STaR Study: Single-Tablet Regimen Rilpivirine/ Emtricitabine/Tenofovir DF Has Non-Inferior Efficacy Compared to Efavirenz/ Emtricitabine/Tenofovir DF and Improves Patient Reported Outcomes

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Clinical Trials.gov: NCT01309243

Background

- **RPV/FTC/TDF is a well-tolerated, once daily single-tablet regimen (STR) treatment option[1,2]**
- **ECHO and THRIVE established RPV+FTC/TDF as non-inferior to EFV+FTC/TDF in ART-naïve patients**
  - **These studies were blinded, placebo-controlled and used multi-pill regimens which had different food requirements resulting in twice-daily dosing**
- **STaR is the first study to compare the efficacy, safety and tolerability of the two single-tablet regimens, RPV/FTC/TDF and EFV/FTC/TDF**

1. COMPLERA. US Prescribing Information 01/2013 Gilead Sciences, Inc.
2. EVIPLERA. Summary of Prescribing Characteristics 01/2013. Gilead Sciences, Inc.

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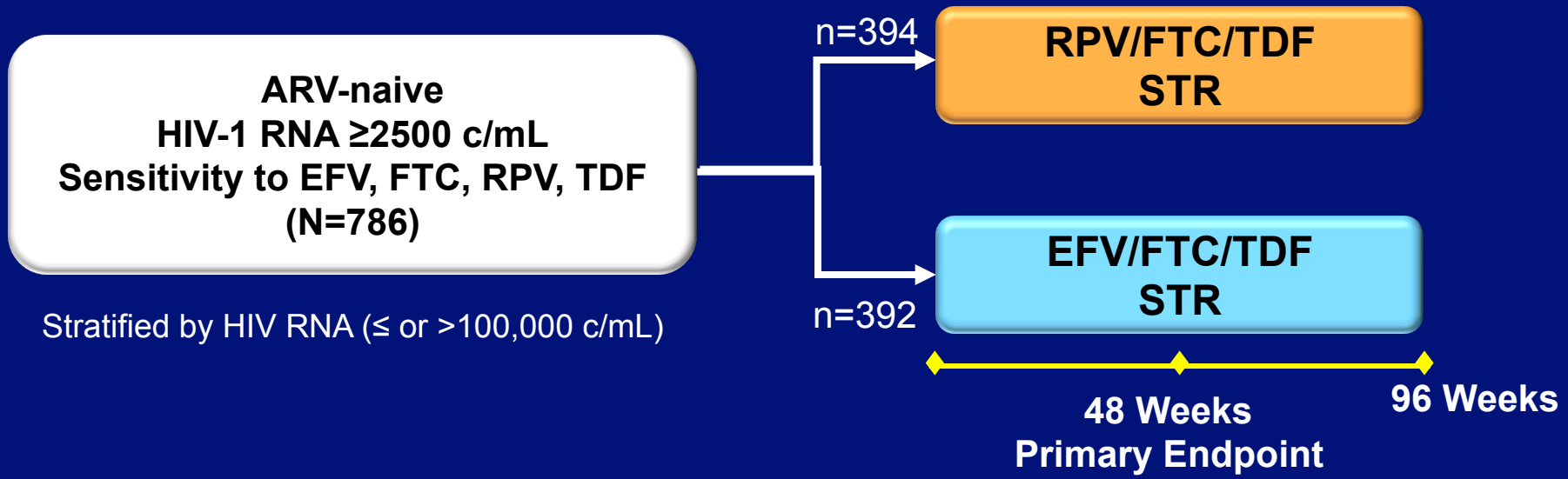
Study Design

Multicenter, international, randomized, open-label, Phase 3b, 96-week study



Primary endpoint: Efficacy of the 2 STRs by proportion with HIV-1 RNA <50 c/mL at Week 48 (FDA Snapshot analysis); non-inferiority margin of 12%

Secondary endpoints:
- Safety and efficacy of the 2 STRs by proportion with HIV-1 RNA <50 c/mL at Week 96 (FDA Snapshot analysis)
- Change in CD4 cell count at Weeks 48 and 96
- Genotype/phenotype resistance at time of virologic failure
- HIV Symptom Index Questionnaire
- Quality of Life (SF-12, v2)
- Treatment Satisfaction Questionnaire

