

# Virologic Suppression on Maraviroc in Treatment-Naïve Patients With R5 HIV-1 is Similar to Efavirenz at High Baseline Viral Load, and Maraviroc Discontinuations for Adverse Events are Less Likely to Show Drug Resistance: 48-Week Results From the MERIT Study

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## Background

- The MERIT study compared twice-daily maraviroc (MVC) plus zidovudine/lamivudine (Combivir, CBV) with once-daily efavirenz (EFV) + CBV in treatment-naïve patients with R5 HIV-1 (original Trofile assay, Monogram Biosciences)
- A *post-hoc* reanalysis of MERIT (MERIT-ES) has been undertaken which repeated the pre-specified study comparisons in a subgroup of MERIT patients eligible for study entry according to a newer, enhanced Trofile assay
  - The MERIT-ES analysis showed similar week 48 virologic responses between the two treatment arms<sup>1</sup>
- Randomization in MERIT was stratified by screening HIV-1 RNA levels (< 100,000 versus ≥ 100,000 copies/mL) and by geographic location (Northern Hemisphere versus Southern Hemisphere)
- Virologic responses in these randomization subgroups and non-virologic discontinuations for adverse events in the MVC versus EFV treatment arms were assessed in the MERIT-ES dataset

## Methods

- Baseline characteristics, proportions < 50 HIV-1 RNA copies/mL at week 48 (ITT analysis) and TLOVR outcomes over 48 weeks (for limit of quantification <50 copies/mL) were compared between baseline randomization strata and treatment arms in the MERIT-ES dataset
- Time to overall discontinuation (Kaplan-Meier), time to adverse event (AE)-related discontinuations and the development of post-discontinuation resistance to study drug were assessed by treatment arm

## Results

- Baseline characteristics were broadly similar between randomization strata (Table 1) with the following exceptions:
  - The majority of black and female patients were located in the Southern hemisphere
  - Proportionately more patients (~7%) in the Southern hemisphere had screening HIV-1 RNA ≥ 100,000 copies/mL than in the Northern hemisphere
  - Baseline CD4<sup>+</sup> cell counts were lower in patients with screening HIV-1 RNA ≥ 100,000 copies/mL

