

# Longitudinal Resistance Analyses of the Phase 3 EVG/COBI/FTC/TDF Studies

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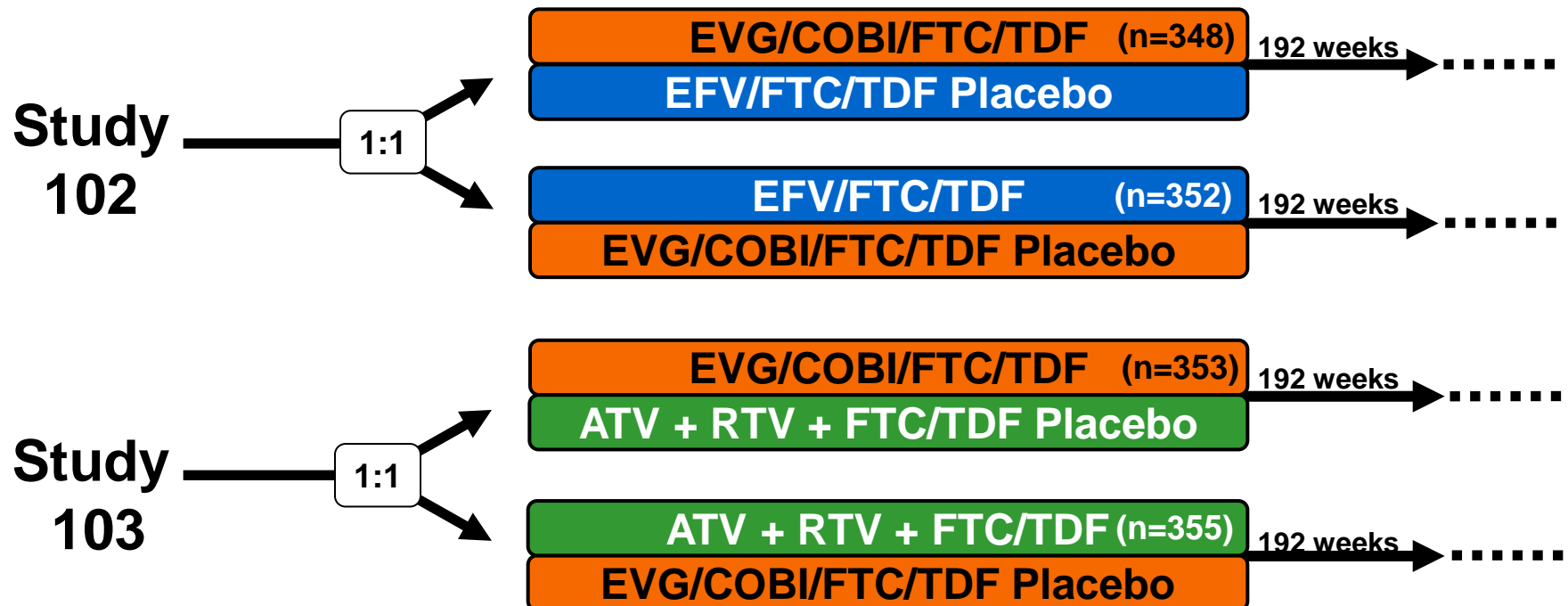
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# Introduction

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- Elvitegravir (EVG)/cobicistat (COBI)/emtricitabine (FTC)/tenofovir DF (TDF) has been co-formulated as the first integrase strand transfer inhibitor-containing single-tablet regimen Stribild™ (STB, EVG/COBI/FTC/TDF)



# HIV-1 RNA <50 c/mL through Week 144 (Missing=Failure)

Subjects with HIV-1 RNA <50 c/mL (%)

Study 102	89%	86%	82%
	86%	83%	78%

◆ EVG/COBI/FTC/TDF (n=348)  
■ EFV/FTC/TDF (n=352)

