Virological Correlates Associated with Treatment Failure at Week 48 in the Phase 3 Study of Maraviroc in Treatment-Naive Patients

Reported by Jules Levin
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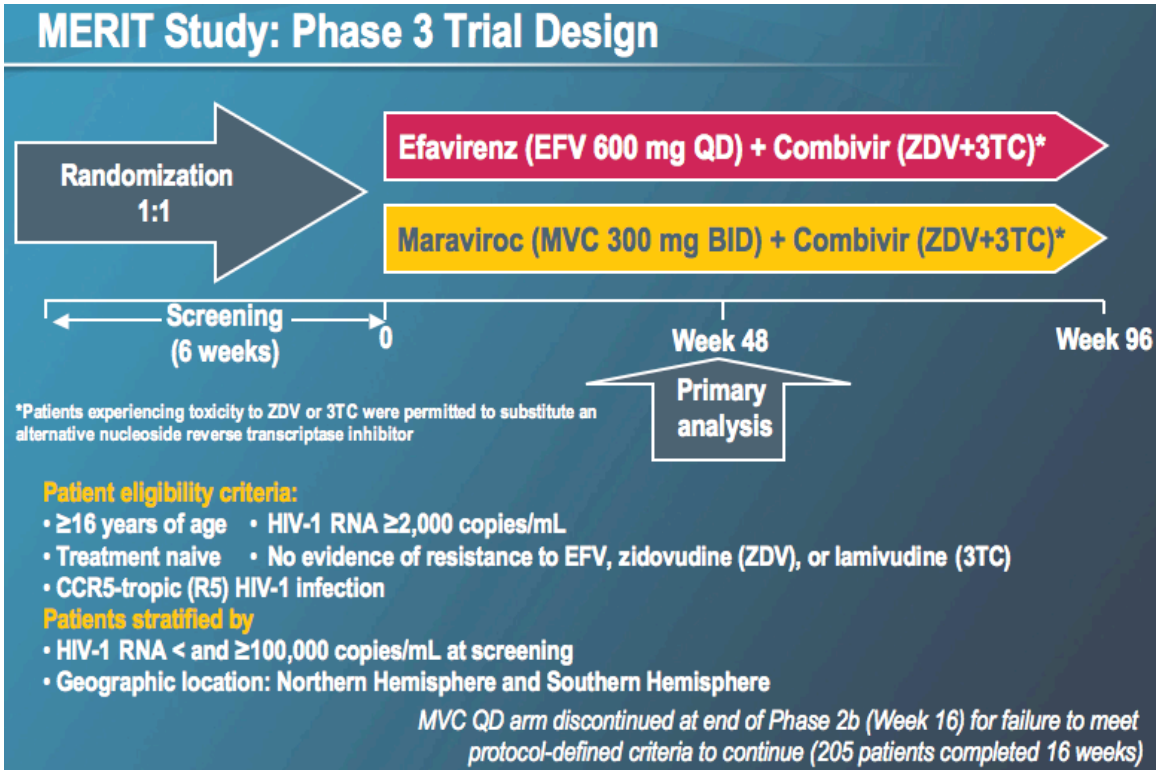
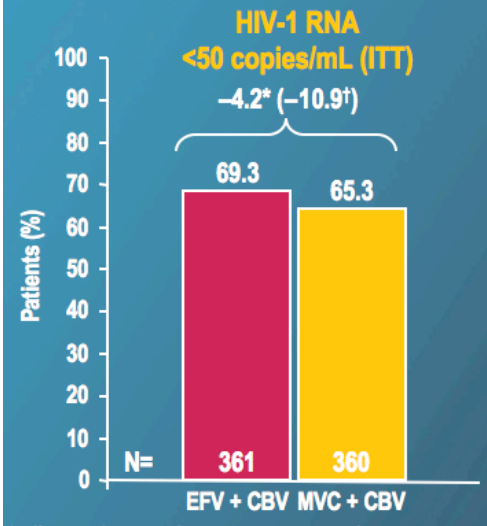
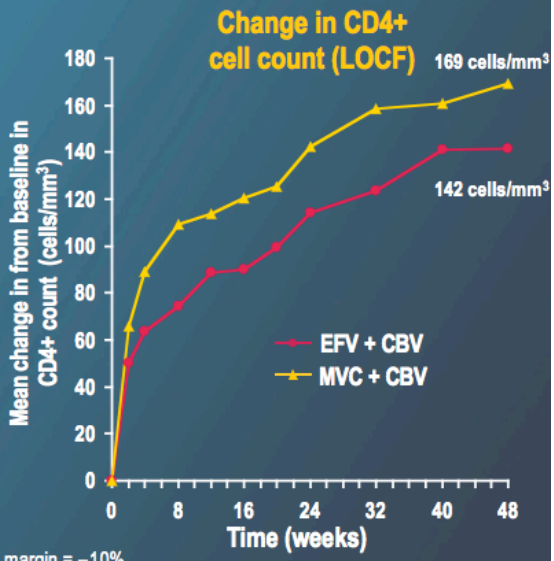


