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 & THRIVE[1]
  - For both treatment groups, suboptimal adherence and higher baseline viral load were associated with lower responses[1,2]

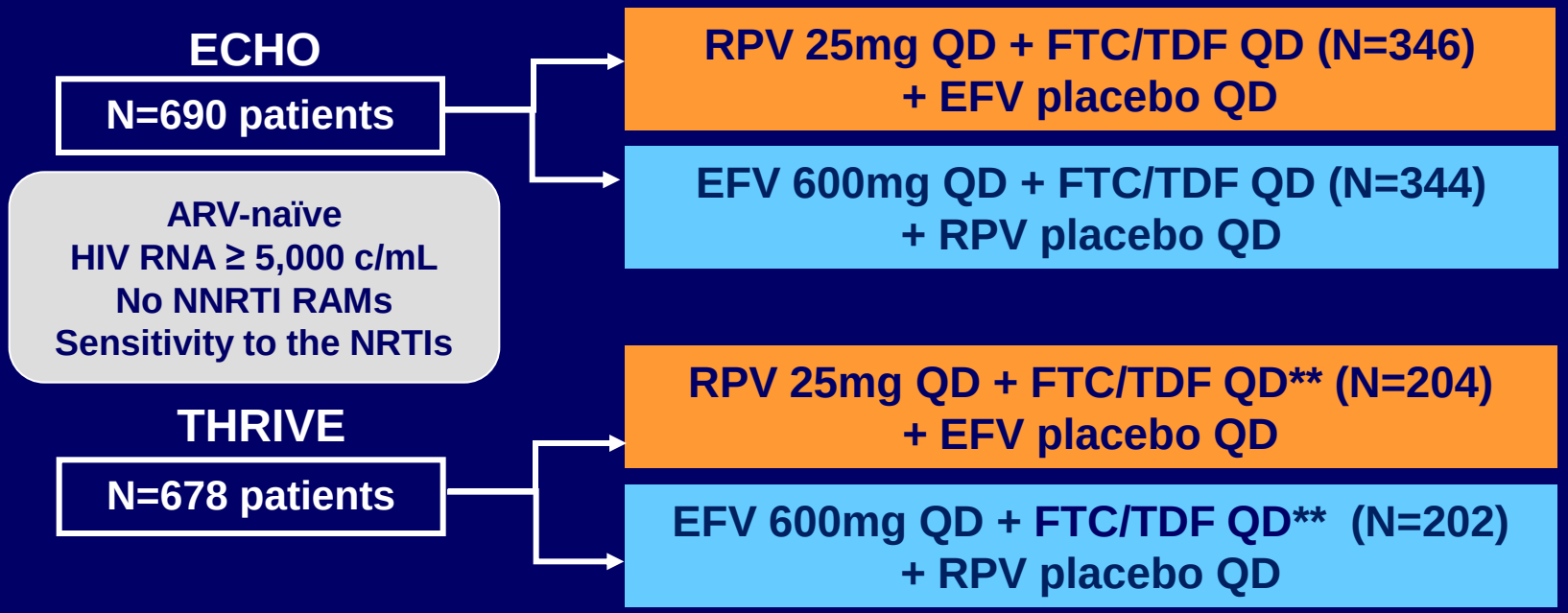
- The FTC/TDF subset from the pooled ECHO & THRIVE studies is the only direct comparative data for the components of the 2 available single-tablet regimens (STR) of FTC/RPV/TDF and EFV/FTC/TDF

1. Cohen C, et al. JAIDS 2012;60:33-42
2. Brochot A, et al. EACS 2011; Belgrade, Serbia. #PS12/7

Pooled ECHO and THRIVE: W96 FTC/TDF Dataset

Study Design

Randomized, double-blind, double-dummy*, multicenter, 96-week study



* 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)

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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