Study 103	92%	87%	81%
	88%	85%	79%

● EVG/COBI/FTC/TDF (n=353)  
■ ATV + RTV + FTC/TDF (n=355)

# Objectives

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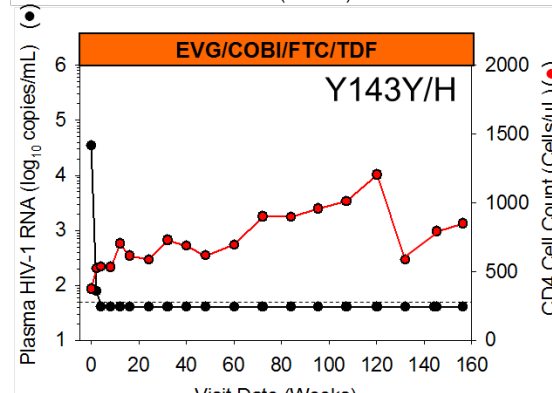
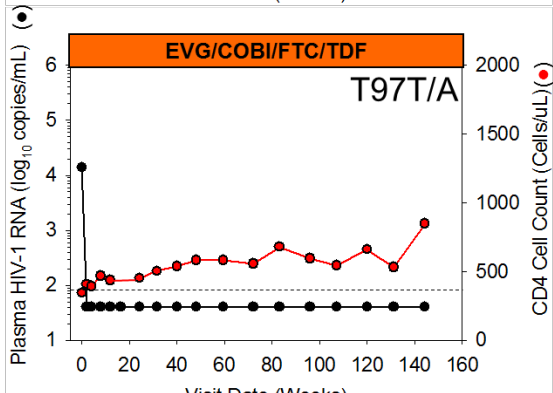
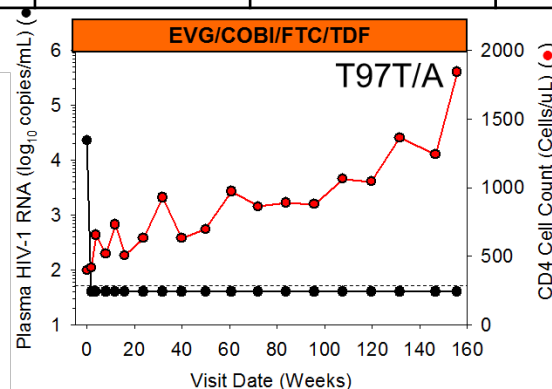
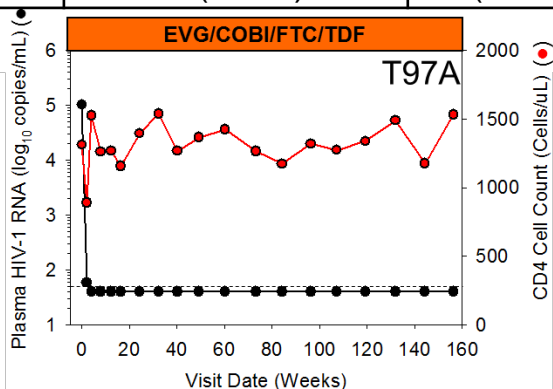
- Determine the impact of pre-existing HIV-1 drug resistance on treatment outcome through Week 144
- Describe the HIV-1 drug resistance mutations that developed through Week 144
  - Population sequencing and phenotypic analyses
  - Integrase phenotypic analyses of patient-derived clones
- Determine the frequency and order of mutation development using the first failure samples for the EVG/COBI/FTC/TDF subjects with emergent resistance

# Baseline HIV-1 Primary Drug Resistance Mutations in These Studies had No Impact on EVG/COBI/FTC/TDF Treatment through Week 144