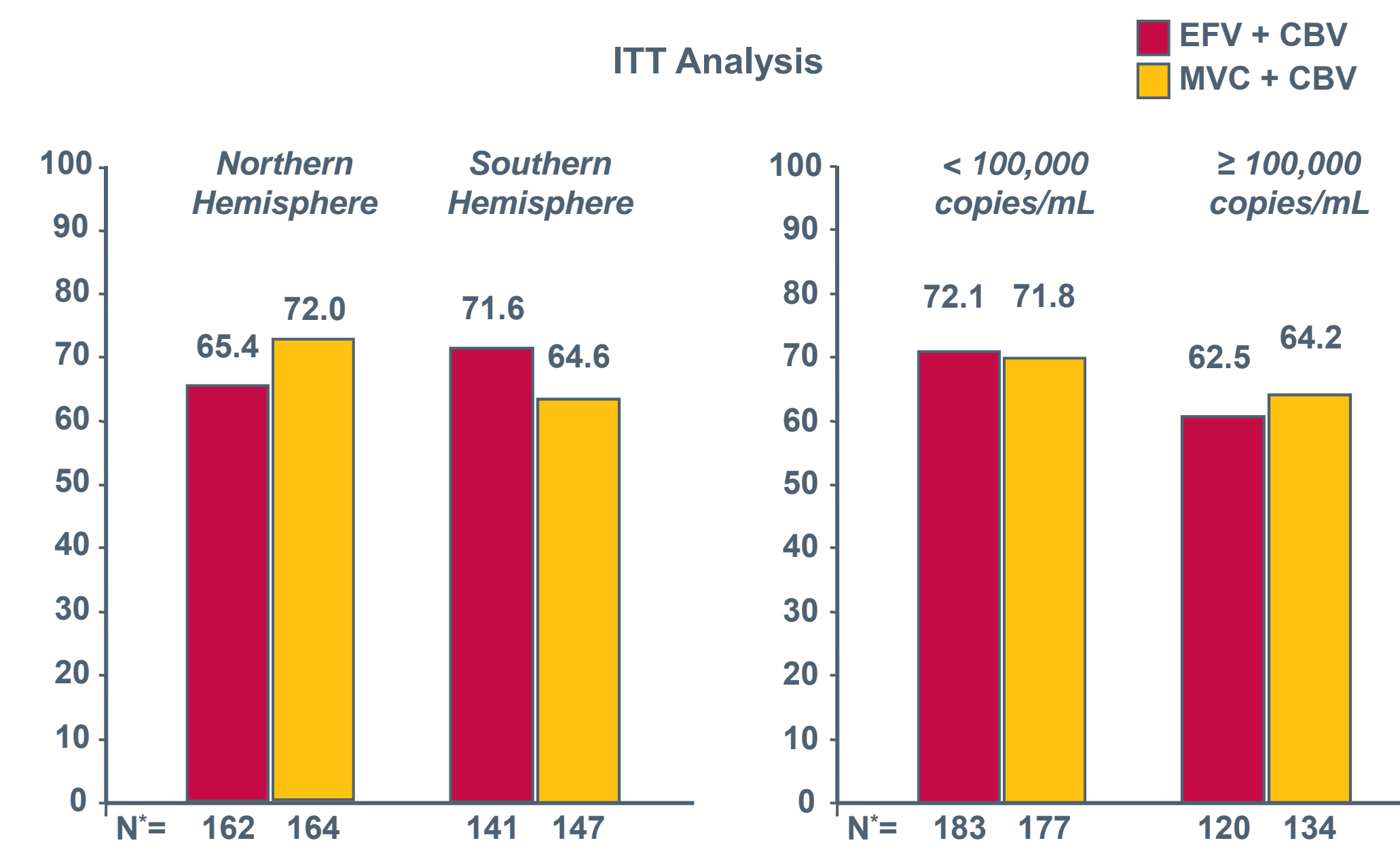
Table 1: Patient baseline characteristics (MERIT-ES) by (a) geographic location and (b) screening HIV-1 RNA randomization strata

(a)	Northern Hemisphere		Southern Hemisphere	
	EFV + CBV N=162	MVC + CBV N=164	EFV + CBV N=141	MVC + CBV N=147
Mean age, yrs (range)	38.0 (19-77)	36.6 (20-65)	36.5 (18-64)	36.2 (21-69)
Male, n (%)	133 (82.1)	142 (86.6)	80 (56.7)	78 (53.1)
Race, n (%)				
White	114 (70.4)	122 (74.4)	47 (33.3)	45 (30.6)
Black	32 (19.8)	19 (11.6)	86 (61.0)	95 (64.6)
Asian	2 (1.2)	3 (1.8)	1 (0.7)	1 (0.7)
Other	14 (8.6)	20 (12.2)	7 (5.0)	6 (4.1)
Median CD4 <sup>+</sup> count, cells/mm <sup>3</sup> (range) <sup>a</sup>	262 (52-966)	244 (6-937)	258 (36-711)	242 (5-793)
Mean HIV-1 RNA, log <sub>10</sub> copies/mL (SD) <sup>a</sup>	4.81 (0.56)	4.81 (0.61)	4.85 (0.64)	4.92 (0.67)
HIV RNA ≥ 100,000 copies/mL, n (%)	60 (37.0)	65 (39.6)	60 (42.6)	69 (46.9)