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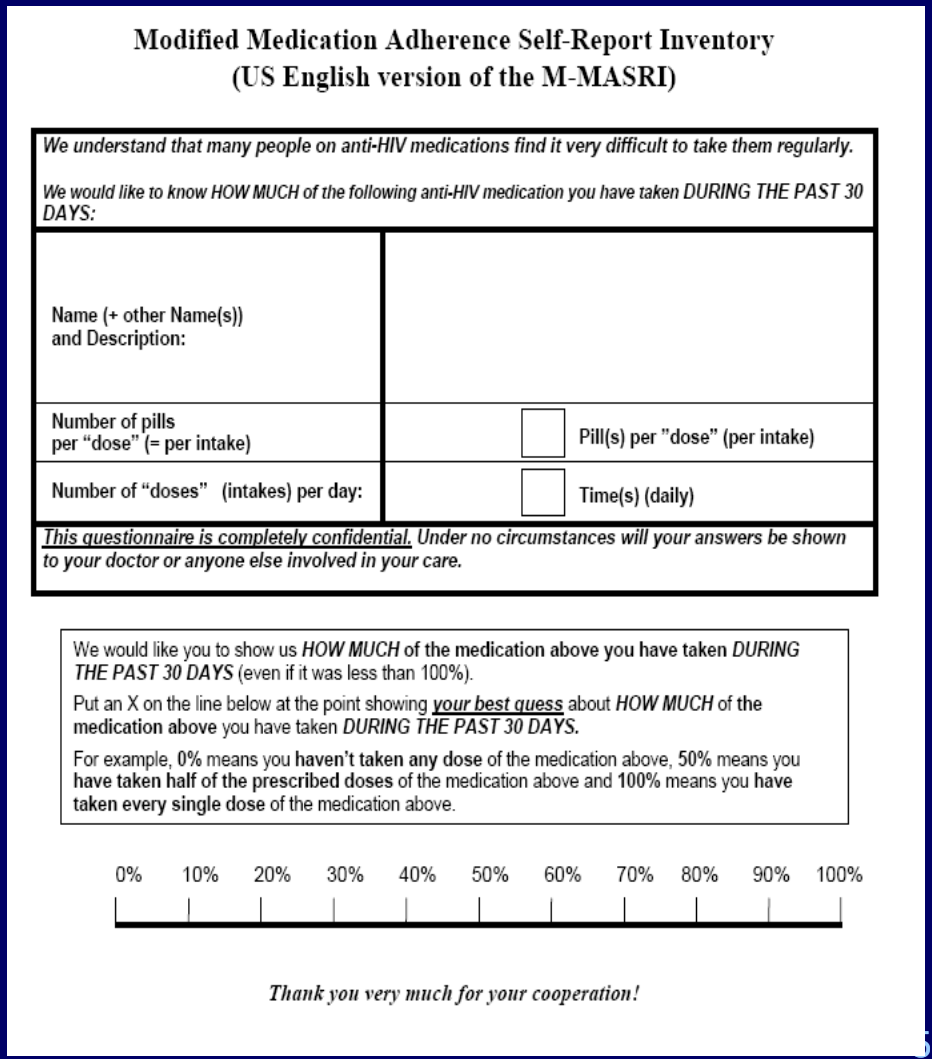
Adherence Measures

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



Modified Medication Adherence Self-Report Inventory
(US English version of the M-MASRI)

We understand that many people on anti-HIV medications find it very difficult to take them regularly.

We would like to know HOW MUCH of the following anti-HIV medication you have taken DURING THE PAST 30 DAYS:

Name (+ other Name(s)) and Description:	
Number of pills per "dose" (= per intake)	☐ Pill(s) per "dose" (per intake)
Number of "doses" (intakes) per day:	☐ Time(s) (daily)

This questionnaire is completely confidential. Under no circumstances will your answers be shown to your doctor or anyone else involved in your care.

We would like you to show us *HOW MUCH* of the **medication above you have taken** *DURING THE PAST 30 DAYS* (even if it was less than 100%).

Put an X on the line below at the point showing ***your best guess*** about *HOW MUCH* of the **medication above** you have taken *DURING THE PAST 30 DAYS.*

For example, **0%** means you **haven't taken any dose** of the medication above, **50%** means you **have taken half of the prescribed doses** of the medication above and **100%** means you **have taken every single dose** of the medication above.