Resistance Mutation	Number of Subjects n (%)	Week 144 Snapshot			Week 144 Resistance Analysis (Analyzed/Resistant)
		Success	Failure	No Data in Window	
<b>Any Primary NNRTI Mutation</b>	<b>95/701 (13.6%)</b>	<b>75 (78.9%)</b>	<b>8 (8.4%)</b>	<b>12 (12.6%)</b>	<b>8/1</b>
K103N	27 (3.9%)	22 (81.5%)	2 (7.4%)	3 (11.1%)	3/0
Y181C/I/V	4 (0.6%)	4 (100%)	0	0	0/0
G190A/S	2 (0.3%)	1 (50.0%)	1 (50.0%)	0	1/0
<b>Any Primary NRTI Mutation</b>	<b>52/701 (7.4%)</b>	<b>41 (78.8%)</b>	<b>4 (7.7%)</b>	<b>7 (13.5%)</b>	<b>5/2</b>
Any TAM	17 (2.4%)	13 (76.5%)	0	4 (23.5%)	1/0
2 TAMs	6 (0.9%)	3 (50.0%)	0	3 (50.0%)	0/0
M41L	9 (1.3%)	8 (88.9%)	0	1 (11.1%)	1/0
D67N	7 (1.0%)	4 (57.1%)	0	3 (42.9%)	0/0
K219E/N/Q/R	7 (1.0%)	4 (57.1%)	0	3 (42.9%)	0/0
<b>Any Primary PI Mutation</b>	<b>18/701 (2.6%)</b>	<b>14 (77.8%)</b>	<b>2 (11.1%)</b>	<b>2 (11.1%)</b>	<b>1/0</b>

# Baseline HIV-1 Primary Drug Resistance Mutations in These Studies had No Impact on EVG/COBI/FTC/TDF Treatment through Week 144

Resistance Mutation	Number of Subjects n (%)	Week 144 Snapshot			Week 144 Resistance Analysis (Analyzed/Resistant)
		Success	Failure	No Data in Window	
<b>Any Primary INSTI Mutation</b>	<b>4/363 (1.1%)</b>	<b>4 (100%)</b>	<b>0 (0%)</b>	<b>0 (0%)</b>	<b>0/0</b>
T97A	3 (0.8%)	3 (100%)	0	0	0/0
Y143H	1 (0.3%)	1 (100%)	0	0	0/0



# Resistance Analysis Population

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## Suboptimal Virologic Responder

< 1 log<sub>10</sub> decrease by Week 8  
confirmed at next visit  
confirmation sample analyzed

## Virologic Rebound

<50 c/ml then ≥400 c/mL twice or  
>1 log<sub>10</sub> increase from nadir twice  
confirmation sample analyzed

## Early Discontinuation – any reason

≥400 c/mL at last on study drug  
no confirmation required

## Viremic at Week 48, 96, 144

≥400 c/mL at last on study drug  
no confirmation required

# Emergent Drug Resistance in Subjects with Virologic Failure through Week 144

Integrated Analysis of Studies 102 and 103

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	<b>EVG/COBI/FTC/TDF (n = 701)</b>	<b>EFV/FTC/TDF (n = 352)</b>	<b>ATV + RTV + FTC/TDF (n = 355)</b>
<b>Resistance Analysis Population <sup>a</sup>% (n)</b>	<b>6.0% (42)</b>	<b>8.0% (28)</b>	<b>5.4% (19)</b>
<b>Developed Any Primary Resistance to Study Drugs % (n)</b>	<b>2.6% (18)</b>	<b>4.0% (14)</b>	<b>0.6% (2)</b>



