# Similar Declines in HIV-1 RNA (Viral load, VL) from Baseline (BL) to 96 Weeks Observed in Subjects Randomized to ABC/3TC or TDF/FTC each with Lopinavir/Ritonavir (LPV/r) in the HEAT Trial (EPZ104057)

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## Abstract

**Background:** **HEAT, a randomized, double-blind, placebo-matched, study in ART-naïves demonstrated the non-inferiority of ABC/3TC (N=343) to TDF/FTC (N=345) with QD LPV/r at 48 and 96 weeks. To further assess antiviral potency of the two triple combinations, we analyzed HIV-1 RNA levels throughout 96 weeks.**

**Methods:** **A longitudinal piecewise linear model was fitted to estimate the rate of VL changes in 4 different phases: initial (BL through week 2), early (weeks 2-12), intermediate (weeks 12-24), and long-term (weeks 24-96 or withdrawal). BL VL was included as a continuous covariate. Similar models also analyzed BL VL as categorical data (copies/mL): 1) <100,000 or ≥100,000, and 2) <100,000, 100,000 to <250,000, 250,000 to <500,000, or ≥500,000.**

**Results:** **No differences in HIV-1 RNA changes were seen between treatment arms in all 4 phases (p>0.05), hence treatment was not included in the final model. BL VL levels significantly impacted the rate of HIV-1 RNA decline in all 4 phases in both arms. In the initial phase, each unit increase in BL VL ($log_{10}$ copies/mL) increased the rate of VL decline by 0.083 $log_{10}$ copies/mL/week. From week 2 onwards, the estimated rate of VL change varied with the BL VL. HIV-1 RNA decline was exhibited by subjects with BL VL above 2.9 $log_{10}$ copies/mL from weeks 2-12, for subjects with BL VL above 4.2 $log_{10}$ copies/mL from Weeks 12-24, and for subjects with BL VL above 5 $log_{10}$ copies/mL from Week 24 onwards. The categorical models showed significant rates of HIV-1 RNA decline in one or more of the BL VL categories from BL through Week 24, but not from Week 24 onwards.**

**Conclusion:** **These analyses did not reveal any differences in the HIV-1 RNA profiles between the treatment arms over 96 weeks. The comparable viral dynamics and long-term profiles suggest similar intrinsic potency of the two triple regimens studied.**

## Introduction

- **The HEAT study was a multicenter, randomized, double-blind, placebo-matched study in ART naïve subjects that demonstrated the non-inferiority of ABC/3TC to TDF/FTC each in combination with LPV/r QD at Week 48 and was subsequently confirmed at Week 96.**
- **Longitudinal modeling of the viral load (VL) levels over the duration of the study (baseline (BL) to Week 96) was studied in association with baseline VL and treatment.**

## Methods

- **A piecewise linear longitudinal model was used to model the VL levels over the duration of the study (BL to Week 96).**
- **The model estimated the VL changes in 4 different phases: initial (BL through Week 2), early (Week 2 through Week 12), intermediate (Week 12 through Week 24), and long term (Week 24 onwards).**
- **Baseline viral load (continuous) and treatment were studied as independent variables in the model.**
- **Similar models were also studied with baseline viral load included as categorical variable:**
  - **BL VL <100,000 copies/mL or ≥100,000 copies/mL;**
  - **BL VL <100,000 copies/mL; 100,000 to <250,000 copies/mL; 250,000 to <500,000 copies/mL; or ≥500,000 copies/mL.**
- **The models were implemented using the Proc Mixed procedure in SAS 9.1.**

## Results

- **A total of 688 subjects were enrolled and exposed to at least one dose of study drug (Intent-to-Treat-Exposed (ITT-E) Population) in the HEAT Study. Baseline demographics and characteristics of these subjects are shown in Table 1.**