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

Thank you very much for your cooperation!

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Adherence Results at Week 96

Adherence	RPV+FTC/TDF	EFV+FTC/TDF
M-MASRI*		
mean	98%	98%
>95%	87%	85%
Investigator-reported		
mean	99%	97%
>95%	95%	89%
Any concentration always above limit of detection**	98%	96%

* 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

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Baseline Demographic & Disease Characteristics by M-MASRI Adherence Category

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

*$p<0.05$

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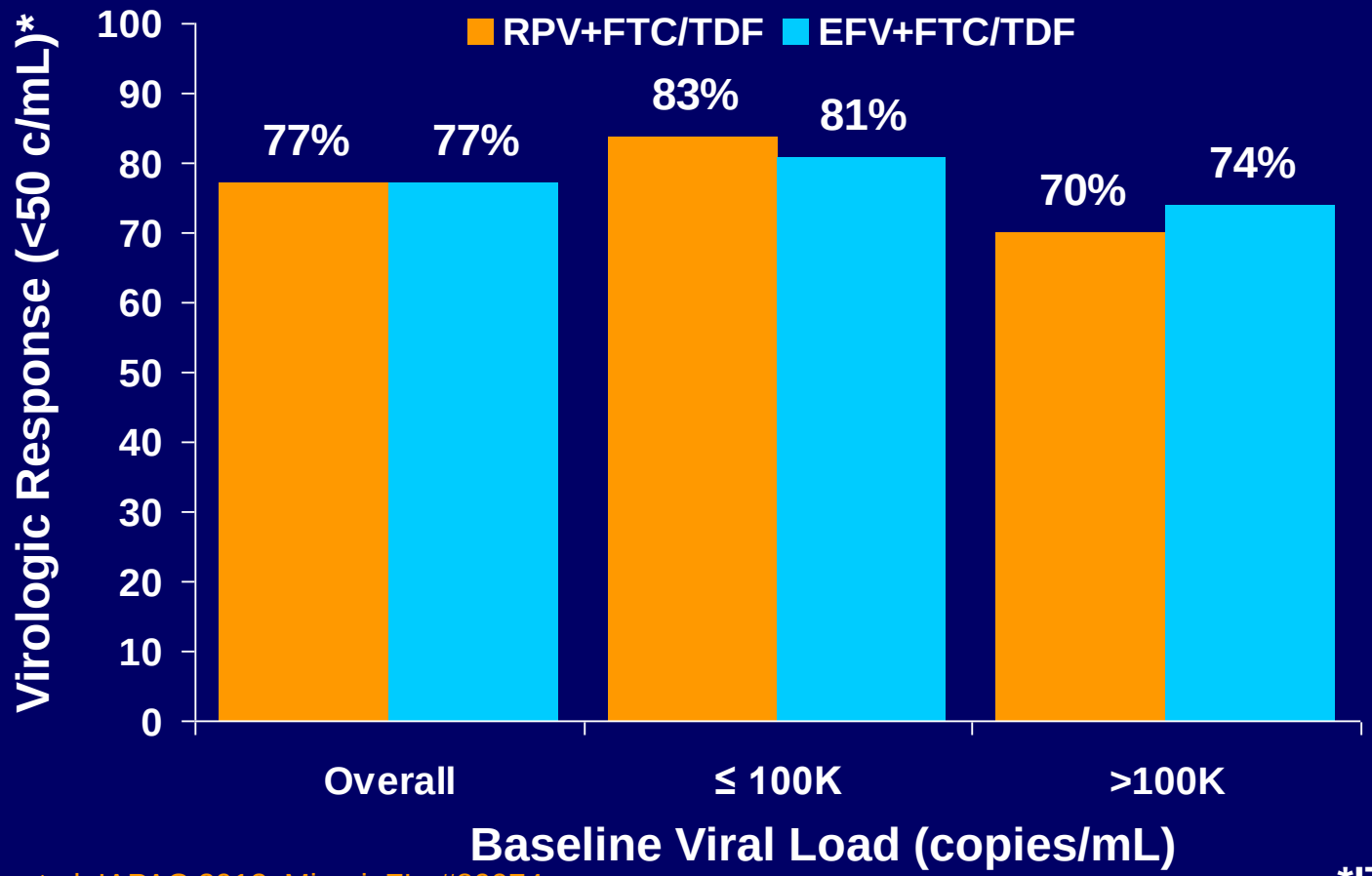
Virologic Response*: by Baseline VL at Week 96