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Baseline Demographics and Characteristics

	RPV/FTC/TDF n = 394	EFV/FTC/TDF n = 392
Median age, years (Q1, Q3)	37 (29, 45)	35 (28, 45)
Male	93%	93%
White race	68%	67%
Black race	25%	24%
Latino ethnicity	15%	19%
Mean CD4 cell count, cells/mm^3 (SD)	396 (180)	385 (187)
Mean HIV-1 RNA, log_{10} copies/mL, (SD)	4.8 (0.7)	4.8 (0.6)
≤100,000 copies/mL, n (%)	260 (66%)	250 (64%)
>100,000 to 500,000 copies/mL, n (%)	98 (25%)	117 (30%)
>500,000 copies/mL, n (%)	36 (9%)	25 (6%)

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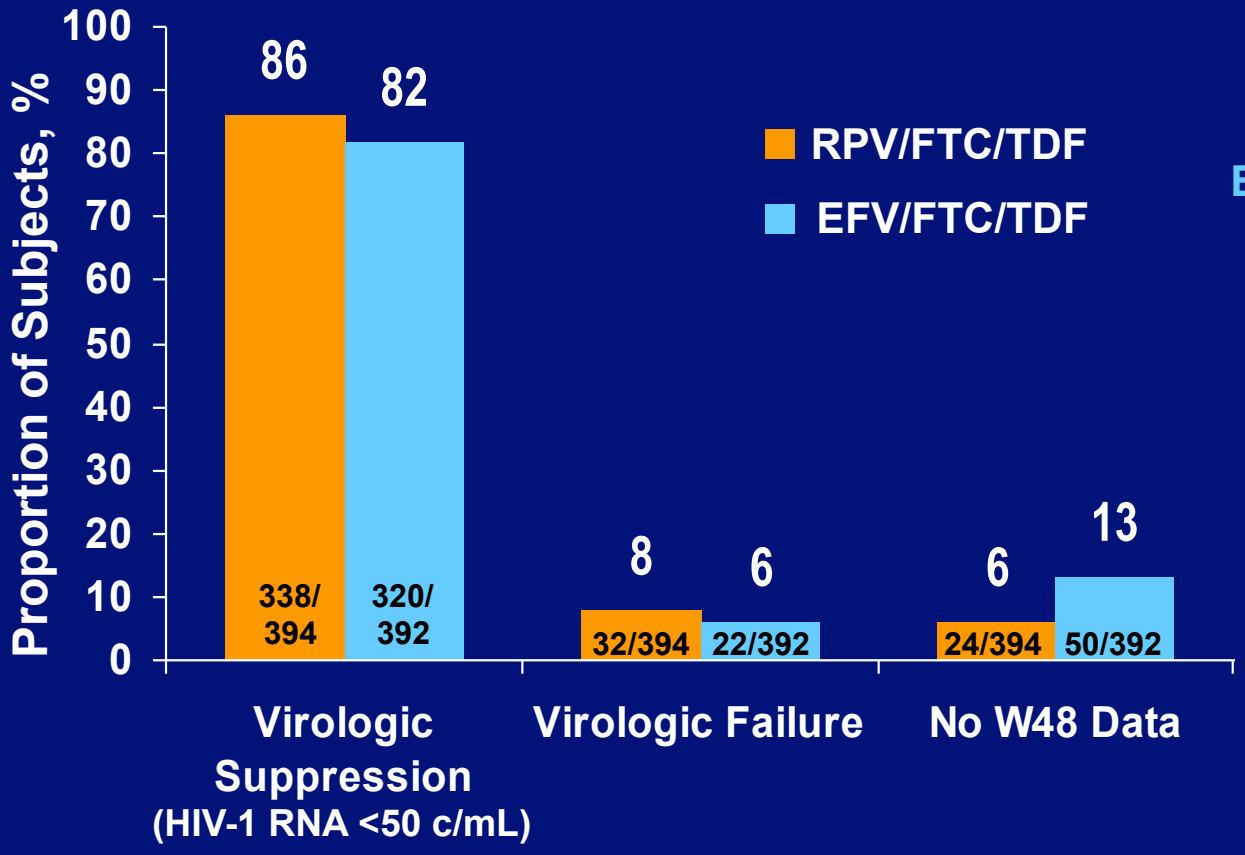
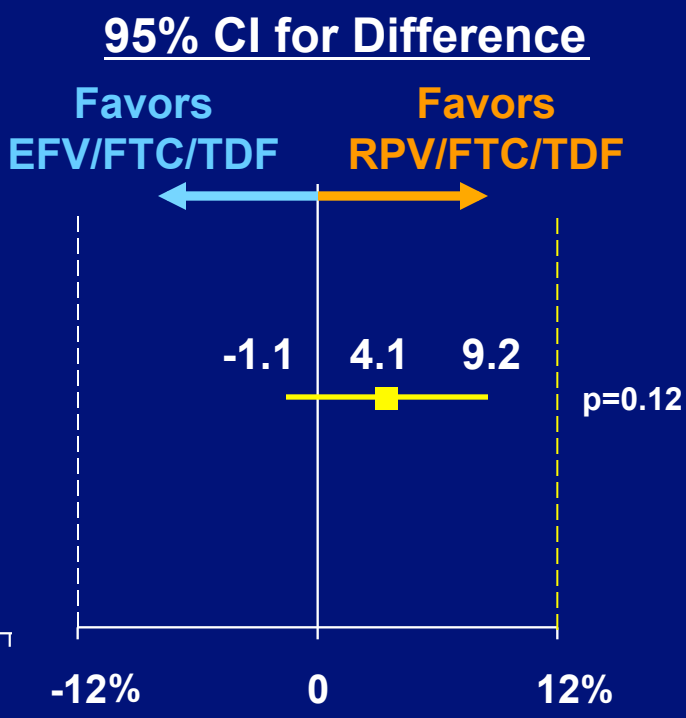
Virologic Suppression and CD4+ Change at Week 48 FDA Snapshot Analysis – ITT Population

