressure in their cohort of over 17,000 HIV-infected patients.⁶ They noted that in HIV-infected patients with a median of 2.3 years of follow-up, the following risk factors were significantly associated with the development of hypertension: male gender, higher BMI, older age, and higher blood pressure at baseline. Neither cumulative exposure to nucleoside reverse transcriptase inhibitors nor cumulative exposure to protease inhibitors was associated with development of hypertension.
- Finally, in a recently published analysis from an observational cohort study including 444 HIV-infected patients starting their first antiretroviral regimen, including 47 lopinavir/ritonavir (LPV/r)-treated patients, a higher risk of blood pressure changes for LPV/r-treated patients was described, compared to patients treated with other antiretroviral medications such as efavirenz (EFV, n=159) or nelfinavir (NFV, n=112).⁷

In the current analysis, we compare LPV/r to EFV and NFV with respect to effects on blood pressure in two prospective, randomized clinical trials.

Methods

Retrospective evaluation of two randomized, prospective, controlled clinical trials in antiretroviral-naïve subjects:

- Placebo-controlled: LPV/r + stavudine (d4T) + lamivudine (3TC) versus NFV + d4T + 3TC (Study 863);
- Open label: LPV/r + coformulated zidovudine + 3TC (AZT/3TC) versus EFV + AZT/3TC (Study 613). This study used a de-intensification design in which subjects randomized to LPV/r + AZT/3TC discontinued AZT/3TC if they had plasma HIV-1 RNA <50 copies/mL at three consecutive visits. The earliest subjects could have discontinued AZT/3TC was at week 24. Subjects randomized to EFV + AZT/3TC remained on triple combination therapy throughout the study.

Blood pressure was assessed every 4–8 weeks in Study 863 and every 4 weeks in Study 613.

Mean changes from baseline to each study visit in systolic and diastolic blood pressure (SBP and DBP) were evaluated through 48 weeks for each study. Two methods were used:

- Method 1: Observed cases: mean change from baseline to each visit including only those subjects with measurements at both baseline and the visit of interest
- Method 2: Average value: mean change from baseline to the average of all post-baseline measurements.⁷

Systolic and diastolic blood pressure measurements were used to categorize subjects at baseline and week 48 based on the JNC classification of blood pressure for adults:

- Normal (systolic <120 and diastolic <80 mmHg)
- Pre-hypertension (systolic 120–139 or diastolic 80–89 mmHg)
- Stage 1 hypertension (systolic 140–159 or diastolic 90–99 mmHg)
- Stage 2 hypertension (systolic ≥160 or diastolic ≥100 mmHg)

Adverse events of hypertension were summarized through 48 weeks in each study.

Results

Study 863 (LPV/r + d4T + 3TC vs. NFV + d4T + 3TC)

643 subjects with post-baseline blood pressure measurements were followed for up to 48 weeks (80% completed 48 weeks of treatment). Demographic characteristics were similar between treatment groups: 20% female, 57% white, mean age of 38.

Mean change in BP using Method 1: Observed cases.

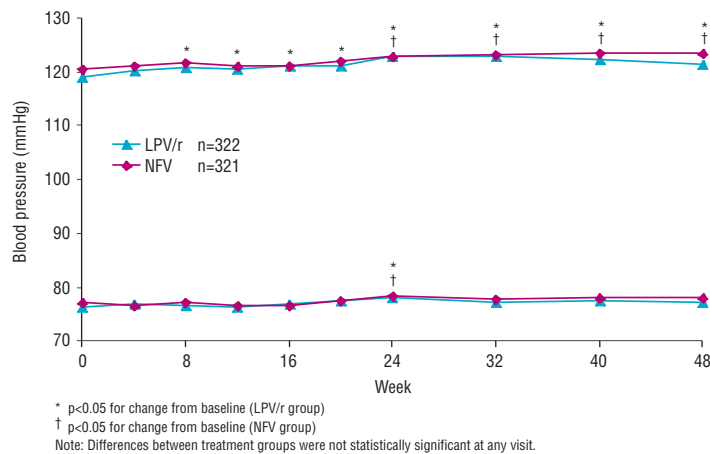
- Baseline mean SBP values were 118.9 (LPV/r) and 120.5 (NFV) mmHg. Statistically significant mean increases from baseline to week 48 were observed in each treatment group (LPV/r: +2.8 mmHg; NFV: +2.4 mmHg). No significant differences between treatment groups were observed for changes from baseline in mean SBP at any visit.
- Baseline mean DBP values were 76.4 (LPV/r) and 77.0 (NFV) mmHg. Mean changes in DBP from baseline to week 48 were not statistically significant, and no significant differences between treatment groups were observed at any visit.

Mean change in BP using Method 2: Average post-baseline value.

