# THE BRAVO STUDY

## *Raltegravir without a Protease Inhibitor is Highly Efficacious in Heavily pre-treated Individuals*

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## Background

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- There are limited treatment options for patients with multi-drug class resistance. Raltegravir (RAL), the first integrase inhibitor, was approved based on the BENCHMRK studies.
  - n=699 with triple class resistance were randomized to receive an optimized antiretroviral background regimen (OBR) or OBR plus raltegravir. Response rates: 62% on raltegravir achieved HIV RNA levels < 50 copies/mL at week 16, compared to 35% on placebo
- In the BENCHMRK studies, 94% of subjects received a protease inhibitor as part of the OBR. Thus, there are limited data assessing the activity of raltegravir with a regimen not including a protease inhibitor in treatment experienced patients.
- We assessed the efficacy of raltegravir used with or without a protease inhibitor in treatment experienced patients.

## Methods

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- We reviewed records of all subjects who received raltegravir as part of Merck's Expanded Access Program with at least 12 weeks of data at participating sites
- Eligibility: limited treatment options due to resistance or intolerance to multiple ARV, resistance to ≥ 1 drug in each of 3 ART classes, viremic on current ART
- The cohort on RAL with a PI was compared to those on RAL without a PI
- Primary endpoint: Proportion achieving VL < 400 at week 12
  - Secondary endpoint : Proportion achieving VL < 75 at week 12
- Baseline differences were controlled for using multiple logistic regression. A forward stepwise procedure with maximum likelihood estimation of the regression coefficients was used. The likelihood ratio criterion determined the significance of individual factors in the regression model.

## Methods - 2

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- Data: Demographics, duration of raltegravir, concomitant ART, number of ARTs used for the first time with RAL, baseline genotypic resistance test, baseline and subsequent HIV RNA and CD4 cell counts
- Genotypic susceptibility scores (GSS) of the background regimen determined from the most recent genotypic resistance test prior to initiation of RAL. The Stanford HIV database was used to calculate the GSS score using these scores:
  - 0: intermediate or high-level resistance
  - 0.5: low-level resistance
  - 1.0: susceptible / potential low-level resistance
- Inclusion of maraviroc or new use enfuvirtide in the regimen assigned a score of 1.0
- Low-dose ritonavir (< 600 mg per day) not considered a separate drug.
- Each site received IRB approval

## Baseline Characteristics

| | PI (N = 332) | Non-PI (N = 110) | P value |
|---|---|---|---|
| **Age, yrs. (mean)** | 47 | 47 | 0.45 |
| **Male** | 295 (89%) | 92 (84%) | 0.15 |
| **Race** | | | |
| White | 197 (59%) | 52 (47%) | 0.23 |
| African-American | 82 (25%) | 34 (31%) | |
| Hispanic | 43 (13%) | 21 (19%) | |
| Other | 10 3%) | 3 (3%) | |
| **Baseline HIV VL, log** | 5.06 | 5.01 | 0.58 |
| **Number ARVs*** | 4.1 | 3.8 | 0.0004 |
| **Number New ARVs#** | 2.5 | 2.3 | 0.014 |
| **GSS^** | 1.8 | 1.7 | 0.43 |

*Antiretrovirals
^ Genotypic susceptibility score
# first use

## ART in Background Regimen (1)

| | Total (n) | PI based regimen (n) | Non-PI based regimen (n) |
|---|---|---|---|
| **Protease inhibitors** | 332 | 332 | 0 |
| Darunavir | 288 | 288 | 0 |
| Tipranavir | 15 | 15 | 0 |
| Atazanavir | 14 | 14 | 0 |
| Lopinavir | 10 | 10 | 0 |
| Fosamprenavir | 8 | 8 | 0 |
| Other PI* | 6 | 6 | 0 |
| **NNRTIs^** | 209 | 130 | 79 |
| Etravirine | 193 | 120 | 73 |
| Efavirenz | 8 | 5 | 3 |
| Nevirapine | 7 | 4 | 3 |

## ART in Background Regimen (2)

| NRTIs | Total (n) | PI based regimen (n) | Non-PI based regimen (n) |
|---|---|---|---|
| Tenofovir | 259 | 185 | 74 |
| Emtricitabine | 230 | 164 | 66 |
| Lamivudine | 104 | 82 | 22 |
| Abacavir | 55 | 41 | 14 |
| Zidovudine | 30 | 18 | 12 |
| Stavudine | 17 | 13 | 4 |
| Didanosine | 13 | 11 | 2 |
| **Other#** | 83 | 50 | 33 |
| Enfuvirtide | 52 | 33 | 19 |
| Maraviroc | 30 | 16 | 14 |

