Differential Impact of Non-adherence on Week 96 Outcomes in the FTC/TDF Subset of Pooled ECHO and THRIVE Studies Comparing Rilpivirine (RPV) vs. Efavirenz (EFV) in Treatment-naïve, HIV-1 Infected Adults

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Background

- RPV demonstrated a high virologic response rate (84% vs. 82%; HIV-1 RNA <50 c/mL, TLOVR) and was non-inferior to EFV in ARV-naïve adults at Weeks 48 and 96 in ECHO & THRIVE¹
  
  - For both treatment groups, suboptimal adherence and higher baseline viral load were associated with lower responses¹,²

- The FTC/TDF subset from the pooled ECHO & THRIVE studies is the only direct comparative data for the components of the 2 available single-tablet regimens (STR) of FTC/RPV/TDF and EFV/FTC/TDF

2. Brochot A, et al. EACS 2011; Belgrade, Serbia. #PS12/7
Randomized, double-blind, double-dummy*, multicenter, 96-week study

**Study Design**

- **ECHO**
  - N=690 patients
  - ARV-naïve
  - HIV RNA ≥ 5,000 c/mL
  - No NNRTI RAMs
  - Sensitivity to the NRTIs

- **THRIVE**
  - N=678 patients

RPV 25mg QD + FTC/TDF QD (N=346) + EFV placebo QD

EFV 600mg QD + FTC/TDF QD (N=344) + RPV placebo QD

RPV 25mg QD + FTC/TDF QD** (N=204) + EFV placebo QD

EFV 600mg QD + FTC/TDF QD** (N=202) + RPV placebo QD

* Study design resulted in 3 pills multiple times per day based on meal requirements:
  - RPV or RPV placebo - with a meal, preferentially in am
  - EFV or EFV placebo - on empty stomach at bedtime

** Excludes subjects on
  - ZDV/3TC (N=204) or ABC/3TC (N=68)
Objectives & Methods

1. Compare baseline demographics of adherent vs. non-adherent subjects
   - Fisher’s exact test and Wilcoxon Rank-Sum test

2. Characterize the impact of adherence & baseline HIV-1 RNA (VL) on Wk 96 efficacy for RPV vs. EFV with FTC/TDF
   - Efficacy: VL <50 c/mL; ITT-TLOVR
   - Adherence categories: >95%, >90 to ≥95%, or ≤90%
   - Baseline VL categories: >100,000 or ≤100,000 c/mL

3. Evaluate predictors of Wk 48 virologic response
   - Patients who discontinued for reasons other than virologic failure (VF) were excluded for this analysis (non-VF censored)
   - Multivariate analysis: Demographics, disease characteristics, adherence, study drug exposure, ECHO vs. THRIVE
1. Modified Medication Adherence Self-Report Inventory (M-MASRI)
   - Patient self-reported adherence using visual analogue scale estimating % doses taken during past 30 days
   - Mean values used from Wk 4, 8, 12, 16 and then every 8 wks
   - Classified as adherent if >95% doses taken

2. Investigator-reported Adherence
   - Blinded to M-MASRI, thus based only on discussions with study subjects

3. Indirect Adherence Measure
   - Study drug concentration below limit of quantification at any time point
## Adherence Results at Week 96

<table>
<thead>
<tr>
<th>Adherence</th>
<th>RPV+FTC/TDF</th>
<th>EFV+FTC/TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td><em><em>M-MASRI</em> mean &gt;95%</em>*</td>
<td>98%</td>
<td>98%</td>
</tr>
<tr>
<td></td>
<td>87%</td>
<td>85%</td>
</tr>
<tr>
<td><strong>Investigator-reported mean &gt;95%</strong></td>
<td>99%</td>
<td>97%</td>
</tr>
<tr>
<td></td>
<td>95%</td>
<td>89%</td>
</tr>
<tr>
<td><strong>Any concentration always above limit of detection</strong></td>
<td>98%</td>
<td>96%</td>
</tr>
</tbody>
</table>

* 1027 of 1,096 (94%) FTC/TDF subjects had M-MASRI data
** 997 of 1,096 (91%) FTC/TDF subjects had limit of detection data
## Baseline Demographic & Disease Characteristics by M-MASRI Adherence Category