- 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



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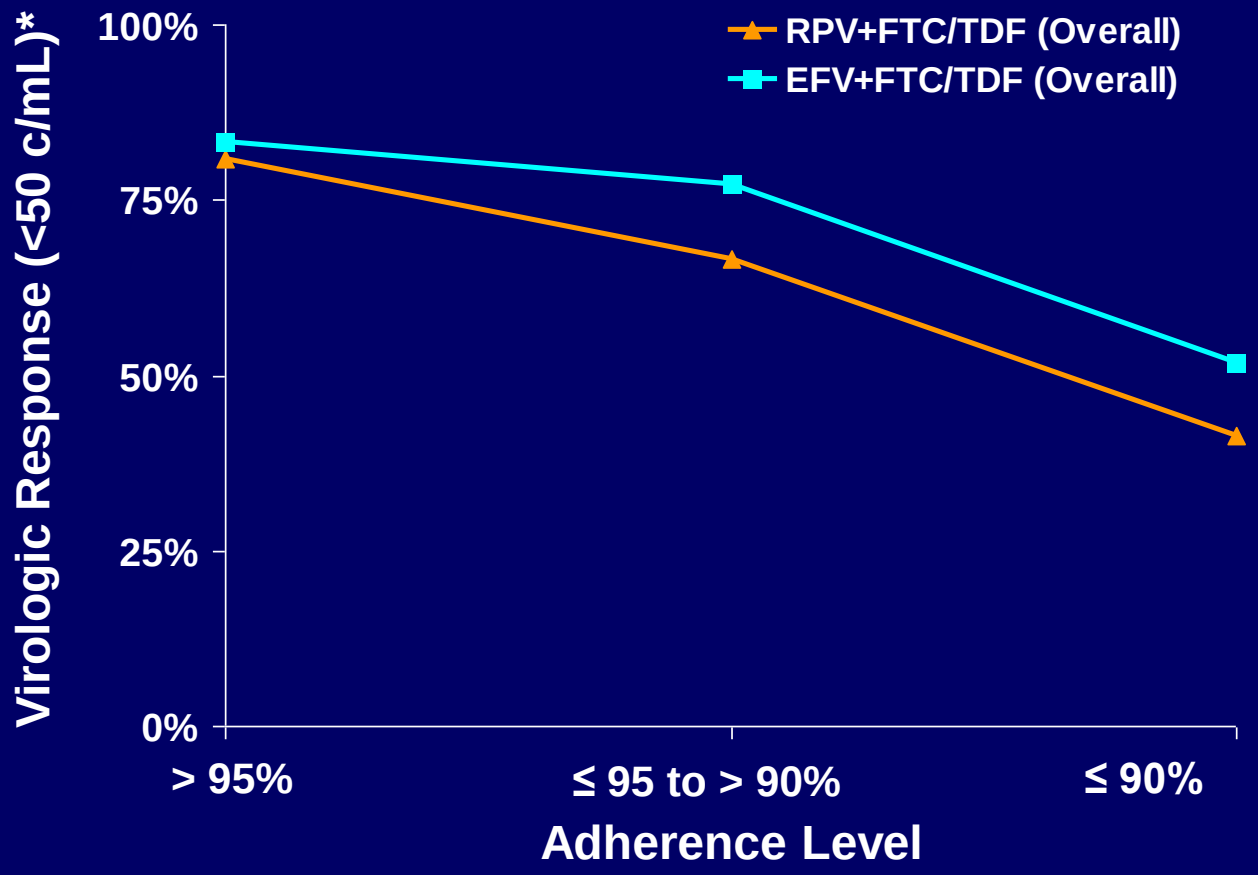
*ITT TLOVR

