

Elvitegravir/Cobicistat/Emtricitabine/Tenofovir DF Demonstrates Comparable Efficacy to Efavirenz/ Emtricitabine/Tenofovir DF in Subjects with Adherence <95%

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Introduction

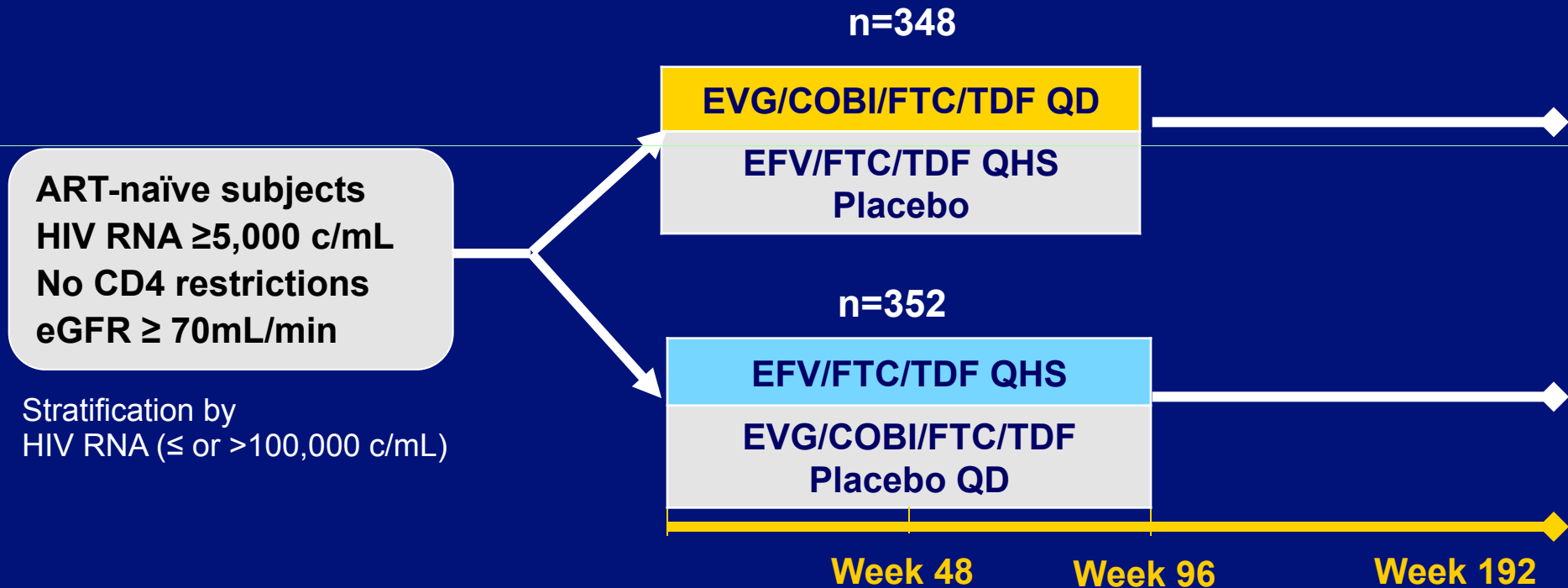
- Elvitegravir/cobicistat/emtricitabine/tenofovir DF (EVG/COBI/FTC/TDF [Stribild]) was well tolerated and demonstrated non-inferior efficacy to efavirenz/emtricitabine/tenofovir DF (EFV/FTC/TDF) with HIV-1 RNA <50 copies/mL (c/mL) by snapshot analysis at Week (Wk) 48 (88% vs. 84%, respectively) and Wk 96 (84% vs. 82%, respectively) in a randomized, controlled trial of HIV-1-infected, treatment naïve subjects
- $\geq 95\%$ adherence to antiretroviral therapy is generally required to maintain HIV viral suppression and to prevent the emergence of drug resistance¹⁻³
- However, suboptimal adherence to antiretroviral therapy occurs, and it is helpful to understand the efficacy of EVG/COBI/FTC/TDF and EFV/FTC/TDF in subjects with <95% adherence