RPV/FTC/TDF is non-inferior to EFV/FTC/TDF





Mean CD4+ count change (cells/mm^3): RPV/FTC/TDF +200 vs EFV/FTC/TDF +191 (p=0.34)

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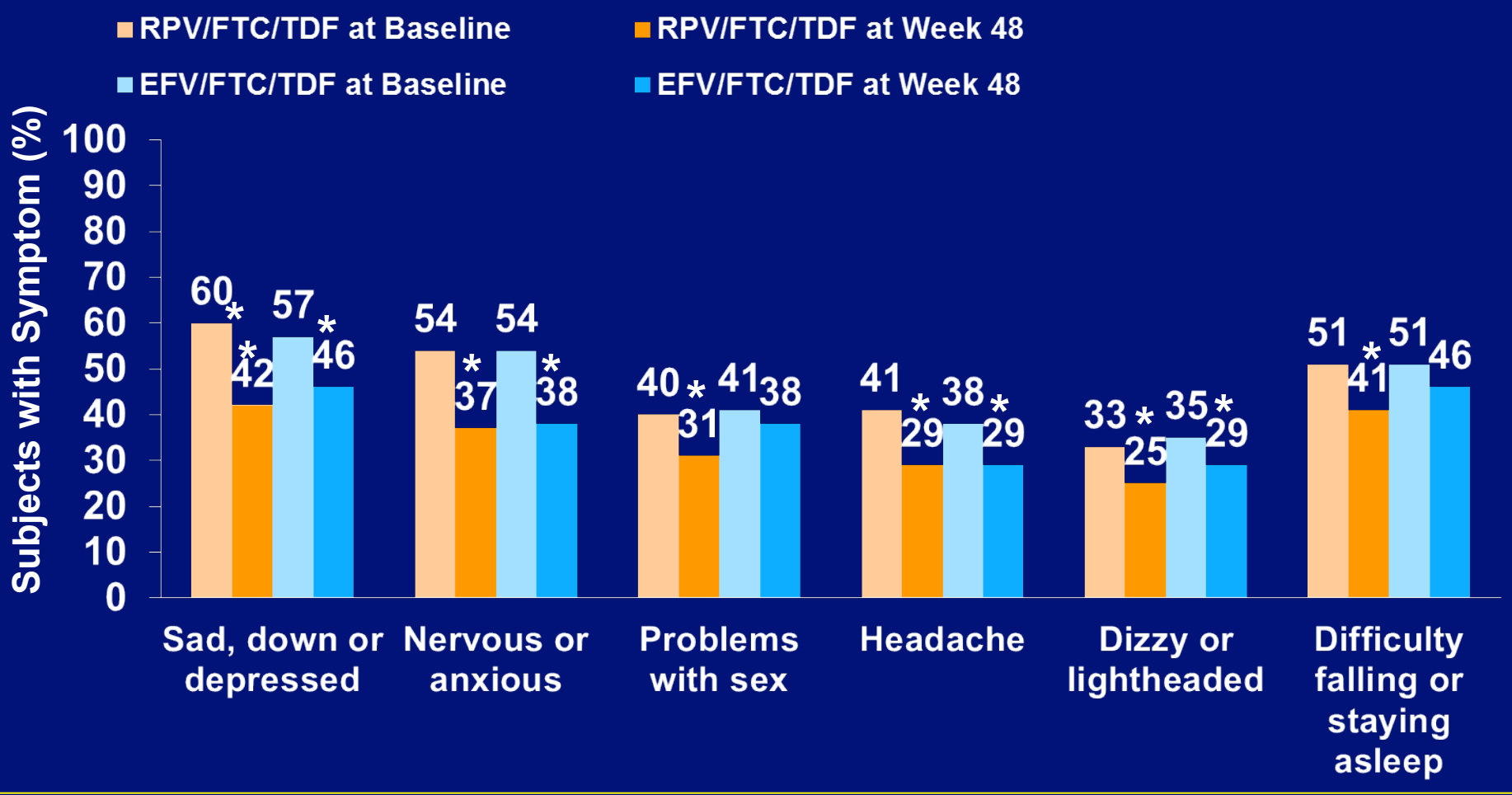
HIV Symptom Index Q

Baseline & Week 4

HIV Symptom Index Questionnaire is split up over Slides 6-8 but will be a single figure in the poster



There were no statistically significant differences between arms at Week 48 for psychiatric or nervous system symptoms on the HIV Symptom Index Questionnaire