### Table 1. Baseline Demographics and Characteristics of the HEAT Study, ITT-E Population

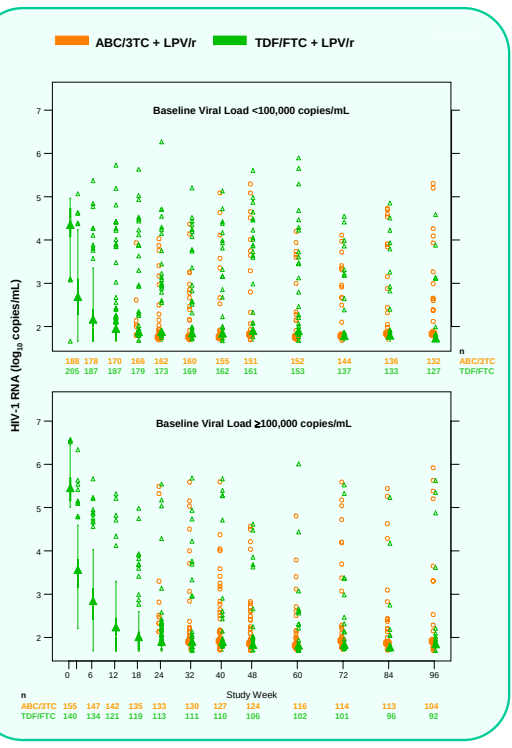
| | ABC/3TC + LPV/r (N=343) | TDF/FTC + LPV/r (N=345) |
|---|---|---|
| **Age (y), mean (SD)** | 38 (9.8) | 39 (9.6) |
| **Sex, n(%)** | | |
| **Male** | 287 (84%) | 276 (80%) |
| **Female** | 56 (16%) | 69 (20%) |
| **Race, n (%)** | | |
| **African American** | 122 (36%) | 124 (36%) |
| **Asian** | 6 (2%) | 9 (3%) |
| **White** | 177 (52%) | 174 (50%) |
| **Mixed Race** | 2 (<1%) | 1 (<1%) |
| **Other** | 36 (10%) | 37 (11%) |
| **Baseline VL, median (range)** | 4.90 (2.66 to 6.99) | 4.84 (1.69 to 6.57) |
| **Baseline VL category, n (%)** | | |
| **<100,000 copies/mL** | 188 (55%) | 205 (59%) |
| **100,000 to 250,000 copies/mL** | 68 (20%) | 75 (22%) |
| **250,000 to <500,000 copies/mL** | 37 (11%) | 33 (10%) |
| **≥500,000 copies/mL** | 50 (15%) | 32 (9%) |

- **The median baseline viral load was comparable between the two treatment arms, 4.9 $log_{10}$ copies/mL in the ABC/3TC arm versus 4.84 $log_{10}$ copies/mL in the TDF/FTC arm. The proportion of subjects with baseline viral load ≥100,000 $log_{10}$ copies/mL was somewhat higher in the ABC/3TC arm (45%) than in the TDF/FTC arm (41%).**
- **The box plot of the viral load responses by treatment arm and baseline viral load categories (<100,000 copies/mL versus ≥100,000 copies/mL) are displayed in Figure 1. As evident from the graphs, the viral load responses were comparable between the treatment arms and viral suppression (<50 copies/mL) was achieved by both arms in majority of the subjects in both baseline viral load categories.**
- **A longitudinal model was fitted to the viral load data from baseline through Week 96. Treatment was not found to be a significant predictor for viral load levels in the modeling process and was not included in the final model. In contrast, baseline viral load level significantly affected the rate of viral load changes in all 4 phases of the study (BL to Week 2, Week 2 to Week 12, Week 12 to Week 24, and Week 24 or after).**
- **The final fitted model included baseline viral load (continuous covariate), the 4 linear phases, and their interactions, all statistically significant with p<0.01. Table 2 summarizes the parameter estimates from the final model.**

### Acknowledgements

**The authors would like to thank all subjects who participated in the HEAT study and to the study investigators, site personnel, and GSK study teams for their invaluable contributions.**