Methods

- We performed a pre-planned adherence analysis, $\geq 95\%$ or $< 95\%$, using pill count on all subjects randomized and treated in Study GS-US-236-0102 with either EVG/COBI/FTC/TDF or EFV/FTC/TDF through week 96
- The key endpoint was the proportion of subjects with $\geq 95\%$ or $< 95\%$ adherence having HIV-1 RNA < 50 copies/mL by FDA snapshot analysis at week 96
- An additional endpoint was the change from baseline in CD4 cell count in subjects with $\geq 95\%$ or $< 95\%$ adherence
- Statistical analysis
 - Non-inferiority evaluation of EVG/COBI/FTC/TDF to EFV/FTC/TDF was conducted using a pre-defined non-inferiority margin of 12%
 - Difference in percentages of virologic success and its 95% CI were calculated based on baseline HIV-1 RNA stratum-adjusted MH proportion
 - For CD4 cell count change, P-values were from ANOVA model adjusted for baseline HIV-1 RNA level

GS-US-236-0102

Study Design



Primary Analysis:

Non-inferiority evaluation (12% margin) of EVG/COBI/FTC/TDF to EFV/FTC/TDF by proportion of subjects with HIV-1 RNA < 50 copies/mL at 48 weeks by FDA snapshot approach

Secondary Analysis:

Efficacy, safety, and tolerability of EVG/COBI/FTC/TDF compared to EFV/FTC/TDF at week 96

Adherence measured by pill count up to week 96

Baseline Demographics and Disease Characteristics

Adherence Category	≥95%		<95%	
	EVG/COBI/FTC/TDF n=256	EFV/FTC/TDF n=263	EVG/COBI/FTC/TDF n=90	EFV/FTC/TDF n=86
Age (years), Median	38	38	36	35
Male (%)	88	89	88	93
Race and ethnicity				
White (%)	66	68	48	55
Black/African heritage (%)	27	22	42	38
Hispanic/Latino (%)	26	27	16	17
HIV-1 RNA				
Median (log ₁₀ copies/mL)	4.74	4.78	4.77	4.73
>100,000 copies/mL, n (%)	84 (33)	87 (33)	33 (37)	26 (30)
CD4 count				
Median (cells/mm ³)	381	388	355	357
≤200, n (%)	26 (10)	37 (14)	17 (19)	13 (15)
History of IV drug use, n (%)	9 (4)	6 (2)	2 (2)	5 (6)