# Emergent Drug Resistance in Subjects with Virologic Failure through Week 144

## Integrated Analysis of Studies 102 and 103

		<b>EVG/COBI/FTC/TDF (n = 701)</b>	<b>EFV/FTC/TDF (n = 352)</b>	<b>ATV + RTV + FTC/TDF (n = 355)</b>
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<b>Emergent Primary Resistance Mutations % (n)</b>	<b>NRTI-R</b>	<b>FTC/TDF 2.4% (17)</b>	<b>FTC/TDF 1.1% (4)</b>	<b>FTC/TDF 0.6% (2)</b>
		M184V/I 2.4% (17)	M184V/I 1.1% (4)	M184V/I 0.6% (2)
		K65R 0.7% (5)	K65R 0.9% (3)	K65R 0
	<b>3rd agent</b>	<b>EVG 2.1% (15)</b>	<b>EFV 4.0% (14)</b>	<b>ATV + RTV 0% (0)</b>
		E92Q 1.3% (9)	K103N 3.7% (13)	
		N155H 0.7% (5)	K101E 1.4% (5)	
Q148R 0.4% (3)		V108I 1.1% (4)		
T66I 0.3% (2)		Y188F/H/L 0.9% (3)		
T97A 0.1% (1)	M230L 0.6% (2)			
		V90I 0.3% (1)		
		G190A 0.3% (1)		
		P225H 0.3% (1)		
	<b>Primary PI-R</b>	<b>0.1% (1)</b>	<b>0.6% (2)</b>	<b>0% (0)</b>

# Cross-Resistance by Phenotypic Analysis of the EVG/COBI/FTC/TDF Virologic Failures with Resistance Through Week 144 (Integrated Analysis of Studies 102 and 103)

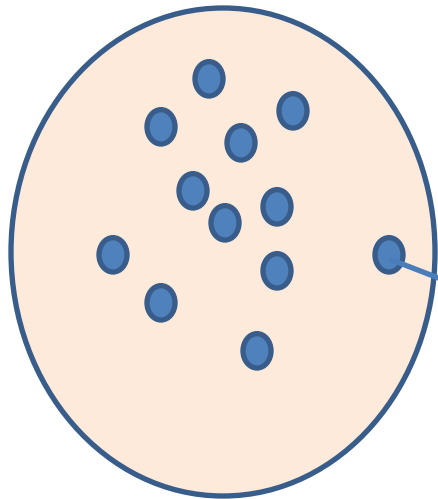
Virology Subject (Study)	Time of Virology Analysis	Genotype		Phenotype (Fold-Change vs WT)																
		NRTI-R	INSTI-R	NRTIs						NNRTIs			PIs						INSTIs	
				ABC	ddl	3TC	FTC	TFV	d4T	ZDV	EFV	ETR	NVP	AMP	ATV	DRV	IDV	LPV	TPV	EVG
<b>Baseline to Week 48 ("Year 1")</b>																				
332 (103)	W12	M184V																		
503 (102)	W16	K65K/R M184M/I																		
648 (102)	W16	M184V	E92Q																	
476 (103)	W16	ND	T66T/I E92E/Q N155N/H E157E/Q	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	
562 (103)	W24	M184V	N155H																	
182 (102)	W24	M184I	E92Q																	
359 (103)	W24	M184V	Q148R																	
257 (102)	W32	K65R M184V	E92Q S153A																	
101 (102)	W32	M184V	E92E/Q Q148Q/R N155H/N																	
299 (103)	W32	A62A/V K65R M184V	Q148R G140C																	
012 (102)	W40	A62A/V K65R M184V	E92Q H51H/Y L68V																	
041 (102)	W40	M184V	T66T/I E92E/Q																	
667 (102)	W48	M184V	E92Q																	
<b>Week 48 to Week 96 ("Year 2")</b>																				
425 (103)	W72	M184V	E92Q																	
322 (102)	W84	M184V	N155H																	
545 (102)	W96	A62V K65R M184V	N155H																	
<b>Week 96 to Week 144 ("Year 3")</b>																				
516 (103)	W132	M184V	T97A G163G/R																	
461 (103)	W144	M184M/V	ND																ND	

