



# No Change in Glucose Tolerance with Lopinavir/ritonavir (LPV/r) + ZDV/3TC Induction Followed by LPV/r Monotherapy Through 96 Weeks

BA da Silva, M King, M DeHaan, K Wikstrom, K Niemi, GJ Hanna  
Abbott, Abbott Park, IL, USA

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## Background

Impairment of glucose tolerance (IGT) is an important intermediate step in the development of diabetes mellitus (DM). Both IGT and DM are associated with increased risk of cardiovascular disease and mortality.<sup>1,2</sup>

The prevalence of DM in HIV-infected individuals receiving combination antiretroviral therapy appears to be higher (14% vs. 5%) than in HIV-negative individuals, or HIV-positive individuals not receiving combination antiretroviral therapy (7%) in the Multicenter AIDS Cohort Study.<sup>3</sup>

Using invasive hyperinsulinemic euglycemic clamp methods, insulin resistance increases with lopinavir/ritonavir when evaluated for one, 5 or 10 days,<sup>4,5,6</sup> but not when evaluated for 4 weeks or longer.<sup>7,8</sup>

Although the hyperinsulinemic euglycemic clamp method may be useful in assessing insulin resistance over relatively short periods of time, determination of the potential long-term impact of antiretroviral therapy can be practically assessed with less invasive techniques. The measurement of fasting glucose and insulin along with the Homeostasis Assessment Model (HOMA) has been demonstrated to be an appropriate method to assess changes in insulin resistance over time in individuals.<sup>9</sup>

Adiponectin is an adipocyte-derived hormone that is associated with increased insulin sensitivity.<sup>10</sup> Increases in adiponectin have previously been demonstrated with protease inhibitors including LPV/r,<sup>11</sup> but not with efavirenz (EFV).

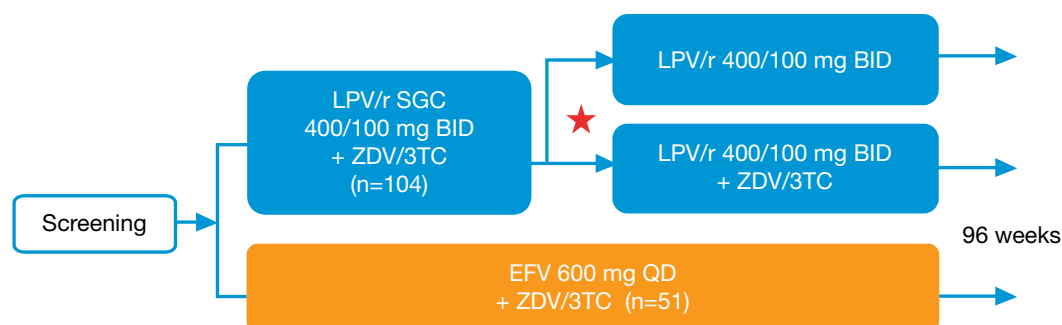
## Objective

Evaluate glucose tolerance using HOMA index and OGTT through 96 weeks in HIV-positive subjects receiving a LPV/r- or EFV-based antiretroviral regimen.

## Methods

This assessment was performed in Study M03-613, in which 155 antiretroviral-naïve HIV-positive subjects were randomized to LPV/r+ZDV/3TC induction for 24-48 weeks followed by LPV/r monotherapy if 3 consecutive HIV-RNA values <50 copies/mL were achieved (n=104), or to EFV+ZDV/3TC for the entire study period (n=51) in a 96-week study.

Figure 1. Study M03-613 Design



### Inclusion criteria

- Antiretroviral-naïve
- HIV-1 RNA >1000 copies/mL
- Any CD4 count
- No resistance to study drugs

★ Deintensification starting at Week 24 if 3 consecutive monthly HIV-1 RNA levels <50 copies/mL

## Methods continued

92/104 subjects randomized to LPV/r + ZDV/3TC achieved 3 consecutive HIV-1 RNA levels <50 copies/mL, deintensified to LPV/r monotherapy, and were followed for a median of 68 weeks on monotherapy.