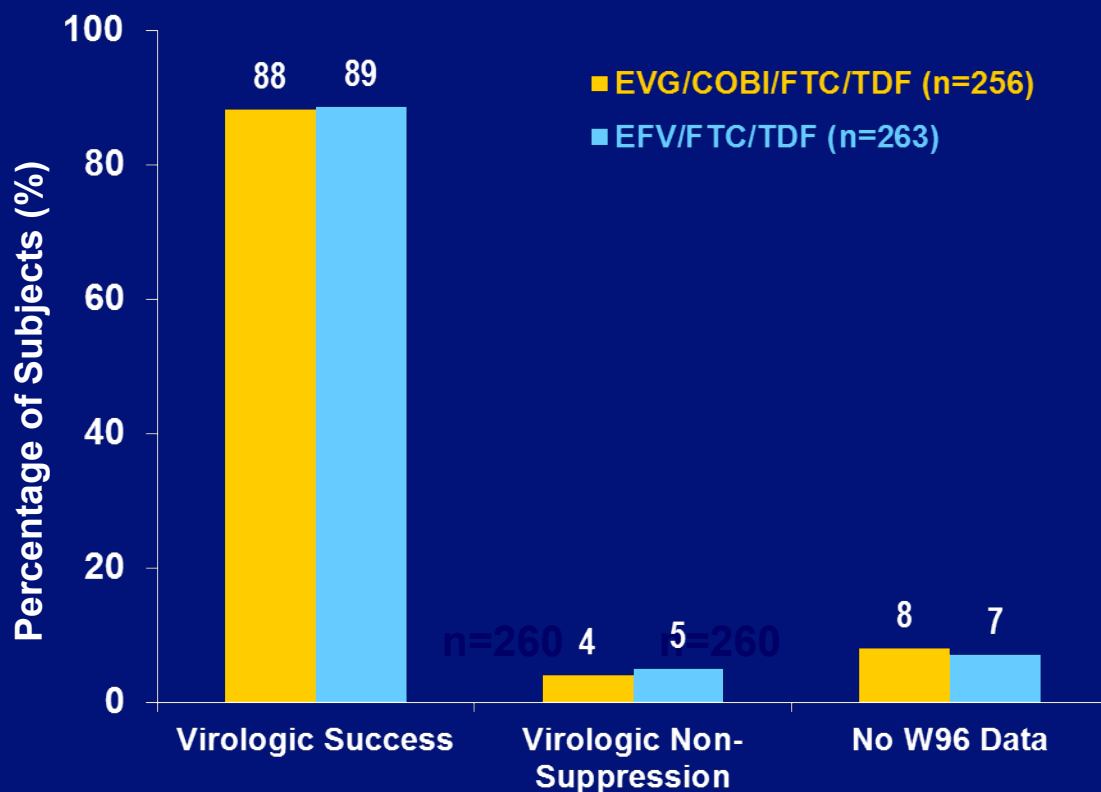
Adherence to Study Drug Up To Week 96

Safety Analysis Set

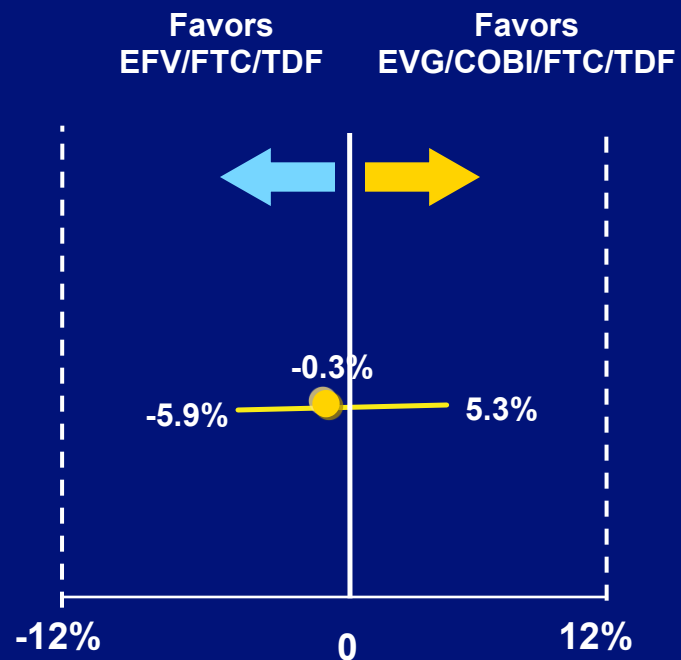
Adherence to study drug ^a	EVG/COBI/FTC/TDF n=348	EFV/FTC/TDF n=352
Number of subjects who returned at least 1 bottle and have calculable adherence	346 (99.4%)	349 (99.1%)
Mean (SD) study drug adherence up to week 96 visit (%)	96.2 (5.14)	96.0 (6.22)
Study drug adherence up to week 96 visit ^b		
≥95%	256 (74.0%)	263 (75.4%)
≥90 to <95%	65 (18.8%)	47 (13.5%)
≥80 to <90%	22 (6.4%)	33 (9.5%)
<80%	3 (0.9%)	6 (1.7%)

- Adherence was calculated based on pill count for the active drugs only.
- Denominator for percentage of drug adherence category is the number of subjects who returned at least 1 bottle and had calculable drug adherence.