**Most resistance emerged during the first 48 weeks**

**FTC resistance in all patients; cross-resistance to 3TC and ddl**

**EVG resistant isolates had RAL cross-resistance**

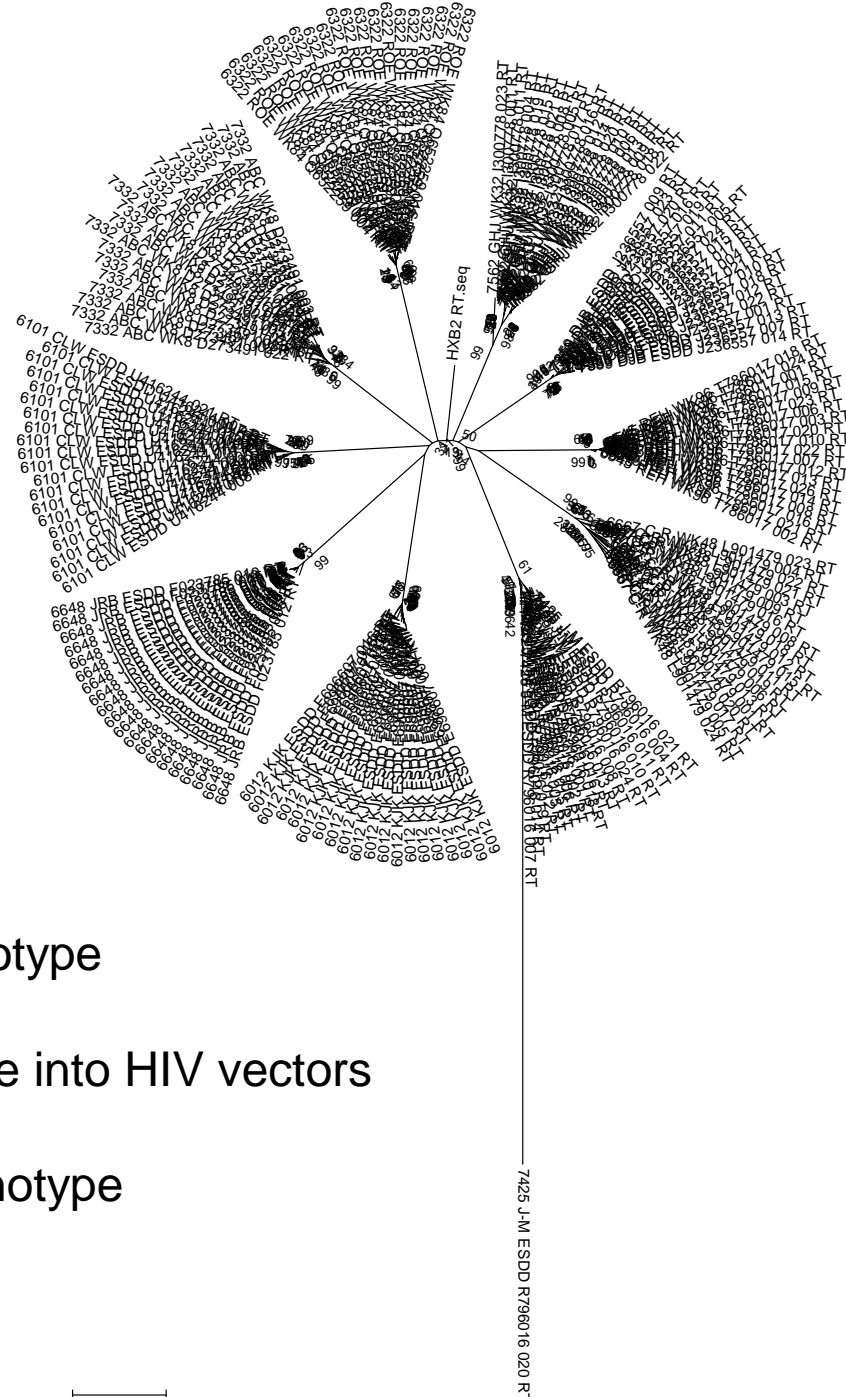
# Clonal Analyses of Patient Isolates



Genotype

Clone into HIV vectors

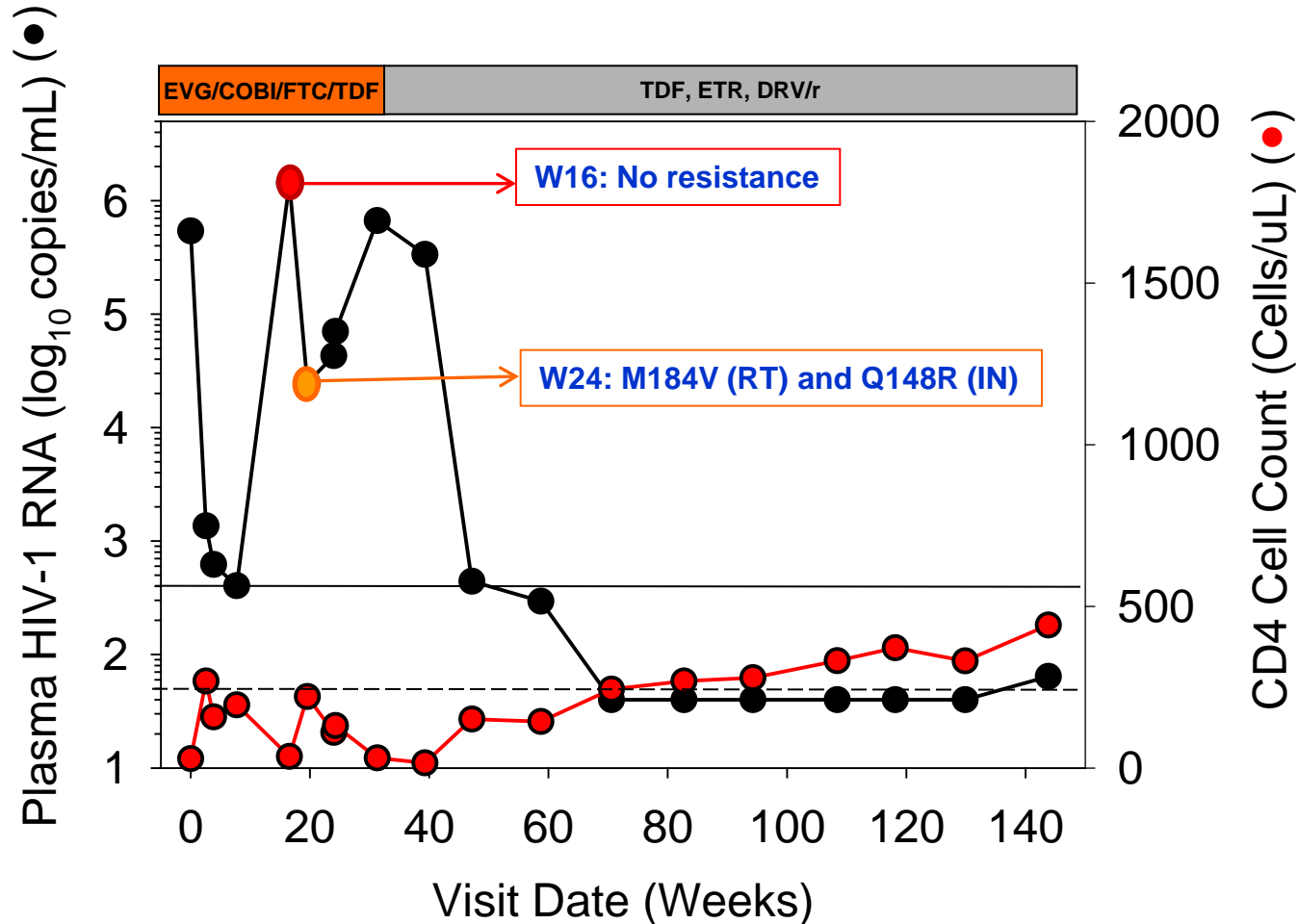