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

- Overall, non-adherence was associated with lower response rates in both arms



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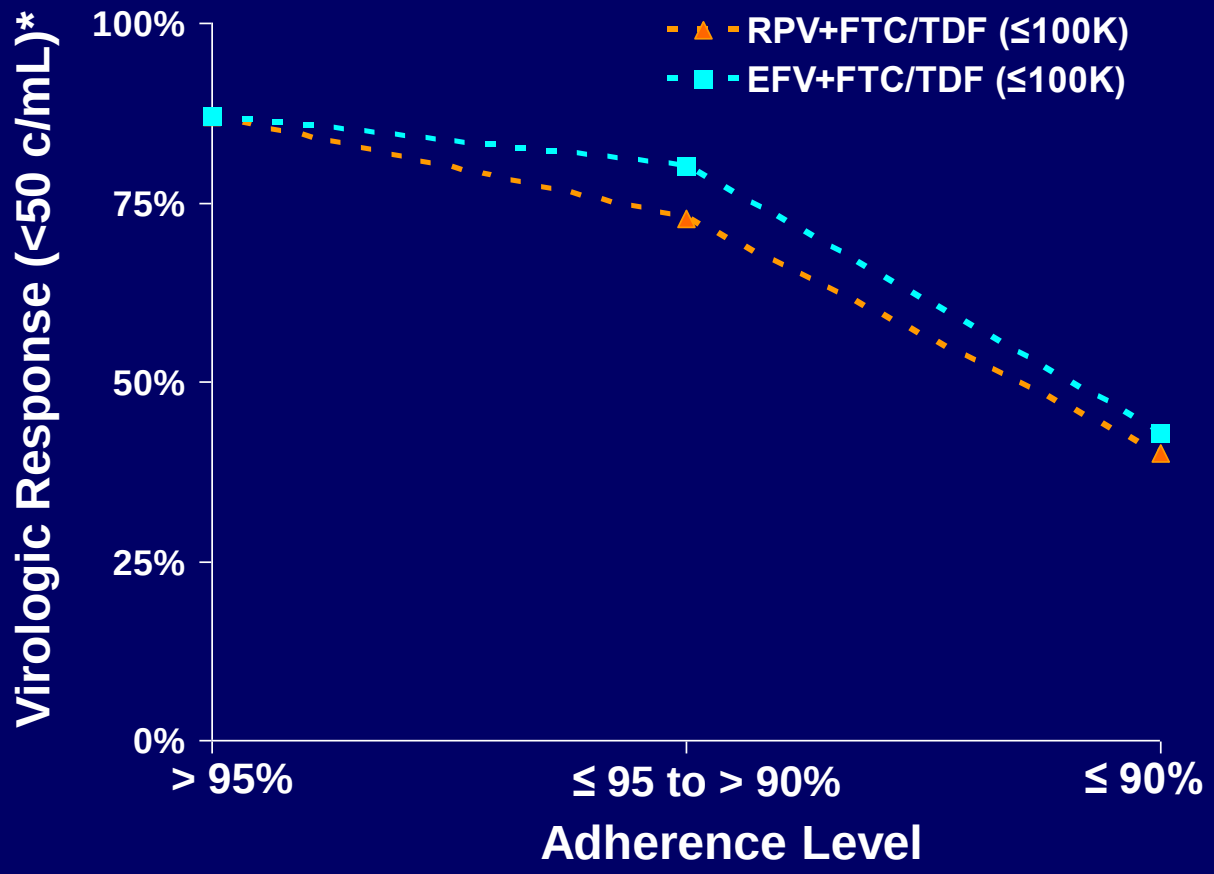
Virologic Response*: VL ≤ 100K by Adherence (M-MASRI) at Week 96