### Figure 1. Box Plot of Viral Load Levels by Treatment Arm and Baseline Viral Load Categories

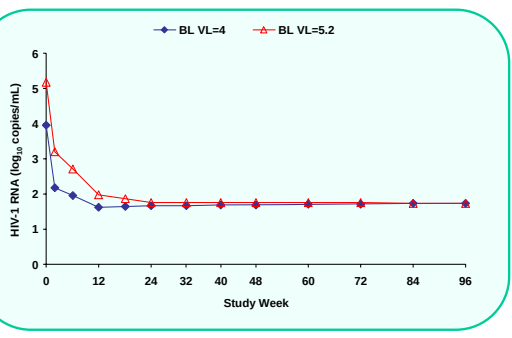



### Table 2. Parameter Estimates of Final Longitudinal Model for Viral Load

| Phase (Weeks) | Effect | Estimate (SE) | p-value |
|---|---|---|---|
| | Intercept | -0.068 (0.079) | 0.392 |
| Initial (0 to 2) | Time | -0.556 (0.048) | <0.0001 |
| | BL VL | 1.008 (0.0157) | <0.0001 |
| | Time × BL VL | -0.083 (0.010) | <0.0001 |
| Early (2 to 12) | Time | 0.159 (0.012) | <0.0001 |
| | Time × BL VL | -0.054 (0.002) | <0.0001 |
| Intermediate (12 to 24) | Time | 0.080 (0.009) | <0.0001 |
| | Time × BL VL | -0.019 (0.002) | <0.0001 |
| Long Term (≥24) | Time | 0.005 (0.002) | 0.002 |
| | Time × BL VL | -0.001 (0.0003) | 0.002 |

- **From baseline through Week 2, each unit increase in BL VL (in $log_{10}$ copies/mL) increases the rate of VL decline by 0.083 $log_{10}$ copies/mL/week. From Week 2 onwards, the estimated rate of VL change varies with the BL VL level. The VL decline was predicted for subjects with BL VL above 2.94 $log_{10}$ copies/mL/week from Week 2 to Week 12 and for subjects with BL VL above 4.2 $log_{10}$ copies/mL/week from Week 12 through Week 24; and for subjects with BL VL above 5 $log_{10}$ copies/mL/week after Week 24.**
- **Figure 2 shows the fitted final model for subjects with baseline viral load 4 $log_{10}$ copies/mL (blue line) and for subjects with baseline viral load 5.2 $log_{10}$ copies/mL (red line).**

### Figure 2. Final Longitudinal Model for Viral Load




- **Similar models were also analyzed with BL VL entered as categorical data. These models showed significant rates of HIV-1 RNA decline in one or more of the BL VL categories from BL through Week 24, but not from Week 24 onwards (results not shown).**

## Discussion

- **Rebounds in VL pose a challenge in modeling VL data and may not be adequately addressed in the linear model considered.**
  - **The current analysis attempted to address this by assuming heterogeneity in the covariance structure for the two responder status groups --- subjects who achieved and maintained a 2 $log_{10}$ copies/mL decline in VL from BL versus those who did not.**
- **The 4 phases of the VL changes were derived visually by examining the individual subject VL profiles and might not be the most optimal time points for model estimation; however, the longitudinal analysis results were consistent with those of the primary analysis.**
- **The current model does not account for the left censoring of the VL levels below the detection limit of 50 copies/mL.**
  - **A value of 49 copies/mL was used when the VL was <50 copies/mL in the analysis; however, it is unlikely that using a more sensitive assay would have shown different results.**
- **The current model does not handle informative dropouts, missing at random was assumed in the analysis.**
- **Nonetheless, these analyses further support previous analysis results that VL responses were comparable between the treatment arms.**

## Conclusions

- **These analyses did not reveal any differences in the HIV-1 RNA profiles between the treatment arms over 96 weeks.**
- **The comparable viral dynamics and long-term profiles suggest similar intrinsic potency of the two triple regimens studied.**