(b)	< 100,000 copies/mL		≥ 100,000 copies/mL	
	EFV + CBV N=183	MVC + CBV N=177	EFV + CBV N=120	MVC + CBV N=134
Mean age, yrs (range)	36.3 (19-65)	35.5 (20-69)	38.9 (18-77)	37.5 (20-65)
Male, n (%)	123 (67.2)	123 (69.5)	90 (75.0)	97 (72.4)
Race, n (%)				
White	93 (50.8)	97 (54.8)	68 (56.7)	70 (52.2)
Black	73 (39.9)	61 (34.5)	45 (37.5)	53 (39.6)
Asian	1 (0.5)	3 (1.7)	2 (1.7)	1 (0.7)
Other	16 (8.7)	16 (9.0)	5 (4.2)	10 (7.5)
Median CD4 <sup>+</sup> count, cells/mm <sup>3</sup> (range) <sup>a</sup>	273 (52-966)	269 (49-937)	233 (36-637)	201 (5-851)
Mean HIV-1 RNA, log <sub>10</sub> copies/mL (SD) <sup>a</sup>	4.48 (0.44)	4.45 (0.48)	5.37 (0.35)	5.41 (0.36)

<sup>a</sup>Values represent an average of pre-dose measurements taken at randomization, screening and baseline.

Figure 1: Higher proportions of patients receiving MVC in the Northern hemisphere achieved HIV RNA < 50 copies/mL at week 48, compared with those receiving EFV. Response rates comparing those with high and low viral load were similar in the MVC and EFV groups



Missing values are classified as failures/non-responders. Only patients with an R5 screening result by enhanced Trofile assay are included. Total number of patients in indicated subgroup, used as the denominator for the percentages quoted.

Table 2: Summary of study outcomes (MERIT-ES) through 48 weeks by (a) geographic location and (b) screening HIV-1 RNA randomization strata for TLOVR analysis

(a)	EFV + CBV		MVC + CBV	
	Northern Hemisphere (N=162)	Southern Hemisphere (N=141)	Northern Hemisphere (N=164)	Southern Hemisphere (N=147)
Responder, n (%)	110 (67.9)	106 (75.2)	114 (69.5)	99 (67.3)
Non-responders, n (%)	52 (32.1)	35 (24.8)	50 (30.5)	48 (32.7)
Virologic failure, n (%)	3 (1.9)	5 (3.5)	13 (7.9)	12 (8.2)
Never suppressed, n (%)	0 (0)	1 (0.7)	3 (1.8)	3 (2.1)
Rebound, n (%)	7 (4.3)	5 (3.5)	12 (7.3)	10 (6.8)
Discontinuations				
AEs, n (%)	34 (21.0)	9 (6.4)	10 (6.1)	3 (2.1)
Subject defaulted, n (%) <sup>a</sup>	6 (3.7)	8 (5.7)	8 (4.9)	12 (8.1)
Other, n (%)	2 (1.2)	7 (5.0)	4 (2.5)	8 (5.4) <sup>b</sup>