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



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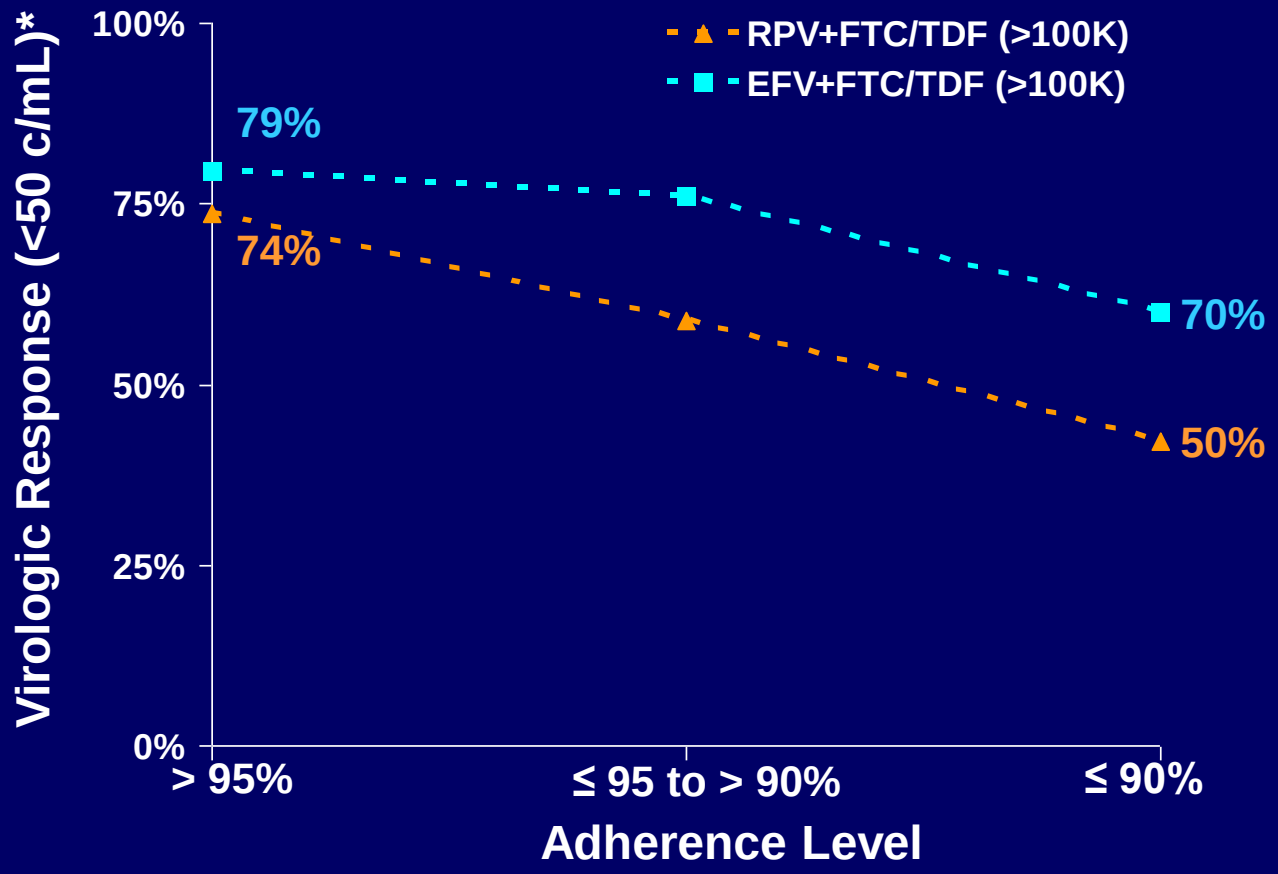
Virologic Response*: VL >100K by Adherence (M-MASRI) at Week 96

- 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%)