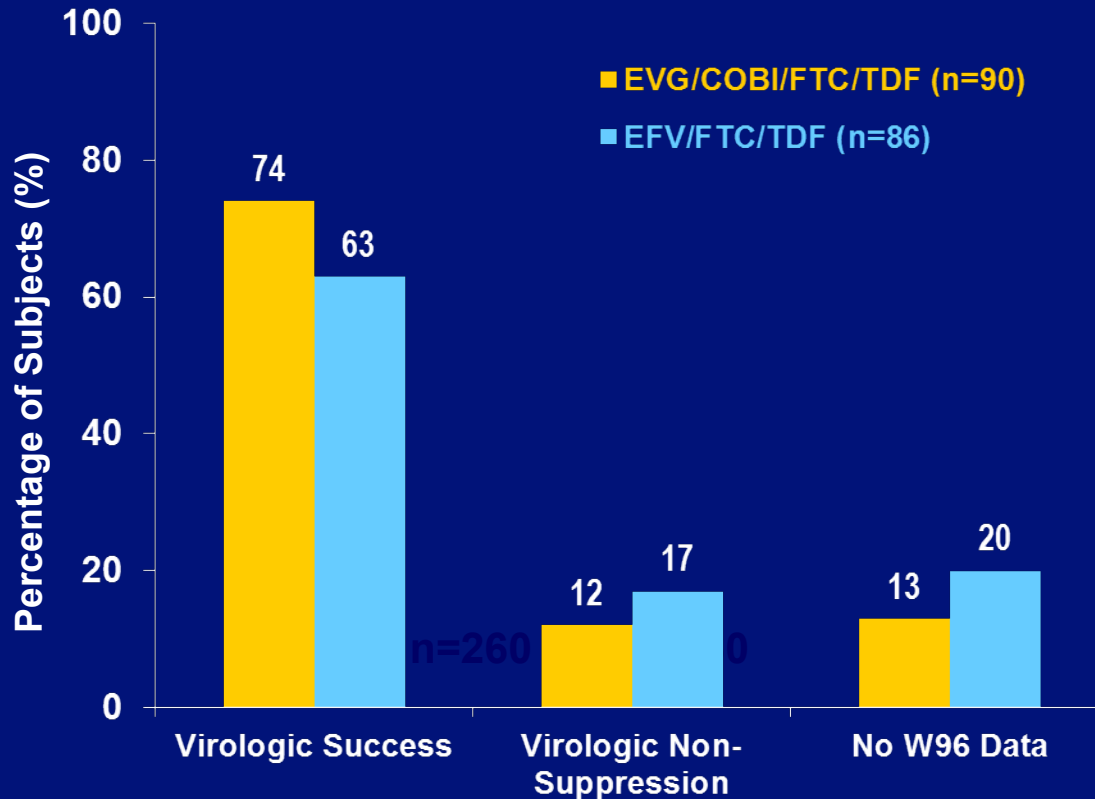
Efficacy in Subjects with $\geq 95\%$ Adherence