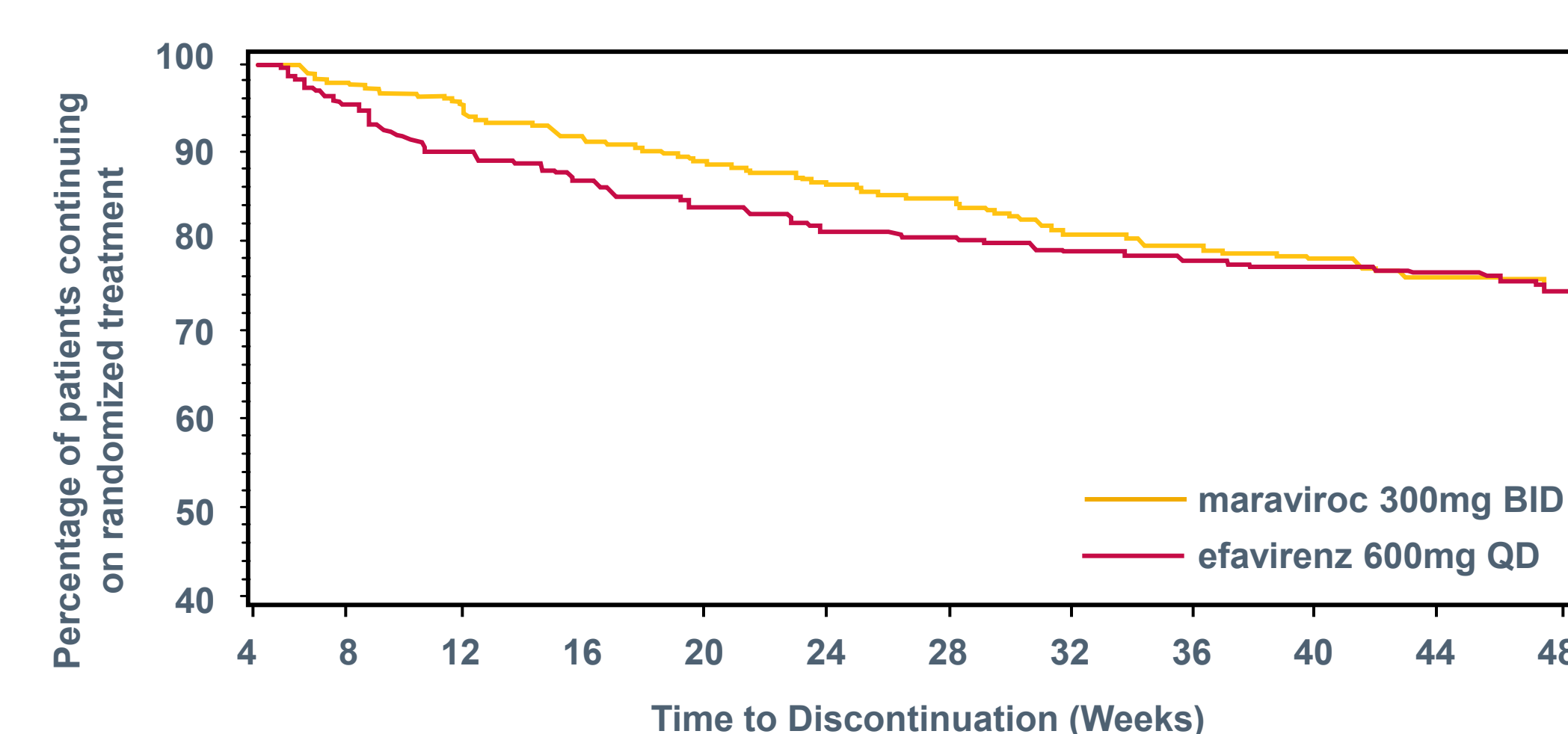
  

(b)	EFV + CBV		MVC + CBV	
	< 100,000 c/mL (N=183)	≥ 100,000 c/mL (N=120)	< 100,000 c/mL (N=177)	≥ 100,000 c/mL (N=134)
Responder, n (%)	133 (72.7)	83 (69.2)	127 (71.8)	86 (64.2)
Non-responders, n (%)	50 (27.3)	37 (30.8)	50 (28.2)	48 (35.8)
Virologic failure, n (%)	6 (3.3)	2 (1.7)	13 (7.3)	12 (9.0)
Never suppressed, n (%)	0 (0)	1 (0.9)	2 (1.1)	4 (3.0)
Rebound, n (%)	8 (4.4)	4 (3.3)	12 (6.8)	10 (7.4)
Discontinuations				
AEs, n (%)	24 (13.1)	19 (15.8)	7 (4.0)	6 (4.5)
Subject defaulted, n (%) <sup>a</sup>	7 (3.8)	7 (5.8)	10 (5.6)	10 (7.4)
Other, n (%)	5 (2.7)	4 (3.3)	6 (3.4)	6 (4.5) <sup>b</sup>

Only patients with an R5 screening result by enhanced Trofile assay are included. All patients received at least one dose of study medication. <sup>a</sup> Withdrawal of consent or loss to follow up; <sup>b</sup> Data include 1 death.