Follow-up included 2-hour OGTT (75 grams) at Baseline and Week 96, and fasting glucose (Roche/Hitachi Modular System), insulin (DPC Immulite 2000 Analyzer) with calculated HOMA at Baseline and Weeks 4, 12, 36, 48, 72 and 96.

HOMA was calculated using the equation:<sup>12</sup>

$$\frac{\text{fasting glucose} \times \text{fasting insulin}}{22.5}$$

IGT was defined using the American Diabetes Association (ADA) definition of a fasting plasma glucose level  $\geq 100$  mg/dl (5.6 mmol/L) but  $\leq 126$  mg/dl (7.0 mmol/L) OR 2-hour values in the oral glucose tolerance test (OGTT) of  $\geq 140$  mg/dl (7.8 mmol/L) but  $\leq 200$  mg/dl (11.1 mmol/L). DM was defined as a fasting plasma glucose of  $\geq 126$  mg/dl (7.0 mmol/L) or a 2-hour value in the OGTT of  $\geq 200$  mg/dl (11.1 mmol/L).<sup>13</sup>

Adiponectin was measured at Baseline and Weeks 24, 48, 72 and 96.

Differences between treatment groups in baseline characteristics were assessed using a one-way analysis of variance (ANOVA) or Fisher's exact test. Differences between treatment groups in mean changes from Baseline to each visit for laboratory parameters were analyzed using a one-way ANOVA. Results of 2-hour OGTT were assessed by calculating the area under the curve (AUC) for glucose and insulin for each subject, and comparing the mean change in AUC from Baseline to Week 96 between groups using a one-way ANOVA.

## Results

### Baseline Demographics

Baseline demographics for study subjects are shown in Table 1.

**Table 1. Baseline Characteristics**

| Variable                                      | Lopinavir/ritonavir<br>(n=104) <sup>†</sup> | Efavirenz<br>(n=51) <sup>†</sup> | p-value |
|---|---|----------------------------------|---------|
| Gender, number (percent)                      |   |                                  |         |
| Male  | 84 (81%)                                    | 38 (75%)                         | ns      |
| Age, years                                    |   |                                  |         |
| Mean $\pm$ SD                                 | 40.2 $\pm$ 10.6                             | 35.0 $\pm$ 9.1                   | 0.003   |
| Race/ethnicity*                               |   |                                  |         |
| White   | 68 (65%)                                    | 32 (63%)                         |         |
| Black   | 29 (28%)                                    | 17 (33%)                         |         |
| Hispanic                                      | 6 (6%)                                      | 8 (16%)                          |         |
| Other   | 7 (7%)                                      | 2 (4%)                           | ns      |
| HIV-1 RNA level (log <sub>10</sub> copies/mL) |   |                                  |         |
| Mean $\pm$ SD                                 | 4.99 $\pm$ 0.63                             | 4.77 $\pm$ 0.65                  | 0.04    |
| CD4+ T-cell count (cells/mm <sup>3</sup> )    |   |                                  |         |
| Mean $\pm$ SD                                 | 228 $\pm$ 160                               | 250 $\pm$ 167                    | ns      |
| Weight (kg)                                   | 76.5 $\pm$ 14.6                             | 77.9 $\pm$ 15.5                  | 0.01    |