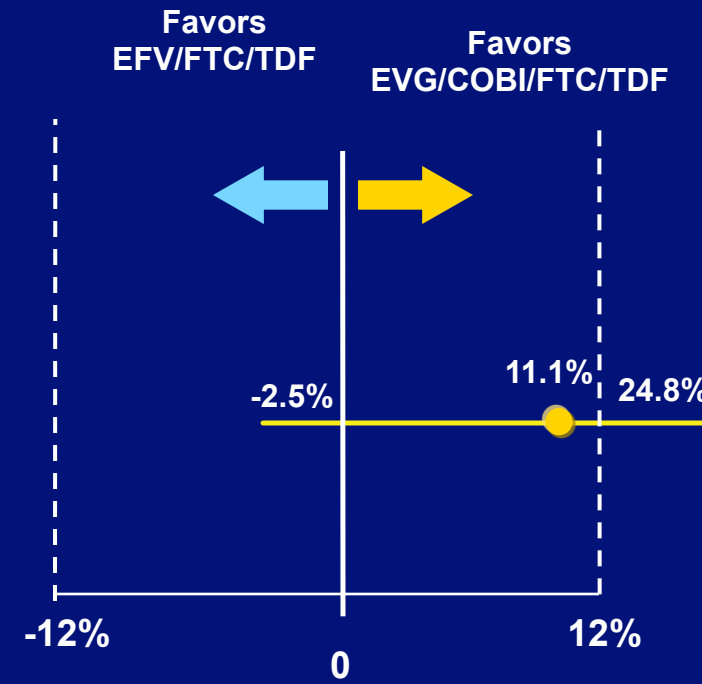
95% CI for Difference



Efficacy in Subjects with <95% Adherence

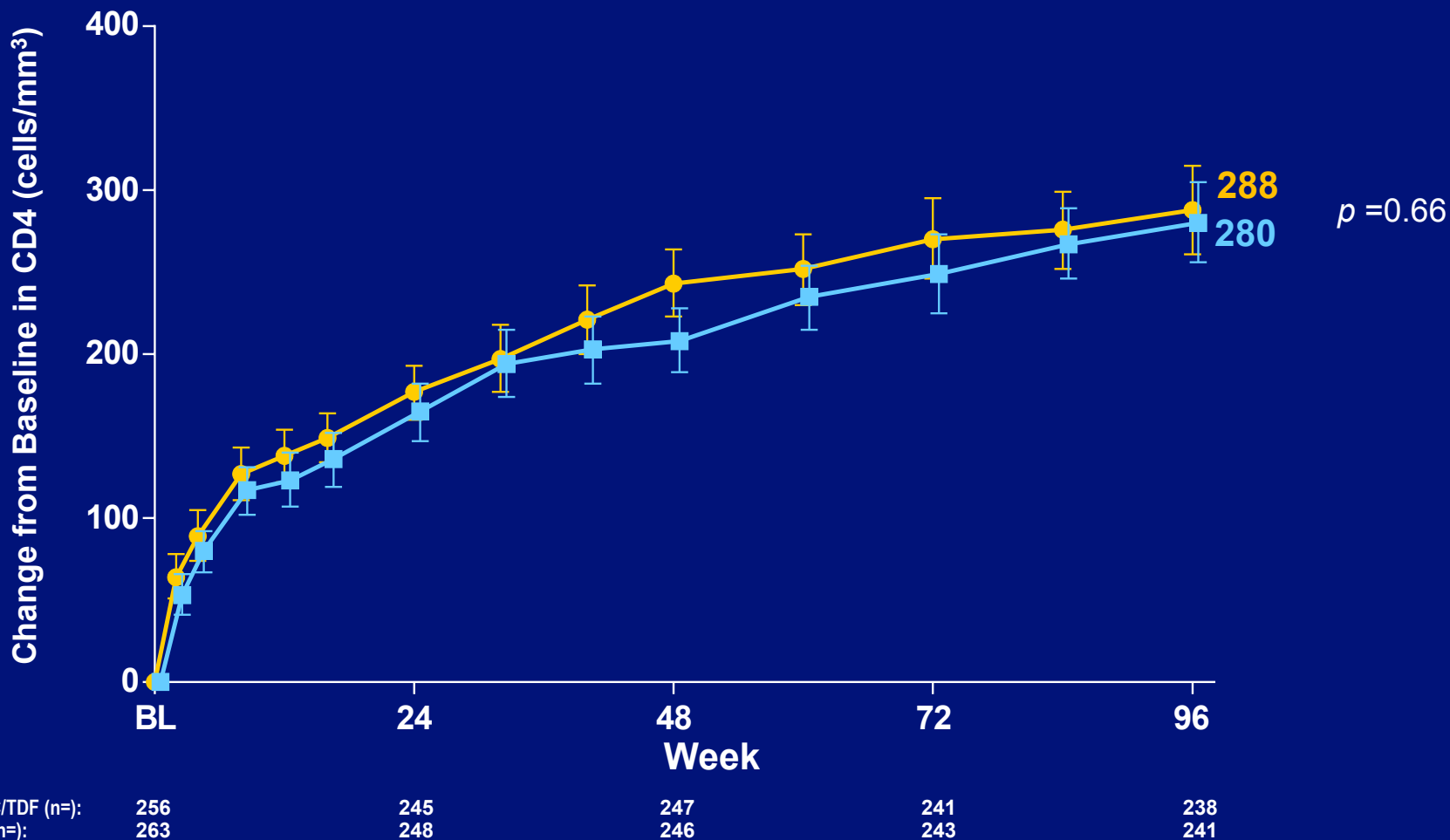


95% CI for Difference



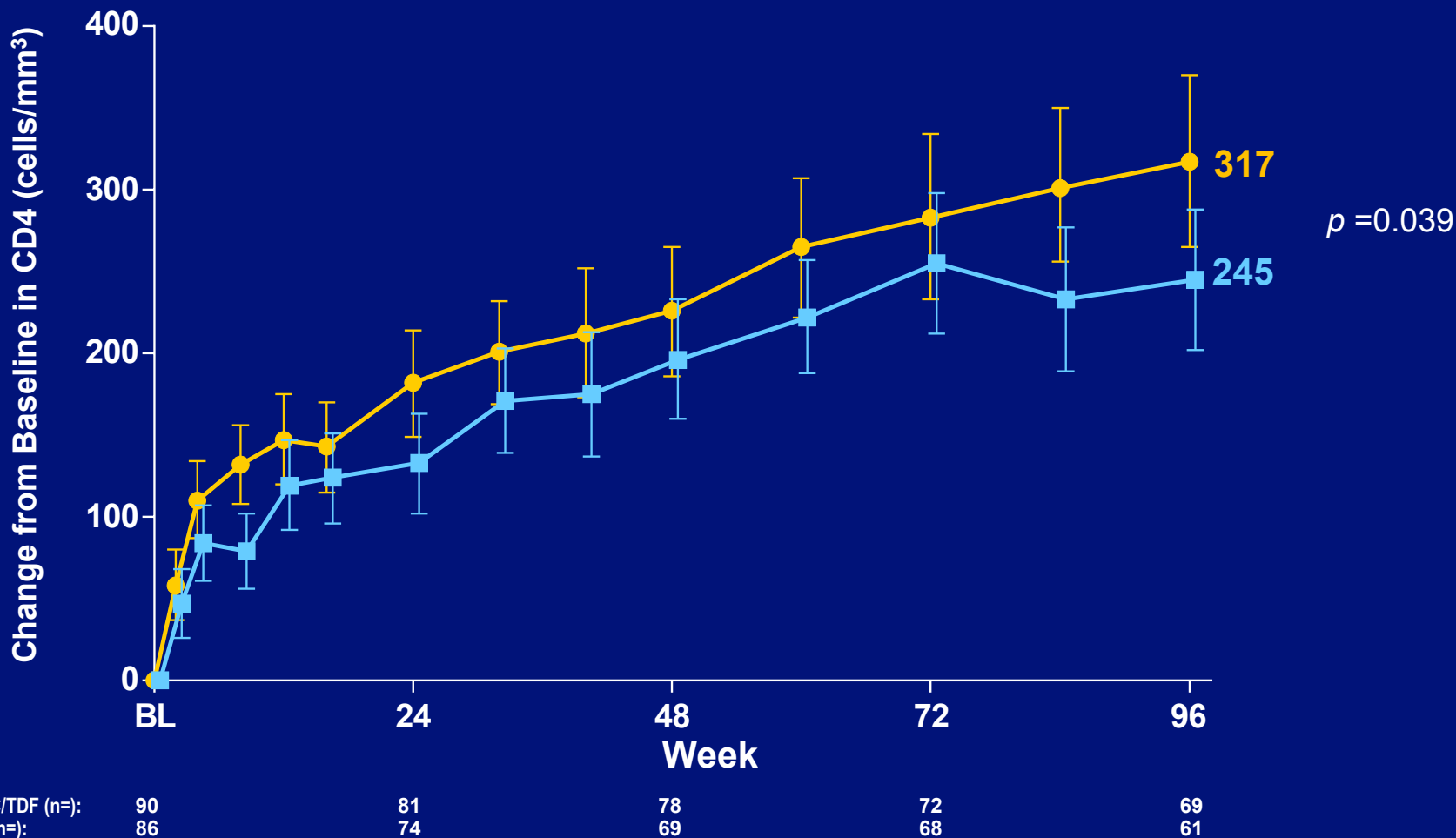
≥95% Adherence

CD4 Cell Count Change From Baseline



<95% Adherence

CD4 Cell Count Change From Baseline



Characteristics of EVG/COBI/FTC/TDF Subjects With Emergent Resistance

Patient	Baseline HIV-1 RNA (copies/mL)	Baseline CD4 Count (cells/mm ³)	Adherence (% by Pill Count)
1	107,000	41	≥95%
2	2,620,000	38	<95%
3	172,000	80	<95%
4	234,000	272	<95%
5	364,000	283	≥95%
6	200,000	17	≥95%
7	183,000	30	<95%
8	31,000	516	<95%
9	150,000	275	≥95%
10	55,600	72	≥95%

Most subjects on EVG/COBI/FTC/TDF with emergent resistance had high baseline viral load (>100,000 copies/mL) and/or low CD4 count (<200 cells/mm³).

Genotypic Analysis of EVG/COBI/FTC/TDF Subjects With Emergent Resistance

Patient	Time of Virology Analysis	Genotype											
		NRTI-R			INSTI-R								
					Primary				Secondary				
1	W16		K65K/R	M184M/I									
2	W16			M184V		E92Q							