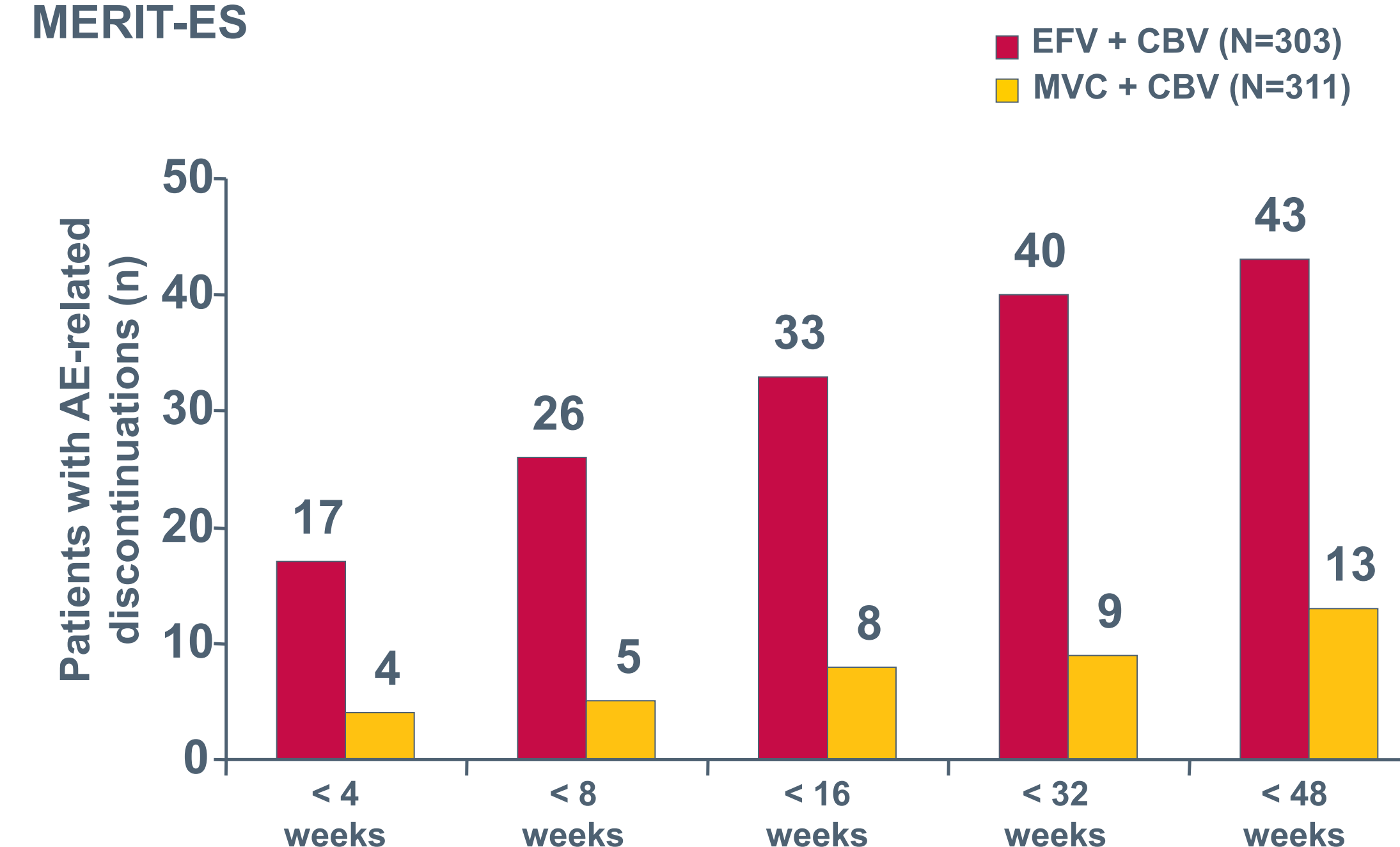
## Time to Failure and Adverse Event Discontinuations

Figure 2: Discontinuations on EFV occurred earlier than on MVC in MERIT-ES



Only patients with an R5 screening result by enhanced Trofile assay are included.