Phenotype



# Phenotypic Analysis of EVG/COBI/FTC/TDF Virologic Failure Isolate Clones: No Cross-Resistance to DTG

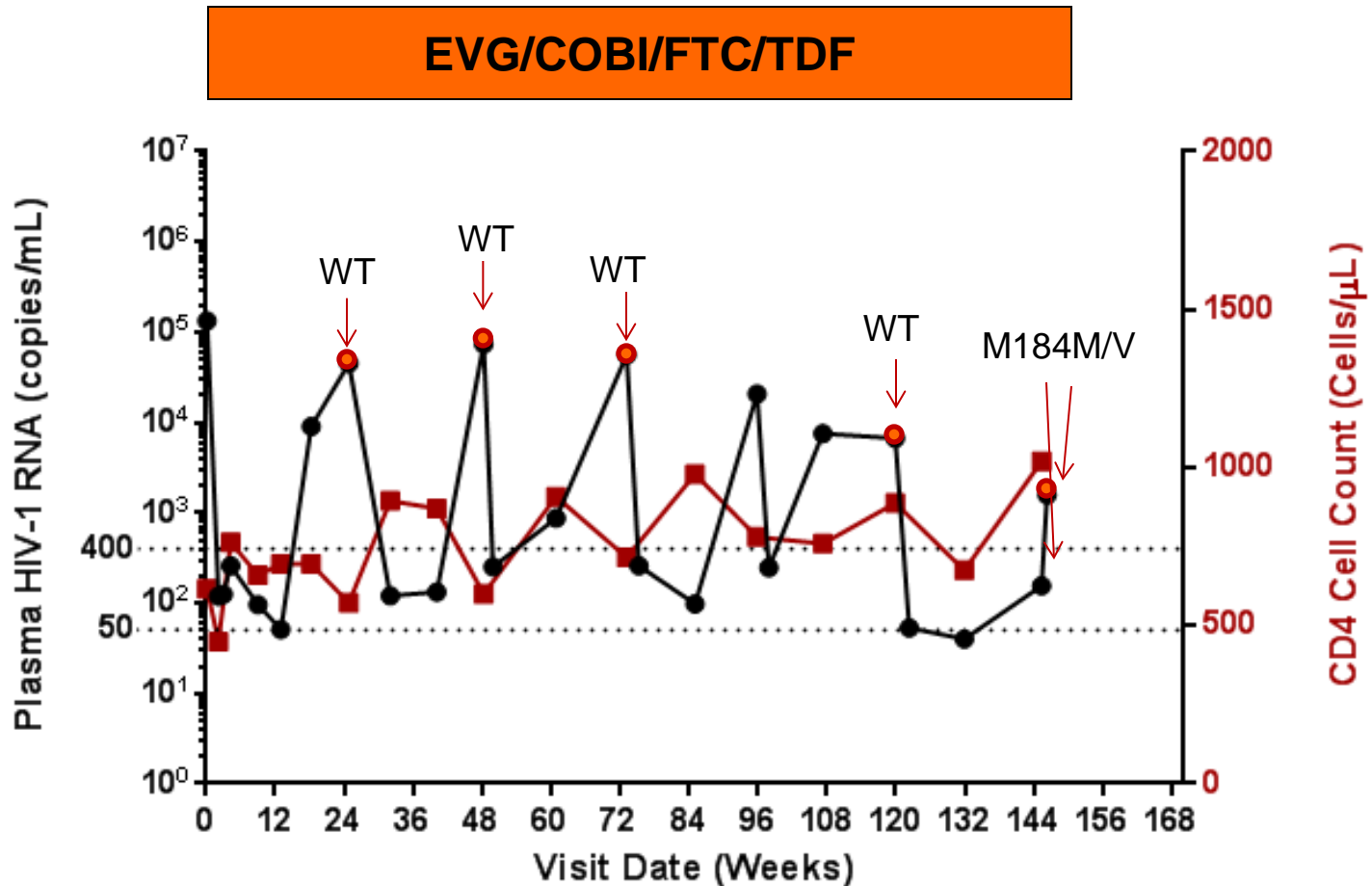
Virology Patient (Study)	Time of Virology Analysis	Genotype			Phenotype		
		NRTI-R	INSTI-R		Fold-Change vs WT		
			Primary	Secondary	EVG	RAL	DTG
<b>648 (0102)</b>	<b>W16</b>	<b>M184V</b>	<b>E92Q</b>		<b>36</b>	<b>3.1</b>	<b>nd</b>
	<i>Clone 7</i>	<i>M184V</i>	<i>E92Q</i>		<b>43</b>	<b>4.20</b>	<b>1.46</b>
	<i>Clone 10</i>	<i>M184V</i>	<i>E92Q</i>		<b>42</b>	<b>4.20</b>	<b>1.60</b>
	<i>Clone 11</i>	<i>M184V</i>	<i>E92Q</i>		<b>32</b>	<b>3.97</b>	<b>1.57</b>