Week 48 Efficacy Results

Includes all patients who received at least one dose of study medication





*Difference (adjusted for randomization strata)
†Lower bound of 1-sided 97.5% confidence interval; non-inferiority margin = –10%
CBV = Combivir

Summary of Discontinuations Through 48 Weeks

Includes all patients who received at least one dose of study medication

Reason for discontinuation	EFV + CBV N=361	MVC + CBV N=360
All, n (%)	91 (25.2)	97 (26.9)
Adverse event, n (%)	49 (13.6)	15 (4.2)
Lack of efficacy, n (%)	15 (4.2)	43 (11.9)
Other reason, n (%)	9 (2.5)	14 (3.9)
Withdrew consent or lost to follow-up, n (%)	18 (5.0)	25 (6.9)

Objectives

- To understand the virological correlates associated with treatment failure at Week 48

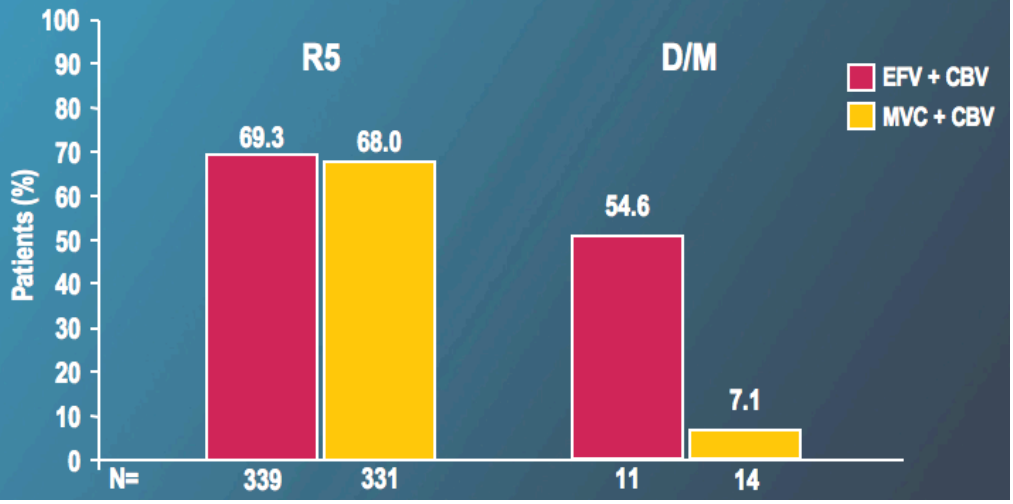
Methods

- Tropism was measured throughout the study using the Trofile™ assay
- Resistance to NRTIs and EFV was evaluated by the PhenoSense GT™ assay
- Resistance to MVC was evaluated using the PhenoSense Entry™ assay, with plateaus in maximum percent inhibition (MPI) <95% as a marker of resistance
- MVC plasma concentrations were determined using sparse PK sampling and combined with adherence data

Percentage of Patients with HIV-1 RNA <50 Copies/mL at Week 48 by Tropism Result at Baseline

Includes all patients who received at least one dose of study medication

- 25 (3.5%) patients had D/M virus at baseline
- In both treatment groups the proportion of patients with D/M virus at baseline who achieved undetectable HIV-1 RNA was reduced relative to patients with R5 virus