- Statistically significant mean increases from baseline to week 48 in SBP were observed in each treatment group (LPV/r: +1.9 mmHg, $p < 0.001$; NFV: +1.2 mmHg, $p = 0.032$); the difference between treatment groups was not statistically significant ($p = 0.35$, one-way ANOVA).
- No significant changes from baseline in average DBP were observed either within treatment groups (mean changes of < 0.4 mmHg in both groups, $p > 0.3$) or between treatment groups ($p = 0.67$ for the difference between groups, one-way ANOVA).

Mean SBP and DBP values over time are displayed in Figure 1.

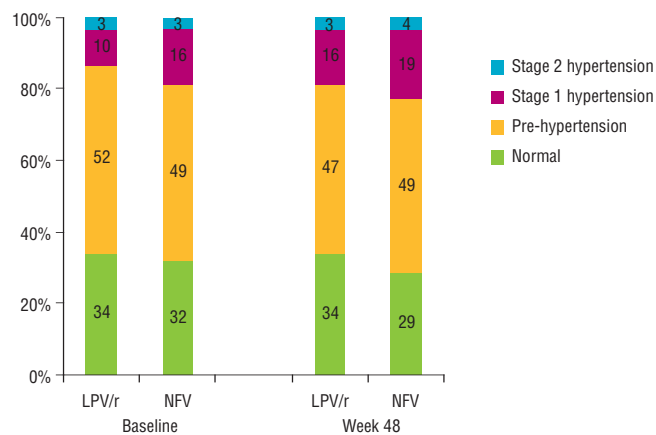
Figure 1. Mean BP Measurements Over Time in Study 863



JNC classification of blood pressure

- Small, statistically non-significant changes between the baseline and final visit were observed based on JNC criteria ($p = 0.17$, Bowker's test of symmetry, Figure 2).
- Differences between treatment groups were not statistically significant either at baseline or week 48 ($p \geq 0.2$, chi-square test).

Figure 2. Classification by JNC 7 Criteria in Study 863



Treatment-emergent adverse events of hypertension were reported for 3% of LPV/r-treated subjects and 5% of NFV-treated subjects ($p = 0.30$) through 48 weeks.

Study 613 (LPV/r + AZT/3TC vs. EFV + AZT/3TC)

Since subjects randomized to LPV/r were allowed to discontinue AZT/3TC as early as week 24 if they met specific plasma HIV-1 RNA criteria (3 consecutive plasma HIV-1 RNA <50 copies/mL), an evaluation of blood pressure was performed both at week 24 (when LPV/r + AZT/3TC was being used by all subjects in the LPV/r arm) and at week 48 (when 95% of subjects in the LPV/r arm were receiving LPV/r monotherapy).

155 subjects with post-baseline blood pressure measurements were included in the analysis (88% completed 48 weeks of treatment). Demographic characteristics were comparable between treatment groups: 21% female, 65% white, mean age of 38.

Mean change in BP using Method 1: Observed cases

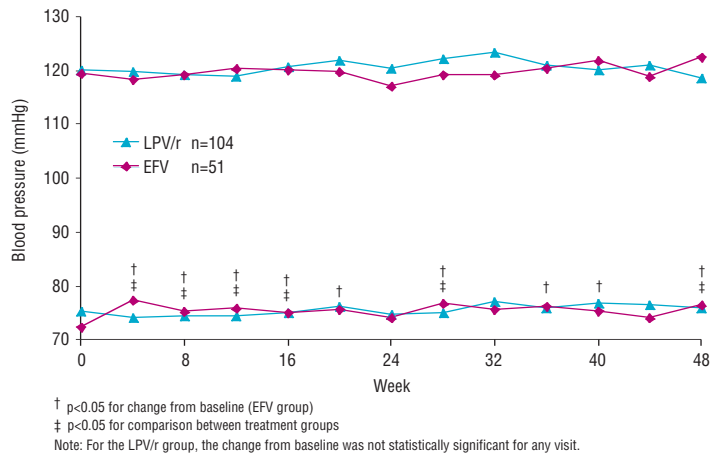
- Baseline mean SBP values were 120.1 (LPV/r) and 118.9 (EFV) mmHg. No statistically significant mean increases from baseline to week 24 or week 48 were observed in either treatment group. A marginally statistically significant difference between treatment groups was observed at week 48 ($p=0.053$), corresponding to a nonsignificant decrease in the LPV/r group (-2.3 mmHg) and a nonsignificant increase in the EFV group (+3.5 mmHg).
- Baseline mean DBP values were 75.6 (LPV/r) and 73.5 (EFV) mmHg. Mean changes in DBP from baseline to week 24 were not statistically significant in either treatment group (LPV/r: -1.2 mmHg; EFV: +1.5 mmHg). Mean changes in DBP from baseline to week 48 were statistically significant for the EFV group (+4.7 mmHg, $p=0.006$) but not the LPV/r group (+0.6 mmHg, $p=0.59$). The difference between treatment groups at week 48 was statistically significant ($p=0.04$).