# First Failure Timepoint Analysis: Can Fail to Detect Resistance



Adherence < 95%, no pill bottles returned at week 8-12, poor adherence Weeks 12-24

# First Failure Timepoint Analysis: Can Fail to Detect Resistance



# First Failure Analysis of Subjects with Emergent EVG/COBI/FTC/TDF Resistance

- Subjects with drug resistance at confirmation visit assessed for resistance at first failure

		EVG/COBI/FTC/TDF (n = 701) Confirmation Sample Resistance Analysis		EVG/COBI/FTC/TDF (n = 701) First Failure Sample Resistance Analysis	
Resistance Analysis Population % (n)		6.0% (42)		2.6% (18)	
Subjects with Data for RT and/or IN		6.0% (42)		2.4% (17)	
Developed Any Primary Resistance to Study Drugs % (n)		2.6% (18)		2.1% (15)	
Baseline to Week 48		1.9% (13)		1.4% (10)	
>Week 48 to Week 96		0.4% (3)		0.4% (3)	
>Week 96 to Week 144		0.3% (2)		0.3% (2)	
Emergent Primary Resistance Mutations % (n)	NRTI-R	FTC/TDF	2.4% (17)	FTC/TDF	2.0% (14)
		M184V/I	2.4% (17)	M184V/I	2.0% (14)
		K65R	0.7% (5)	K65R	0.4% (3)
	INSTI-R	EVG	2.1% (15)	EVG	1.1% (8)
		E92Q	1.3% (9)	E92Q	0.4% (3)
		N155H	0.7% (5)	N155H	0.3% (2)
		Q148R	0.4% (3)	Q148R	0.1% (1)
		T66I	0.3% (2)	T66I/A/V	0.1% (1)
T97A	0.1% (1)	T97A	0.1% (1)		

# Conclusions

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- High and durable efficacy was observed in subjects treated with EVG/COBI/FTC/TDF, EFV/FTC/TDF and ATV + RTV + FTC/TDF through Week 144
  - in subjects with pre-existing primary drug resistance mutations (e.g. K103N in RT or T97A in IN)
  - rate of resistance development to EVG/COBI/FTC/TDF was low (2.6% of treated subjects)
  - Evidence of EVG cross-resistance to RAL; no cross-resistance to DTG
- Longitudinal analyses of resistance at the first failure timepoint
  - M184V/I often develops first
  - First failure analysis can fail to detect resistance
    - Failed to detect mutations in RT (4/18 subjects) and in IN (10/18 subjects) by standard population sequencing
  - Possible role for deep sequencing at early failure timepoints



# Acknowledgements

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- Investigators and patients in these studies
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