3	W24			M184I		E92Q							
4	W32		K65R	M184V		E92Q						S153A	
5	W32			M184V		E92E/Q	Q148Q/R	N155H/N					
6	W40	A62A/V	K65R	M184V		E92Q			H51H/Y	L68V			
7	W40			M184V	T66T/I	E92E/Q							
8	W48			M184V		E92Q							
9	W84			M184V				N155H					
10	W96	A62V	K65R	M184V				N155H					

INSTI-R, integrase strand transfer inhibitor resistance; NRTI-R, nucleoside reverse transcriptase inhibitor resistance

Characteristics of EFV/FTC/TDF Subjects With Emergent Resistance

Patient	Baseline HIV-1 RNA (copies/mL)	Baseline CD4 Count (cells/mm ³)	Adherence (% by Pill Count)
1	19,700	302	<95%
2	12,200	296	<95%
3	955,000	273	≥95%
4	184,000	105	≥95%
5	99,000	399	<95%
6	4,860	478	≥95%
7	23,700	996	≥95%
8	140,000	416	<95%
9	39,900	333	<95%
10	427,000	567	<95%

Less than half of subjects on EFV/FTC/TDF with emergent resistance had high baseline viral load (>100,000 c/mL) and few had low baseline CD4 cell count (<200 cells/mm³).

Genotypic Analysis of EFV/FTC/TDF Subjects With Emergent Resistance

Patient	Time of Virology Analysis	Genotype									
		NRTI-R		NNRTI-R							