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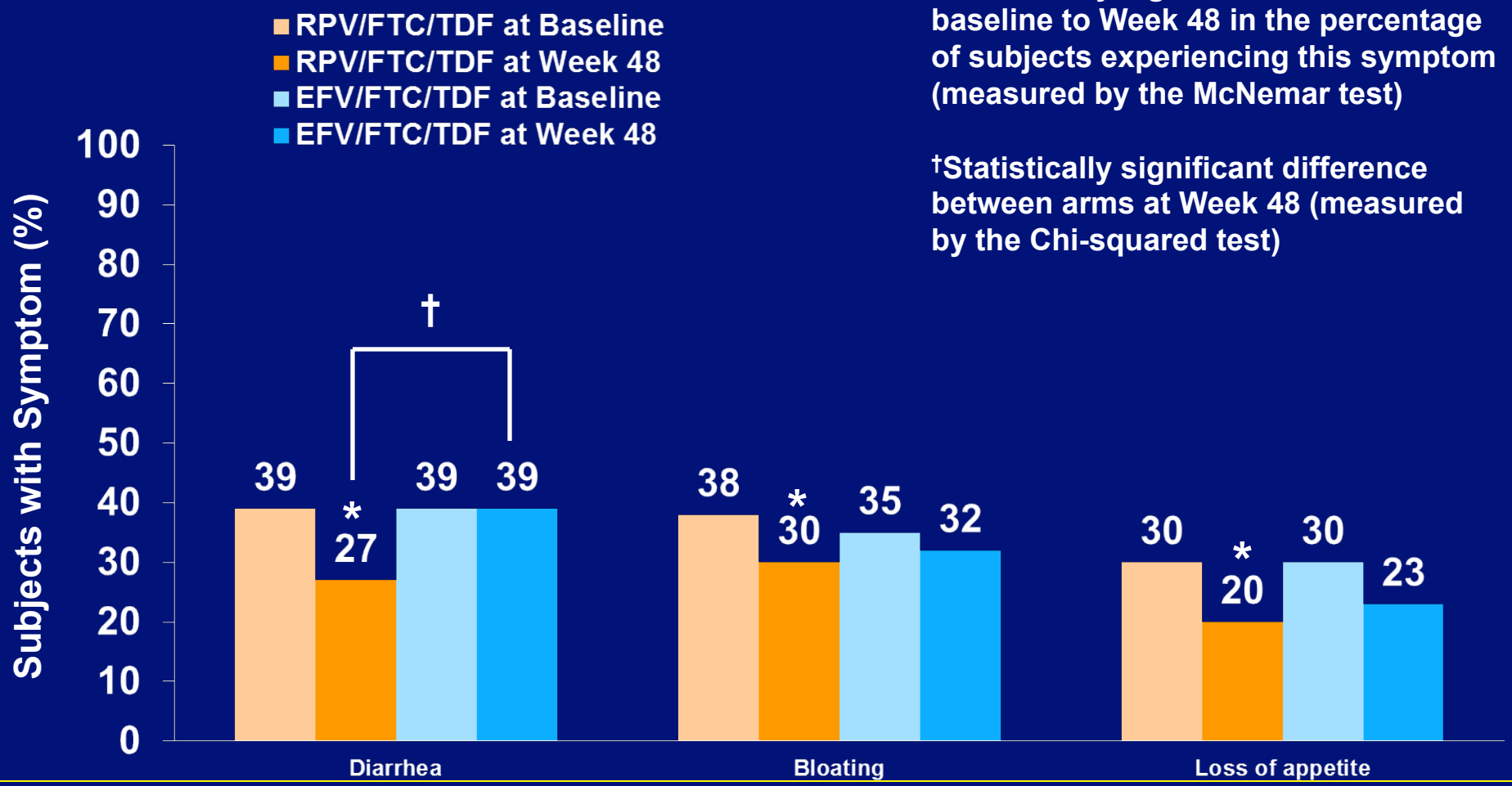
HIV Symptom Index Questionnaire
Baseline & Week 48 Results



*Statistically significant reduction from baseline to Week 48 in the percentage of subjects experiencing this symptom (measured by the McNemar test)

†Statistically significant difference between arms at Week 48 (measured by the Chi-squared test)

- At Week 48, there was a significantly lower rate of subjects reporting symptoms of diarrhea and pain, numbness, or tingling in the hands or feet on the HIV Symptom Index Questionnaire in the RPV/FTC/TDF arm compared to the EFV/FTC/TDF arm
- There were no significant changes from baseline to Week 48 or between arms at Week 48 in the symptoms of changes in