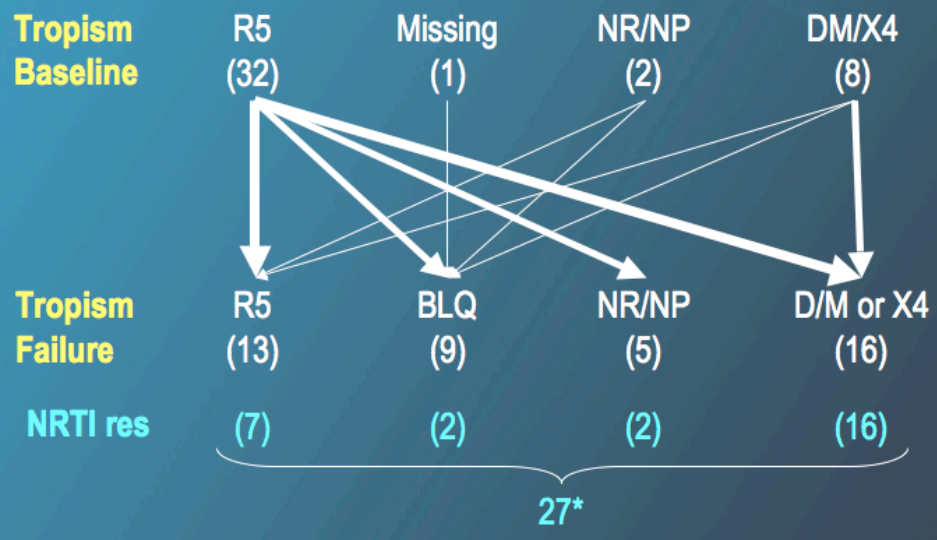
Possible Correlates of Tropism Changes From Screening to Baseline: Combined Treatment Groups

	Tropism change from screening to baseline, N=24	R5 at screening and baseline, N=697
Mean screening HIV-1 RNA, $\log_{10}$ copies/mL	4.79	4.84
Mean screening CD4+ count, cells/mm^3 (min, max)	201 (23, 431)	271 (3, 1,528)
Viral subtype		
B	17 (4.2%)	390 (95.8%)
C	4 (1.9%)	212 (98.1%)
Other/undetermined	3 (4.2%)	68 (95.8%)

Analysis of Virological Correlates Associated with Lack of Efficacy

- Virological analysis of patients who discontinued due to lack of efficacy
  - 43 patients on MVC
  - 15 patients on EFV

Tropism Shift and NRTI Resistance at Failure for Patients on MVC (n=43)



NR/NP = no result/non-phenotypable
BLQ = HIV-1 RNA <500 copies/mL tropism tests were cancelled or censored for these samples
*Excludes two patients with no resistance data at the last timepoint on treatment, but with resistance at earlier visits

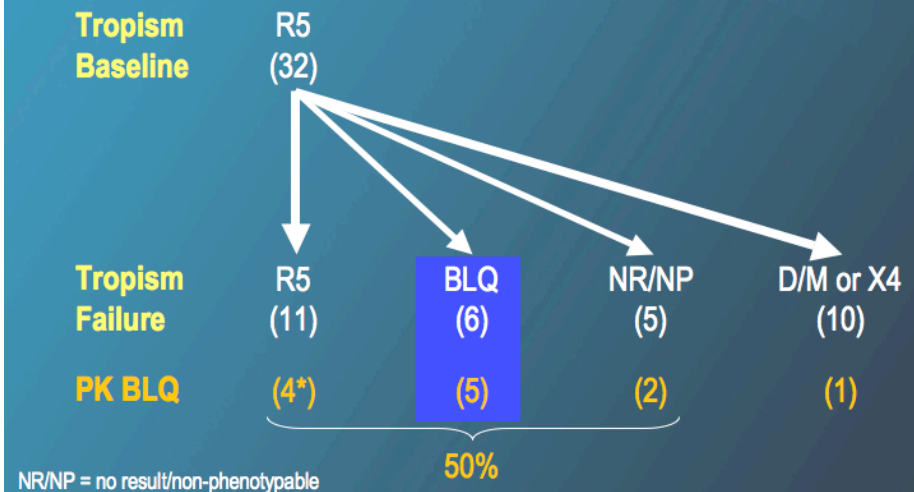
RTI Resistance Selected in Virus from Patients with Treatment Failure