Mean change in BP using Method 2: Average post-baseline value

- No statistically significant mean increases from baseline to week 48 in SBP were observed in either treatment group (LPV/r: +0.2 mmHg, $p=0.83$; EFV: +0.8 mmHg, $p=0.57$); the difference between treatment groups was also not statistically significant ($p=0.73$, one-way ANOVA).
- A statistically significant difference between treatment groups was observed in average DBP change ($p=0.035$, one-way ANOVA): the LPV/r group demonstrated no mean change from baseline (+0.05 mmHg, $p=0.95$), while the EFV group demonstrated a mean increase of 2.9 mmHg ($p=0.009$) from baseline.

Mean SBP and DBP values over time are displayed in Figure 3.

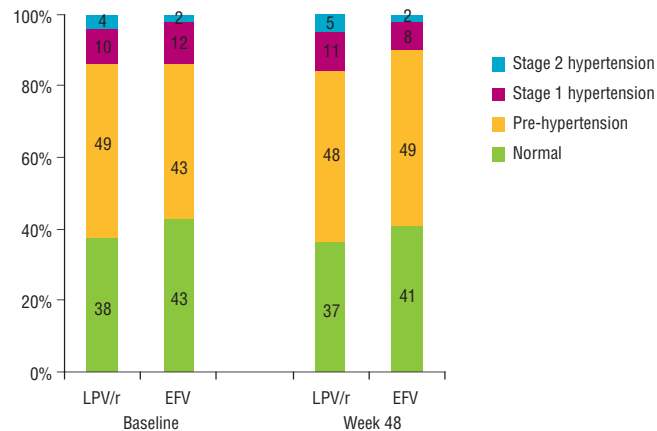
Figure 3. Mean BP Measurements Over Time in Study 613



JNC classification of blood pressure

- No meaningful changes between the baseline and final visit were observed based on JNC criteria ($p > 0.5$, Bowker's test of symmetry, Figure 4).
- Differences between treatment groups were not statistically significant either at baseline or week 48 ($p \geq 0.2$, chi-square test).

Figure 4. Classification by JNC 7 Criteria in Study 613



Treatment-emergent adverse events of hypertension were reported for 4% of LPV/r-treated subjects and 0% of EFV-treated subjects ($p=0.30$) through 48 weeks.

The four subjects receiving LPV/r with events of hypertension included two subjects with transient events (<4 weeks) which resolved without anti-hypertensive medications, one subject who had a baseline blood pressure of 160/100, and one subject whose blood pressure varied between 110/80 and 153/91 mmHg. This subject's last blood pressure measurement was 141/86 mmHg, and he did not receive anti-hypertensive medications at any time during the study.

Summary

Based on this retrospective evaluation of two randomized, prospective, controlled clinical trials of LPV/r versus either NFV (Study 863) or EFV (Study 613):

- We noted no differences between LPV/r- and NFV-treated subjects with respect to mean changes in systolic blood pressure, diastolic blood pressure or the development of adverse events of hypertension. No clinically significant shifts were observed between baseline and week 48 visit based on JNC criteria. These findings do not support a differential effect of LPV/r on blood pressure compared to NFV.
- We noted no increase in systolic BP in subjects treated for up to 48 weeks with either LPV/r or EFV. Diastolic BP increased statistically significantly in the EFV group but not the LPV/r group. No clinically significant shifts were observed between baseline and final visit based on JNC criteria. These findings do not support a deleterious effect of LPV/r on blood pressure, compared to EFV.
- A statistically significant increase in SBP was noted for both treatment groups in study 863, in which subjects received d4T+3TC, while no significant increase was observed in either group in study 613, in which subjects received AZT/3TC (or no NRTIs, after deintensification). While cross-study comparisons should be interpreted cautiously, one possible explanation is that choice of the nucleoside backbone may influence SBP changes; further investigation of the effects of d4T vs. AZT on SBP changes may be of interest.
- Our data appear to contradict the findings of Crane and colleagues which suggested differential effects on blood pressure when using LPV/r compared to either EFV or NFV. Using endpoints similar to those used in the prior analysis (method 2), we identified no differences between LPV/r and NFV in our randomized controlled studies that evaluated considerably more patients on LPV/r. In contrast, there was a difference in DBP for the comparison of LPV/r and EFV with EFV exhibiting a significant mean increase in DBP compared to the LPV/r group at week 48.

Conclusions

- Our results indicate that treatment of antiretroviral-naïve subjects with a LPV/r-based regimen does not adversely impact blood pressure compared to nelfinavir or efavirenz-based regimens.

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Acknowledgements

We gratefully acknowledge all the investigators, study site coordinators, and participants from Study 863 and Study 613. We also acknowledge all Abbott team members of Study 863 and Study 613, especially Marion DeHaan for her help with this presentation.