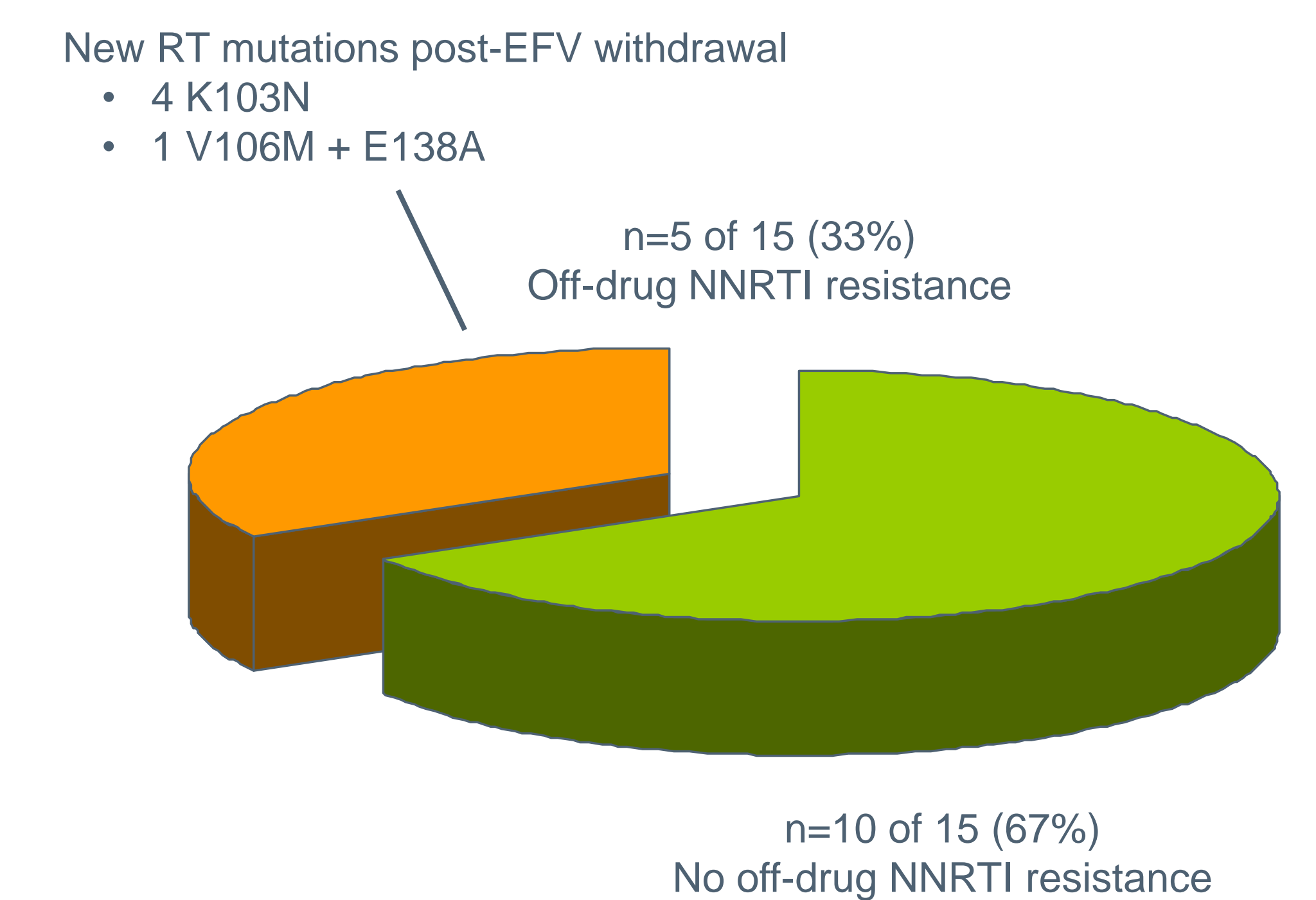
Figure 3: A higher proportion of AE-related discontinuations occurred earlier in the EFV arm compared to the MVC arm in MERIT-ES