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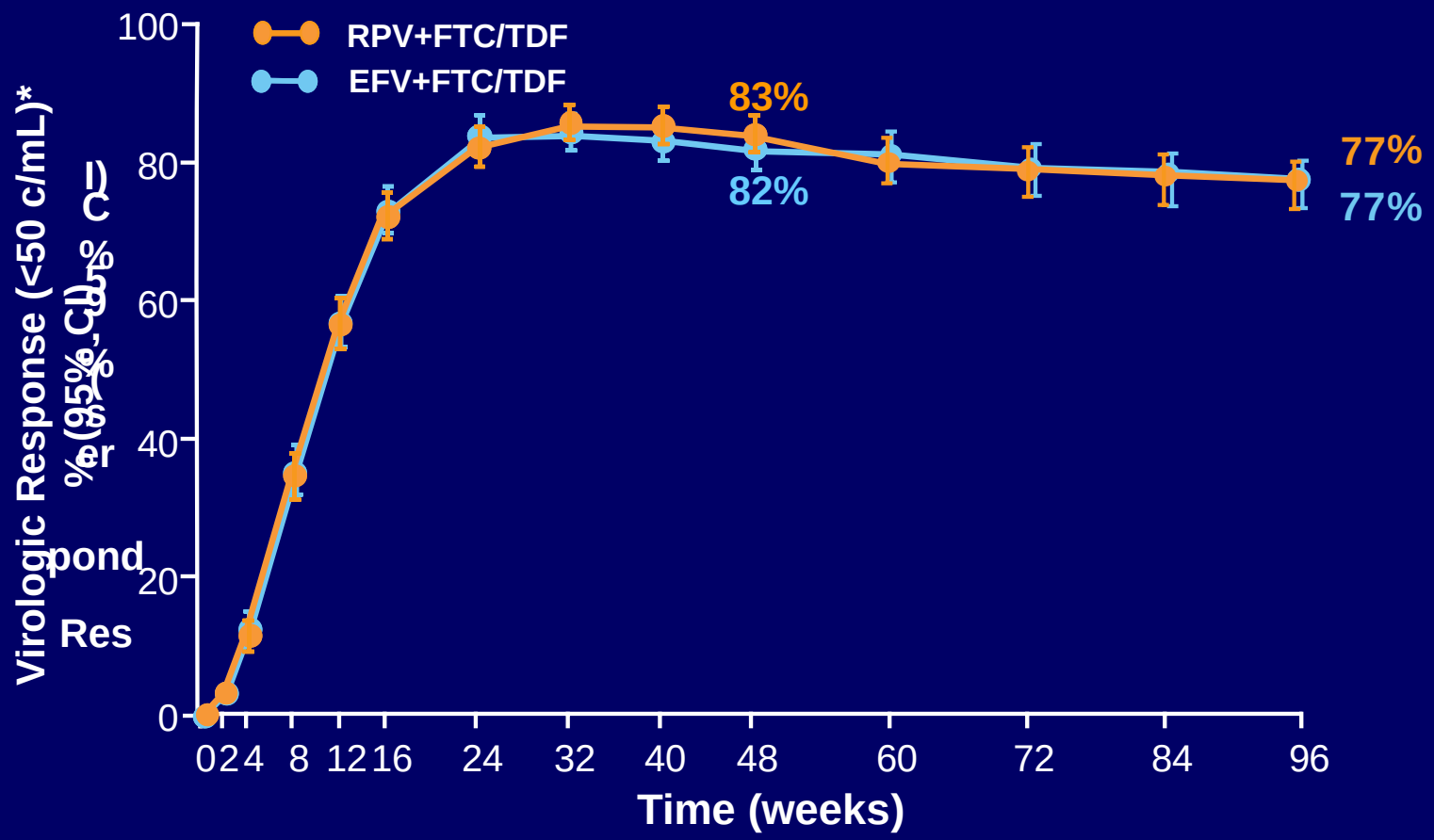
*ITT TLOVR