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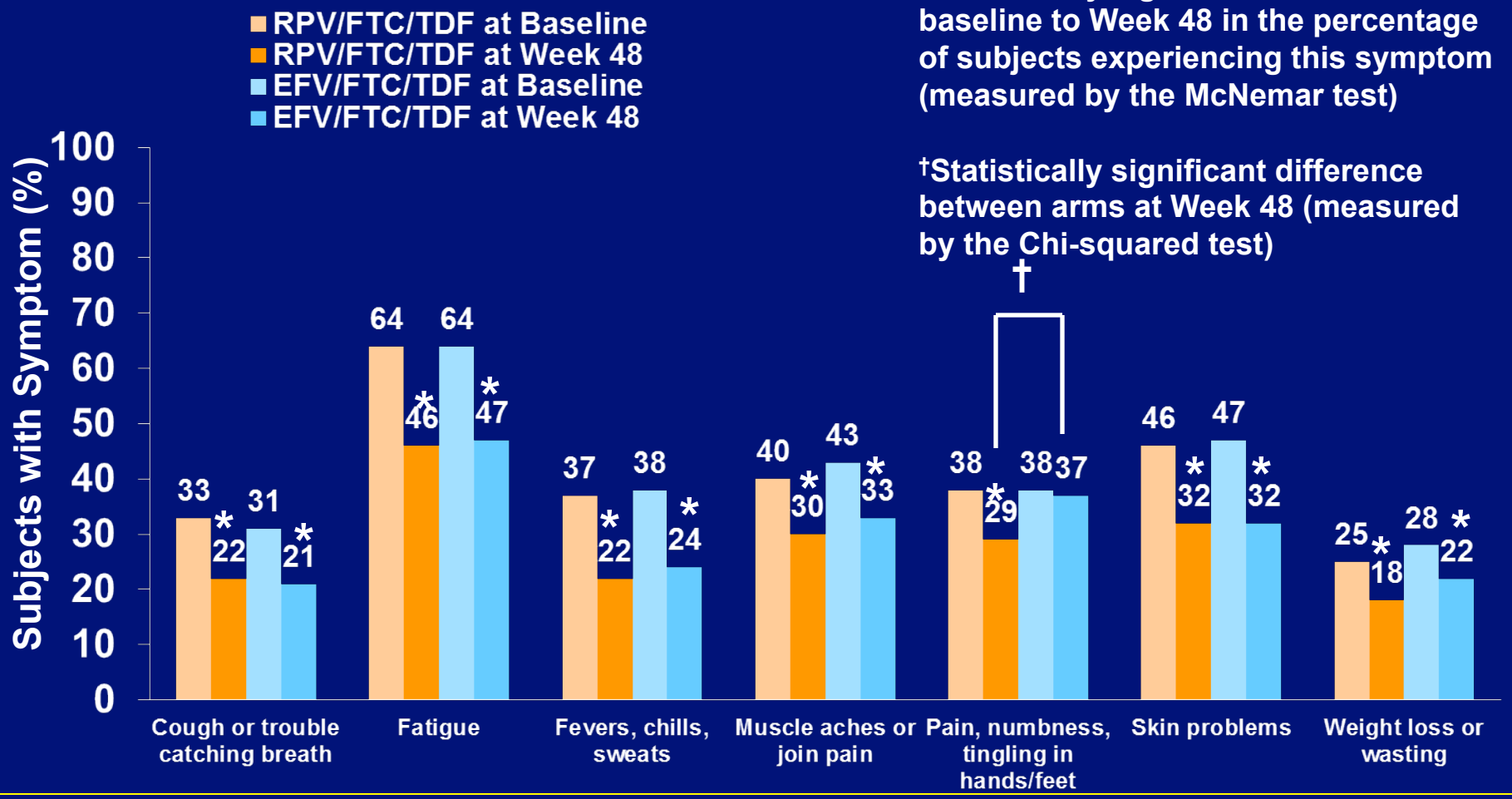
HIV Symptom Index Questionnaire
Baseline & Week 48 Results



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Quality of Life as Measured by SF

Week 48 Results

SF-12 is split up over Slides 9-11 but will be a single table on the poster

Scoring was done according to the SF-12 manual. Scores are normalized to 0-100, with higher scores indicating better health	RPV/FTC/TDF n=389	EFV/FTC/TDF n=388	p value*
General Health Subdomain			
Median score at Week 48	85.0	85.0	0.88
Median change from Baseline to Week 48	0.0	0.0	0.19
Physical Functioning Subdomain			
Median score at Week 48	100.0	100.0	0.68
Median Change from Baseline to Week 48	0.0	0.0	0.27
Role Functioning (Physical) Subdomain			
Median score at Week 48	100.0	100.0	0.81
Median Change from Baseline to Week 48	0.0	0.0	0.95
Role Functioning (Emotional) Subdomain			
Median score at Week 48	100.0	100.0	0.75
Median Change from Baseline to Week 48	0.0	0.0	0.070

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Quality of Life as Measured by SF-12 (v2) Health Survey