1	W8					K103N					
2	W24				K101E/K	K103N/S			G190A/G		
3	W32	K65R	M184M/V			K103N	V108I				
4	W48	K65R	M184M/I			K103N					M230L
5	W48					K103N		Y188Y/F/H/L			
6	W48					K103N					
7	W48			V90V/I	K101E/K	K103K/N	V108V/I				M230M/L
8	W48				K101E/K						
9	W72	K65K/R	M184M/V			K103N					
10	W96					K103N		Y188Y/H		P225P/H	

NNRTI-R, non-nucleoside reverse transcriptase inhibitor resistance; NRTI-R, nucleoside reverse transcriptase inhibitor resistance

Conclusions

- Subjects with <95% adherence on:
 - EVG/COBI/FTC/TDF or EFV/FTC/TDF had lower rate of virologic success at week 96 compared to those with $\geq 95\%$ adherence
 - EVG/COBI/FTC/TDF compared to EFV/FTC/TDF had
 - numerically higher rate of virologic success and
 - significantly larger gains in CD4 cell count
 - EVG/COBI/FTC/TDF who developed resistance tended to have high baseline viral load and/or low baseline CD4 cell count

References

1. Paterson DL, et al. Ann Int Med 2000; 133(1):21-30
2. Paterson DL, et al. Abstract 92. CROI1999; Chicago, IL
3. Bangsberg DR, et al. CID, 2006; 43:939-941