Virologic Response* through Week 96



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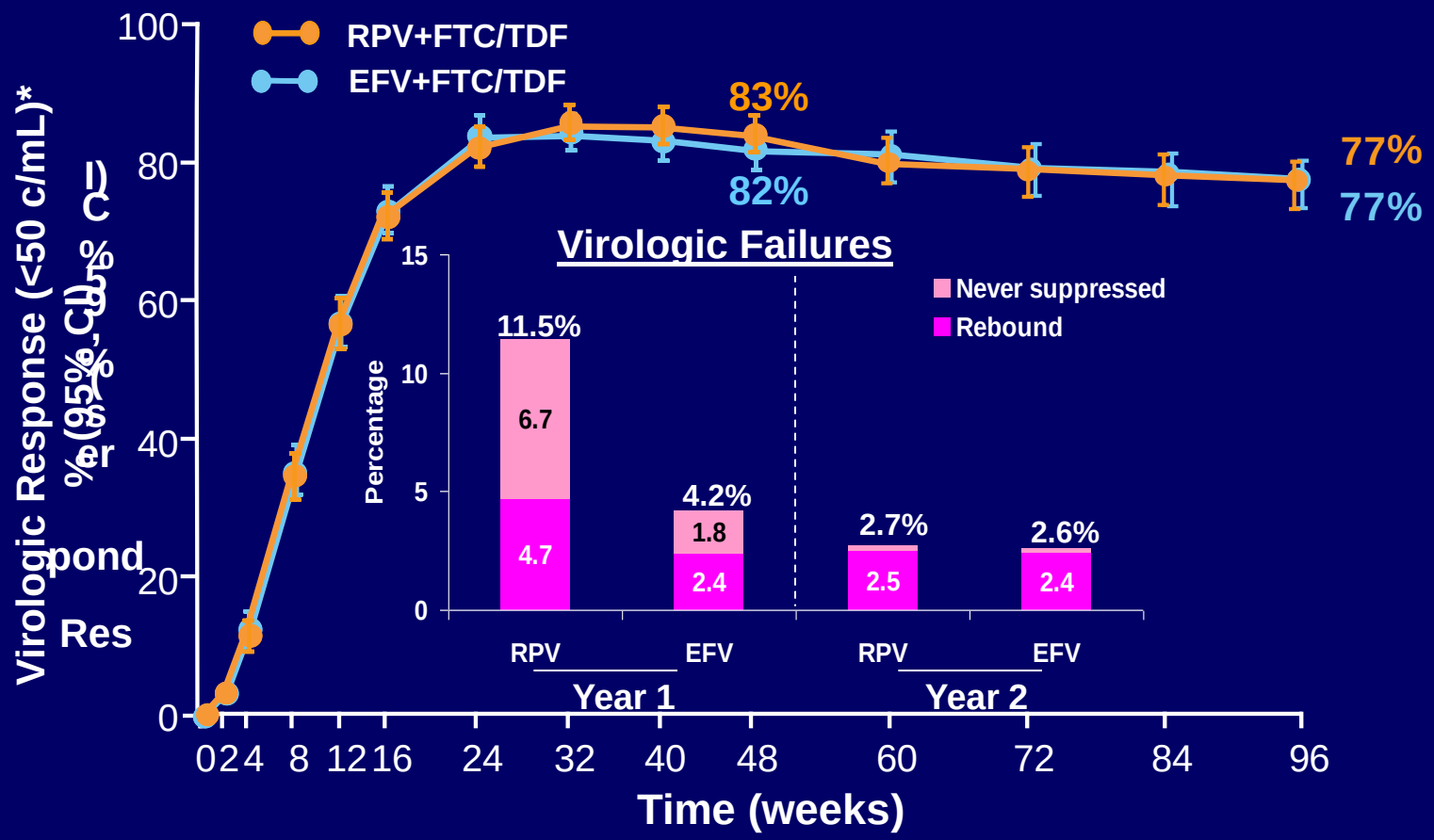
*ITT TLOVR

Virologic Response* & Failures through Week 96



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*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

	RPV+FTC/TDF	EFV+FTC/TDF
Study drug trough concentration	√	√
Investigator-reported adherence	√	√
Baseline VL	√	√
Baseline CD4	√	
Demographics: age, weight, sex, race Study: ECHO vs. THRIVE HBV/HCV coinfection		

- 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

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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)

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Pooled ECHO and THRIVE

Acknowledgements

- We wish to thank all the study subjects and principal investigators
- This study was sponsored by Tibotec Pharmaceuticals

ECHO

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