Week 48 Results

	RPV/FTC/TDF n=389	EFV/FTC/TDF n=388	p value*
Bodily Pain Subdomain			
Median score at Week 48	100.0	100.0	0.82
Median Change from Baseline to Week 48	0.0	0.0	0.22
Vitality Subdomain			
Median score at Week 48	75.0	75.0	0.41
Median Change from Baseline to Week 48	0.0	0.0	0.28
Mental Health Subdomain			
Median score at Week 48	75.0	75.0	0.40
Median Change from Baseline to Week 48	0.0	0.0	0.081
Social Functioning Subdomain			
Median score at Week 48	100.0	100.0	0.79
Median Change from Baseline to Week 48	0.0	0.0	0.26

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Quality of Life as Measured by SF-12 (v2) Health Survey

Week 48 Results

	RPV/FTC/TDF n=389	EFV/FTC/TDF n=388	p value*
Physical Health Composite Score			
Median score at Week 48	56.1	56.1	0.57
Median Change from Baseline to Week 48	0.0	0.9	**0.013**
Mental Health Composite Score			
Median score at Week 48	51.7	51.8	0.93
Median Change from Baseline to Week 48	2.6	0.3	**0.025**

***Wilcoxon Rank Sum Test**

- **Subjects treated with EFV/FTC/TDF showed significantly more improvement from baseline to Week 48 in the physical health composite score**
- **Subjects treated with RPV/FTC/TDF showed significantly more improvement from baseline to Week 48 in mental health composite score**

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HIV Treatment Satisfaction Questionnaire
Week 48 Results

	RPV/FTC/TDF n=297	EFV/FTC/TDF n=280	
Mean Treatment Satisfaction Scale Total (SD) *[Total score range : 0 to 60]*	56.8 (5.62)	56.6 (5.31)	p=0.62
Percent of subjects responding satisfied (4), moderately satisfied (5), or very satisfied (6)			
How convenient have you been finding your treatment to be recently?	98.3%	98.6%	
How flexible have you been finding your treatment to be recently?	94.3%	93.5%	
How satisfied are you with any side effects of your present treatment?	97.3%	94.3%	
How satisfied are you with the demands of your current treatment?	97.6%	98.2%	
How satisfied are you with the extent to which the treatment fits in with your lifestyle?	97.6%	96.8%	
How satisfied are you with your current treatment?	99.0%	98.9%	
How satisfied are you with your understanding of your HIV?	97.7%	96.8%	
How satisfied would you be to continue with your present form of treatment?	99.0%	98.6%	
How well controlled do you feel your HIV has been recently?	99.0%	98.9%	
Would you recommend your present treatment to someone else with HIV?	98.6%	99.3%	

All Grades Treatment-Emerg

All Grade TEAEs of Importance are split up over Slides 13-14 but will be a single table on the poster

	RPV/FTC/TDF n=394	EFV/FTC/TDF n=392	
Nervous System Events, n (%)	**117 (29.7%)**	**198 (50.5%)**	**p< 0.001**
Events >5% of subjects, either arm			
Dizziness	26 (6.6%)	87 (22.2%)	
Insomnia	38 (9.6%)	55 (14.0%)	
Somnolence	10 (2.5%)	27 (6.9%)	
Headache	49 (12.4%)	53 (13.5%)	
Psychiatric Events, n (%)	**62 (15.7%)**	**147 (37.5%)**	**p< 0.001**
Events >5% of subjects†, either arm			
Abnormal Dreams	23 (5.8%)	96 (24.5%)	
Depression	26 (6.6%)	35 (8.9%)	
Anxiety	20 (5.1%)	33 (8.4%)	

*Prespecified evaluation for common adverse events, US Efavirenz Prescribing Information

† 1 (0.3%) suicide occurred in the EFV/FTC/TDF arm, day 36 of study

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All Grades Treatment-Emergent Adverse Events* of Importance

	RPV/FTC/TDF n=394	EFV/FTC/TDF n=392	
Rash Events, n (%)	**68 (17.3%)**	**83 (21.2%)**	**p=0.17**
Events >5% of subjects, either arm			
Folliculitis	21 (5.3%)	4 (1.0%)	
Rash	24 (6.1%)	47 (12.0%)	