<table>
<thead>
<tr>
<th></th>
<th>Adherent (n=886)</th>
<th>Non-Adherent (n=141)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female, n (%)</strong></td>
<td>186 (21)</td>
<td>32 (23)</td>
</tr>
<tr>
<td><strong>Median age (range), years</strong></td>
<td>36 (18-74)</td>
<td>34 (19-78)</td>
</tr>
<tr>
<td><strong>Race, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White*</td>
<td>571 (64)</td>
<td>70 (50)</td>
</tr>
<tr>
<td>Black*</td>
<td>179 (20)</td>
<td>58 (41)</td>
</tr>
<tr>
<td>Asian</td>
<td>110 (12)</td>
<td>11 (8)</td>
</tr>
<tr>
<td><strong>Hispanic ethnicity, n (%)</strong></td>
<td>223 (25)</td>
<td>36 (26)</td>
</tr>
<tr>
<td><strong>Median VL (range), log_{10} c/mL</strong></td>
<td>5.0 (2.2-6.5)</td>
<td>5.0 (3.5-7.3)</td>
</tr>
<tr>
<td><strong>Baseline VL ≤ 100,000 c/mL, %</strong></td>
<td>452 (51)</td>
<td>61 (43)</td>
</tr>
<tr>
<td><strong>Median CD4 cell count (range), cells/mm^3</strong></td>
<td>257 (1-888)</td>
<td>253 (2-743)</td>
</tr>
<tr>
<td><strong>CDC Category C, %</strong></td>
<td>44 (5)</td>
<td>14 (10)</td>
</tr>
<tr>
<td>*<em>HBV/HCV Co-infection</em></td>
<td>62 (7)</td>
<td>18 (13)</td>
</tr>
</tbody>
</table>

*p<0.05
Virologic Response*: by Baseline VL at Week 96

- RPV+FTC/TDF was non-inferior to EFV+FTC/TDF at Week 96
- Baseline VL impacted both arms similarly; with lower responses at higher VL

![Chart showing virologic response by baseline viral load](chart.png)

Virologic Response (<50 c/mL)*

- Overall: 77% for RPV+FTC/TDF, 77% for EFV+FTC/TDF
- ≤ 100K: 83% for RPV+FTC/TDF, 81% for EFV+FTC/TDF
- >100K: 70% for RPV+FTC/TDF, 74% for EFV+FTC/TDF

*ITT TLOVR
Virologic Response*: Overall by Adherence (M-MASRI) at Week 96

- Overall, non-adherence was associated with lower response rates in both arms.
Virologic Response*: \( VL \leq 100K \) by Adherence (M-MASRI) at Week 96

- At low baseline VL, non-adherence was associated with lower response rates in both arms

Virologic Response (\(<50\) c/mL)*

Virologic Response (\(<50\) c/mL)* by Adherence (M-MASRI) at Week 96

- \( RLV+FTC/TDF (\leq 100K) \)
- \( EFV+FTC/TDF (\leq 100K) \)

Adherence Level

> 95% ≤ 95 to > 90% ≤ 90%
Virologic Response*: VL >100K by Adherence (M-MASRI) at Week 96

- At high baseline VL, EFV+FTC/TDF response was less impacted by non-adherence (79% adh. vs. 70% non-adh. ≤95%) compared to RPV+FTC/TDF (74% vs. 50%)

*ITT TLOVR
Virologic Response* through Week 96

![Graph showing virologic response over time with two treatment groups: RPV+FTC/TDF and EFV+FTC/TDF. The graph displays the percentage of responders (% [95% CI]) with a peak of 83% for RPV+FTC/TDF and 82% for EFV+FTC/TDF at Week 48.](image)

*ITT TLOVR

Jayaweera D, et al. IAPAC 2012; Miami, FL. #80074
Virologic Response* & Failures through Week 96

- Virologic Response (<50 c/mL)*
- Percentage

Virologic Failures
- Never suppressed
- Rebound

Year 1
- RPV: 11.5%
- EFV: 4.2%

Year 2
- RPV: 2.7%
- EFV: 2.6%

*ITT TLOVR
### Multivariate Analysis Results at Wk 48

- Week 48 non-VF censored analysis allows for analysis of virologic success and failures by removing non-VF failures (e.g. discontinuations due to adverse events)
- Drug exposure and adherence measures were correlated to each other

<table>
<thead>
<tr>
<th></th>
<th>RPV+FTC/TDF</th>
<th>EFV+FTC/TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study drug trough concentration</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Investigator-reported adherence</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Baseline VL</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Baseline CD4</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Demographics: age, weight, sex, race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study: ECHO vs. THRIVE</td>
<td></td>
<td></td>
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<tr>
<td>HBV/HCV coinfection</td>
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</tbody>
</table>

- Similar results seen when baseline CD4 and VL are treated as categorical data
- Similar results were obtained if any concentration below limit of quantification or self-reported (M-MASRI) were used
Conclusions

• Univariate and multivariate analyses confirm that virologic response to the STR components of RPV+FTC/TDF and EFV+FTC/TDF are impacted by baseline viral load, adherence, and study drug exposure.

• For high baseline VL (>100,000 c/mL), response to EFV+FTC/TDF was less impacted by non-adherence compared to RPV+FTC/TDF.

• Further research is warranted to assess the efficacy and adherence to actual STRs (not STR components) and the association with baseline VL.
  – Study 110 (STAR): FTC/RPV/TDF STR vs. EFV/FTC/TDF STR in ARV-naïve subjects stratified by baseline VL (>100,000 c/mL).
Pooled ECHO and THRIVE

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**ECHO**

**THRIVE**
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