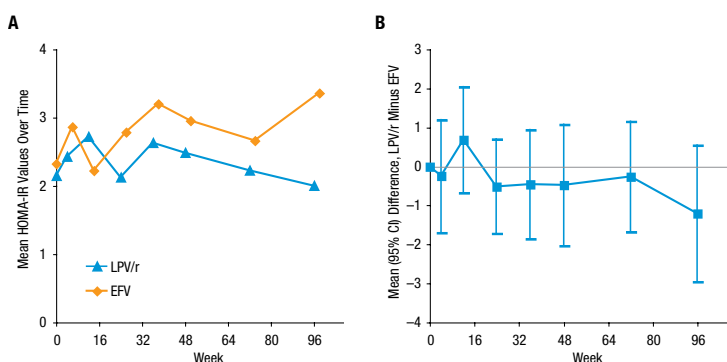
\* Subjects may have indicated more than one race/ethnicity category

<sup>†</sup> Subjects completing 96 weeks, n=74 for lopinavir/ritonavir, n=32 for efavirenz

## Fasting Glucose, Insulin and HOMA Index

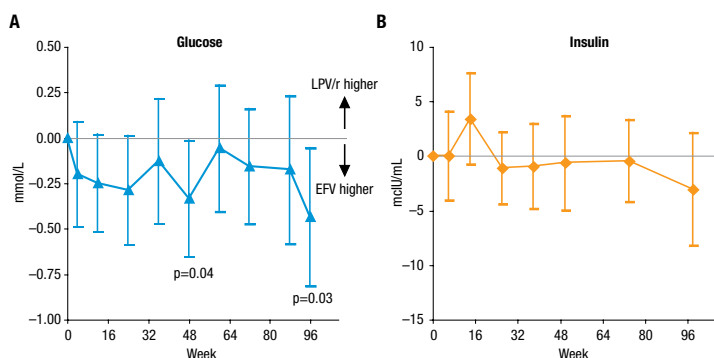
No statistically significant differences were observed between groups in the mean change from baseline to each visit in HOMA index values. Among subjects completing 96 weeks of treatment, mean Baseline HOMA index values were 2.23 (LPV/r) and 2.39 (EFV); mean Week 96 values were 2.00 (LPV/r) and 3.36 (EFV). Within-group changes from Baseline were not statistically significant. Figure 2a illustrates the mean HOMA index values through 96 weeks for both LPV/r and EFV groups. Figure 2b shows the difference in HOMA index between LPV/r and EFV treatment groups.

**Figure 2. (A) Mean HOMA-IR Values Over Time (B) Difference in HOMA-IR Between LPV/r and EFV Groups**



- Mean increases in glucose were generally larger among EFV-treated subjects; increases were statistically significantly greater in EFV-treated vs. LPV/r-treated subjects ( $p < 0.05$ ) at Week 48 and Week 96 (Figure 3a). Among subjects completing 96 weeks of treatment, mean Baseline and Week 96 values (mmol/L) were 4.95 and 5.01 for LPV/r-treated and 4.76 and 5.26 for EFV-treated subjects, respectively.
- No statistically significant differences between groups were observed in the mean change from Baseline in fasting insulin values (Figure 3b). Mean insulin values were generally stable over time.

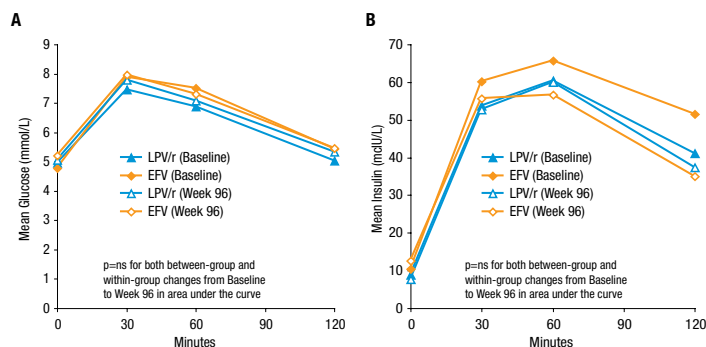
**Figure 3. Difference in Mean Change from Baseline (LPV/r Minus EFV) for Fasting Glucose (A) and Insulin (B)**



## Oral Glucose Tolerance Testing

- 66 (LPV/r) and 34 (EFV) subjects had OGTT at both Baseline and Week 96.
- No changes were observed in mean glucose and insulin area under the curve (AUC) during OGTT between Baseline and Week 96 in either treatment group ( $p > 0.11$ ) or across treatment groups ( $p > 0.28$ ).
- Figure 4 shows mean glucose and insulin over 2 hours following 75 grams of glucose for Baseline and Week 96. No statistically significant changes from Baseline were observed between or within treatment groups.