*Prespecified evaluation for common adverse events, US Efavirenz Prescribing Information

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Adverse Events Leading to Discontinuation of Study Drug*

	RPV/FTC/TDF n=394	EFV/FTC/TDF n=392	
Discontinuations Due to Adverse Event (AE), n (%)	10 (2.5%)	34 (8.7%)	p<0.001
AE Leading to Discontinuation in >1 Subject in either arm			
Dizziness	0	5 (1.3%)	
Depression	0	5 (1.3%)	
Abnormal Dreams	0	4 (1.0%)	
Insomnia	1 (0.3%)	3 (0.8%)	
Suicidal Ideation/Completed Suicide	0	3 (0.8%)†	
Diarrhea	0	2 (0.5%)	
Fatigue	0	2 (0.5%)	
Pyrexia	0	2 (0.5%)	
Anxiety	0	2 (0.5%)	
Depressed Mood	0	2 (0.5%)	
Nightmare	0	2 (0.5%)	

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Grade 3 or 4 Adverse Events and Laboratory Abnormalities

	RPV/FTC/TDF n=394	EFV/FTC/TDF n=392
Grade 3 or 4 Adverse Events, n (%)	29* (7.4%)	54† (13.8%)
Grade 3 or 4 Adverse Events of Interest		
Psychiatric Disorders	6 (1.5%)	13 (3.3%)
Nervous System Disorders	5 (1.3%)	5 (1.3%)
Gastrointestinal Disorders	3 (0.8%)	5 (1.3%)
Skin & Subcutaneous Tissue Disorders	1 (0.3%)	3 (0.8%)
Grade 3 or 4 Laboratory , n (%)	68‡ (17.3%)	63§ (16.2%)

* Specific events occurring in the FTC/RPV/TDF arm in >1 subject: fatigue, syncope, depression, nephrolithiasis

† Specific events occurring in the EFV/FTC/TDF arm in >1 subject: diarrhea, pyrexia, blood creatine phosphokinase increased, hepatic enzyme increased, headache, depression, anxiety, insomnia, bipolar I disorder, suicide attempt

‡ Grade 3 or 4 lab abnormalities occurring in ≥1% in the RPV/FTC/TDF arm: ALT, AST, GGT, amylase, neutrophils, creatine kinase, hyperglycemia, glycosuria, hematuria, lipase

§ Grade 3 or 4 lab abnormalities occurring in ≥1% in the EFV/FTC/TDF arm: ALT, AST, GGT, amylase, creatine kinase, total cholesterol, glycosuria, hematuria

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Conclusions

- Overall, RPV/TDF/FTC was non-inferior to EFV/FTC/TDF through Week 48 for the primary endpoint of virologic suppression
- On the HIV Symptom Index Questionnaire
  - There were significantly lower rates of subjects reporting symptoms of diarrhea and pain, numbness, and tingling in the hands or feet in the RPV/FTC/TDF arm compared to the EFV/FTC/TDF arm
  - There were no significant differences seen between groups at Week 48 for the other symptoms included on the questionnaire
- On the SF-12 (v2), there was significantly more improvement from baseline to Week 48 in the EFV/FTC/TDF arm on the physical health composite score and in the RPV/FTC/TDF arm on the mental health composite score
- There were similar rates of treatment satisfaction at Week 48 in both arms as measured by the HIV Treatment Satisfaction Questionnaire
- Based on adverse event reports, RPV/FTC/TDF is significantly better tolerated than EFV/FTC/TDF
    - Fewer nervous system and psychiatric adverse events common to the Efavirenz Prescribing Information
    - Fewer discontinuations due to adverse events
- Differences in rates of symptoms reported on patient reported outcome measures vs adverse events may be due to
  - The fact that adverse events are spontaneously reported while patient reported outcome questionnaires solicit information about specific symptoms
  - Patient reported outcome questionnaires only address symptoms from the previous 30 days
  - Subjects discontinuing due to adverse events were not included in Week 48 results of patient reported outcome measures

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