*Other PIs were nelfinavir, full dose ritonavir, saquinavir, indinavir
^ 1 patient received delavirdine in the PI group.
#1 patient received vicriviroc

## Results

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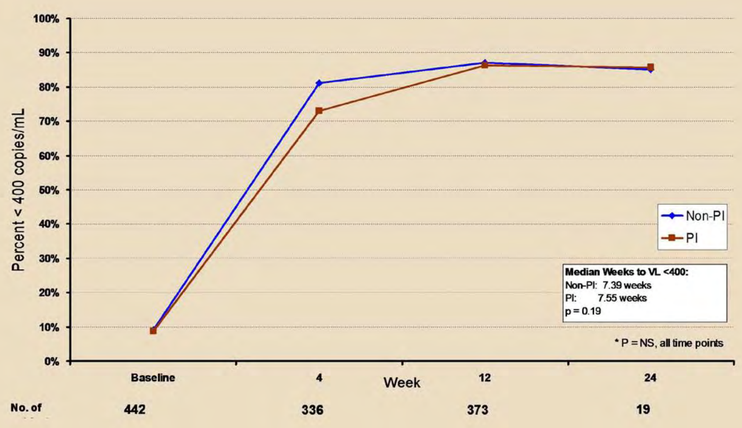
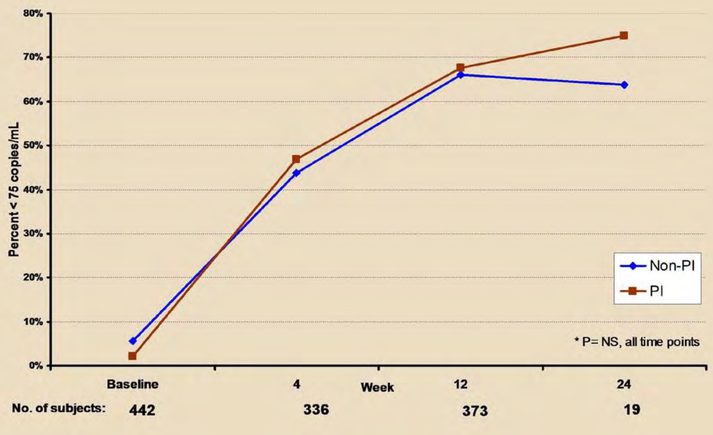
- There were no significant differences between groups except in total number and new ARVs in the regimens (higher in PI group).
- The proportion of patients with VL < 400 and < 75 copies/mL at 12 weeks was nearly identical in the two groups
- Median time to VL < 400: 7.4 (non-PI) *vs.* 7.5 (PI) wks, p = 0.19
- Virologic rebound to ≥ 75 copies/mL occurred in 4 of 110 no-PI patients (3.6%) compared to 13 of 332 PI patients (3.9%).
- Differences in the proportion of patients achieving VL < 400 and VL < 75 at week 12, controlling for GSS, number of ARV's and new ARV's were analyzed using logistic regression
- GSS was a significant predictor (p =0.039) of VL < 400 and < 75 at week 12, whereas treatment group (PI *vs.* no-PI) and number of ARVs was *not* predictive of virologic success

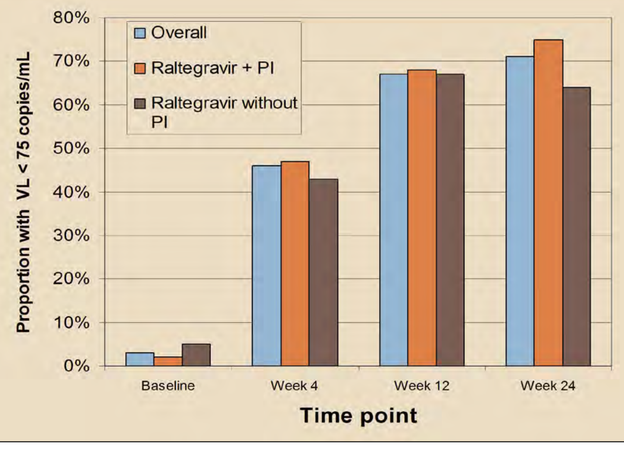
## VL < 400 copies/mL




## VL < 75 copies/mL*




## Percent with VL < 75 copies/mL




## CD4 Cell Counts


## Conclusions

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- In treatment experienced patients with limited treatment options, raltegravir containing regimens result in a high rate of virologic response
- When raltegravir was used with a background regimen without a protease inhibitor, there were no significant differences in efficacy compared to outcomes when used with a protease inhibitor
- GSS predicted efficacy of the regimen containing raltegravir, confirming the importance of combining raltegravir with other active antiretrovirals
- These short term cohort data support further study of raltegravir with novel combinations in this population