Tropism at failure*	MVC (300 mg BID)			
	N	n	M184V	2NRTIres
R5	22	22	10 (45%)	2 (9%)
D/M or X4	19	19	19 (100%)	5 (26%)
Other	2	2	0	0
Total	**43**	**43**	**29 (67%)**	**7 (16%)**

Tropism at failure*	EFV (600 mg QD)				
	N	n	EFVres →	+M184V	+2NRTIres
R5	14	13	8	3	0
Other	1	1	1	1	1
Total	**15**	**14**	**9 (64%)**	**4 (29%)**	**1 (7%)**

* Last valid tropism result while on treatment
N = total patients in group; n = total patients with a valid resistance test; 2NRTI*res* = genotypic resistance to 3TC and ZDV (or substituted NRTI); EFV*res* = genotypic resistance to EFV; Other = missing baseline tropism result (n=1) or no valid tropism data during failure (n=2)

Incomplete Adherence is a Significant Contributor to Treatment Failure in Patients with R5 Virus at Baseline



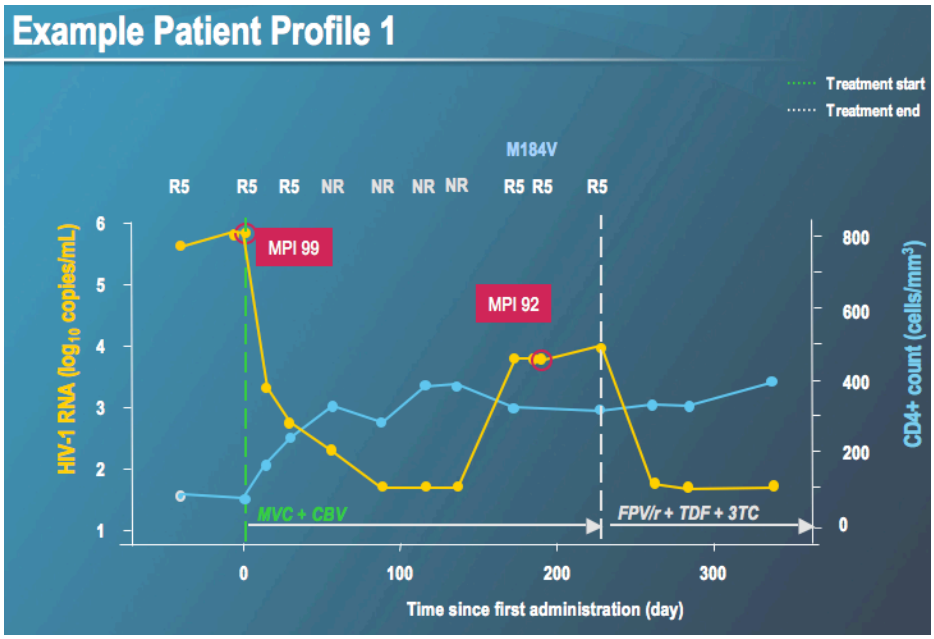
NR/NP = no result/non-phenotypable
BLQ = HIV-1 RNA <500 copies/mL tropism tests were cancelled or censored for these samples
PK BLQ = MVC plasma concentrations below the limit of quantification corresponding to a rebound in viral load
* Includes one patient with no BLQ PK but with documented interruption between visits corresponding to rebound in VL.