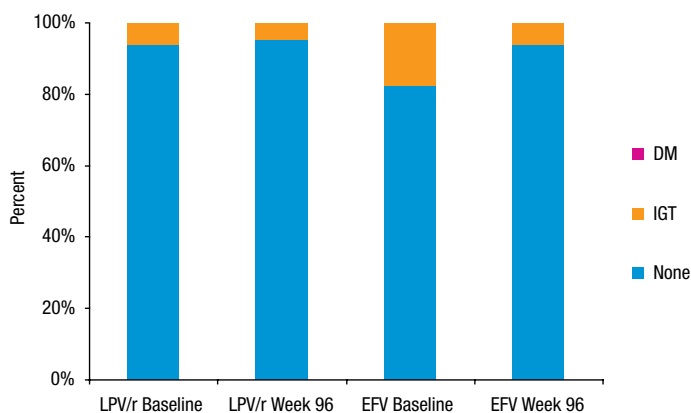
**Figure 4. Mean Glucose (A) and Insulin (B) Values During 2-Hour OGTT**



## Prevalence of Impaired Glucose Tolerance and Diabetes Mellitus

- No subject demonstrated DM by OGTT at Baseline or Week 96. Among subjects completing 96 weeks, no evidence of an increase in IGT was observed (Figure 5).

**Figure 5. Prevalence of Impaired Glucose Tolerance and Diabetes Mellitus**



## Adiponectin Levels Over Time

- Statistically significant mean increases from Baseline to Week 96 in adiponectin were observed for both treatment groups. Among subjects completing 96 weeks of treatment, mean adiponectin increased from 7.3 to 11.5 mcg/mL ( $p < 0.001$ ) in the LPV/r group and from 6.6 to 8.3 mcg/mL ( $p = 0.013$ ) in the EFV group ( $p = 0.004$  for the difference between groups).

## Discussion

- The results from this study demonstrate that there are no changes in glucose tolerance when either a LPV/r- or EFV-based regimen are used to treat HIV infection for 96 weeks. The only difference between regimens was a significantly higher mean increase in fasting glucose for the EFV-based regimen.
- These results are in contrast to short-term data with LPV/r using the hyperinsulinemic clamp method in healthy volunteers for up to 10 days, but are consistent with data from healthy volunteers using LPV/r for 4 weeks, and data from HIV-positive patients through 48 weeks.<sup>6,7,14</sup>
- This suggests that, while there may be short-term effects on glucose tolerance with LPV/r administration, when used for longer duration (4 weeks or greater), no measurable impact on glucose tolerance is apparent.
- In this study, LPV/r monotherapy was used in the majority of subjects in the LPV/r arm from Weeks 24 through 96. Based on the comparison of HOMA assessment at Weeks 24 and 96 in the LPV/r arm, discontinuation of NRTIs (zidovudine/lamivudine) did not impact fasting glucose, fasting insulin or HOMA index.
- The increase in adiponectin levels with long-term LPV/r therapy noted in this study may be a factor in overcoming any short-term insulin resistance reported in short-term insulin clamp studies.

## Conclusions

- Treatment with a LPV/r-based induction-maintenance regimen through 96 weeks was not associated with changes in glucose tolerance assessed by OGTT or HOMA.
- Prevalence of IGT remained low through 96 weeks of LPV/r-based therapy. Findings were generally similar in the EFV group except for a statistically significant mean increase in fasting glucose through 96 weeks.

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