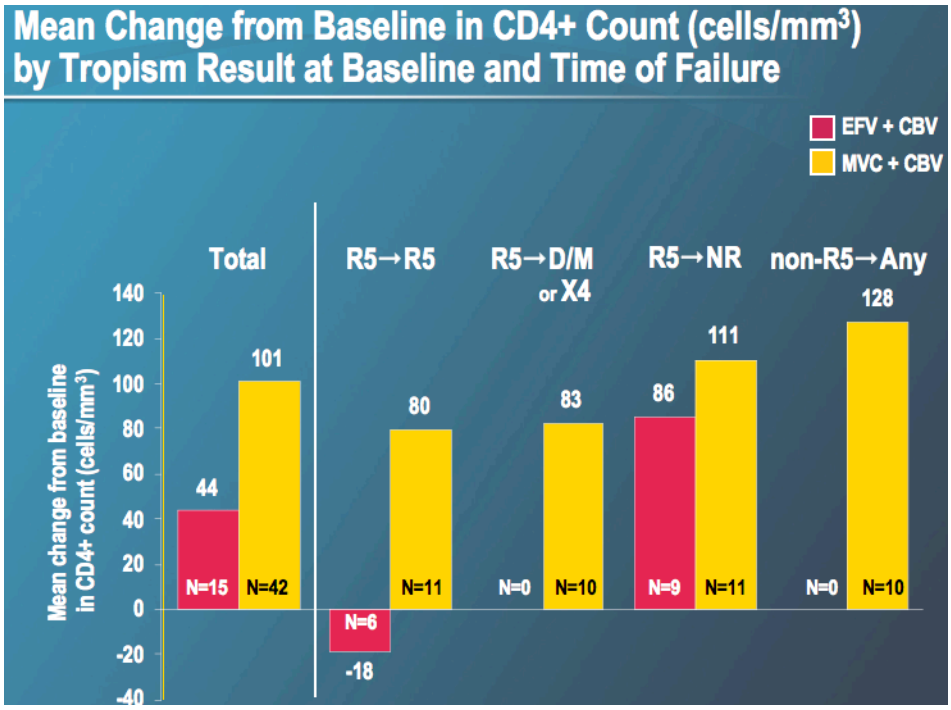
Characteristics of Patients who Failed 300 mg BID MVC with R5 Virus

Country	Race	Sex	Clade	MVC resistance*	NRTI resistance**	PK BLQ
Belgium	Black	M	AG	Yes	M184V	
Argentina	White	M	BF	Yes	M184V, M41M/L	
Poland	White	M	B		M184V	
USA	White	M	B		M184V	
South Africa	Black	M	C		M184V	
Australia	White	M	B			Yes
Puerto Rico	White	M	B			(Note 1)
South Africa	Black	M	C			Yes
South Africa***	Black	M	C			Yes
South Africa	Black	F	C			Yes
UK	White	M	B			
South Africa	Other	M	C			

*By phenotype;**By genotype; *** Tropism was recorded as "BLQ" at last on-treatment timepoint, but 'R5' at all other timepoints
PK BLQ = serum levels of MVC during periodic sampling were below limit of quantification
Note 1: documented non-adherence between visits coinciding with viral load rebound

Heera J, *et al. 15th CROI 2008*; Presentation 40LB


Example Patient Profile 1
Treatment start
Treatment end
M184V
R5 R5 R5 NR NR NR NR R5 R5 R5
MPI 99
MPI 92
HIV-1 RNA (log10 copies/mL)
CD4+ count (cells/mm3)
MVC + CBV
FPV/r + TDF + 3TC
Time since first administration (day)


Mean Change from Baseline in CD4+ Count (cells/mm3) by Tropism Result at Baseline and Time of Failure
EFV + CBV
MVC + CBV
Total
R5→R5
R5→D/M or X4
R5→NR
non-R5→Any
Mean change from baseline in CD4+ count (cells/mm3)
44
101
80
83
86
111
128
-18
N=15
N=42
N=6
N=11
N=0
N=10
N=9
N=11
N=0
N=10

Tropism Summary

- 13 patients (3.8%) receiving MVC had a change in tropism result from R5 to D/M between screening and baseline
  - The response to MVC was significantly reduced in this subgroup
  - Tropism changes were 50% less frequent in patients with clade C HIV-1 than in patients with clade B or other clades
- For subjects with R5 virus at baseline, no appreciable difference in treatment response was seen between the MVC and EFV treatment groups
- A retrospective analysis will be performed to investigate the impact of an enhanced tropism assay on MERIT outcomes
- CXCR4-using virus was detected at failure in 10/32 (31.3%) MVC-treated (300 mg BID) subjects with R5 virus at baseline
- Patients failing MVC had higher CD4+ cell counts at failure than EFV, irrespective of tropism result at failure

Resistance Summary

- Lamivudine resistance mutation (M184V/I) was most common in patients failing in the MVC arm
  - 19/19 patients failing with D/M or X4 virus
  - 10/22 patients failing with R5 virus
- EFV-related resistance mutations were most common in patients failing in the EFV arm
  - 9/14 patients with resistance test data
- Resistance to MVC in patients failing with R5 virus was uncommon
  - 2/12 patients studied
- Viral load rebound in patients failing the MVC arm was more commonly associated with BLQ plasma levels of MVC at the time of failure