- There were 43/303 AE-discontinuations on EFV + CBV (14%) versus 13/311 (4%) on MVC + CBV
- 60% (26/43) AE discontinuations on EFV occurred within the first 8 weeks and 77% (33/43) within the first 16 weeks, versus 38% (5/13) and 62% (8/13), respectively, on MVC

- Fewer patients with an AE-related discontinuation on EFV were virologically controlled (< 50 HIV-1 RNA copies/mL) before discontinuing
  - 30% (13/43) of AE discontinuations on EFV had two consecutive on-treatment HIV-1 RNA measurements < 50 copies/mL prior to discontinuation, versus 38% (5/13) on MVC

Figure 4: 33% (5/15) of AE discontinuations of EFV developed new NNRTI-associated mutations during off-drug follow-up in MERIT-ES



15/43 AE discontinuations on EFV were tested post-treatment for NNRTI resistance mutations; 28/43 were not tested.

- Mutations were observed at one or more visits over a median follow-up of 158 days post-EFV withdrawal (range 74-293 days).
- No mutations were present on active therapy. There were no new NNRTI-associated mutations found during off-drug follow-up of AE discontinuations of EFV or MVC (7/13 MVC AE discontinuations were tested)
- There was no outgrowth of CXCR4-using virus in patients who discontinued MVC therapy due to AEs. At the time of AE-related discontinuation, viral tropism was R5 in 5 (39%) and 13 (30%) of MVC and EFV recipients, respectively; 1 (2%) EFV recipient had dual/mixed tropism. For the remainder of AE-discontinued patients, viral load was below the tropism assay quantitation limit (most patients) or a non-reportable result was obtained
- Discontinuations due to AEs were more frequent in the efavirenz arm than in the maraviroc arm, while virologic failure was more frequent in the maraviroc arm
  - MVC virologic failure was most commonly associated with LAM resistance, while EFV virologic failure was most commonly associated with EFV resistance<sup>2</sup>

## Conclusions

- The MERIT-ES reanalysis showed greater week 48 virologic responses across randomization strata than the original MERIT analysis, particularly for patients with higher screening HIV-1 RNA
- The majority of discontinuations from the EFV + CBV arm over 48 weeks occurred earlier than those on MVC + CBV
- Adverse event discontinuations on EFV were less likely to be virologically suppressed before drug withdrawal and more likely to be associated with the development of drug resistance
  - 33% of patients in the EFV arm who discontinued due to AEs developed off-treatment EFV mutations
- There was no outgrowth of CXCR4-using virus in patients who discontinued MVC therapy due to AEs
- There were no new NNRTI-associated mutations found during off-drug follow-up of AE discontinuations of MVC

## References

- Saag M, Heera J, Goodrich J, et al. Reanalysis of the MERIT study with the enhanced Trofile™ assay (MERIT-ES) [Poster H-1232a]. Presented at: the 48<sup>th</sup> Annual ICAAC/46<sup>th</sup> Annual IDSA Joint Meeting. October 25-28, 2008. Washington, DC, USA.
- Heera J, Saag M, Ive P, et al. Virological correlates associated with treatment failure at week 48 in the phase 3 study of maraviroc in treatment-naïve patients [Abstract 40-LB]. Presented at: 15<sup>th</sup> Conference on Retroviruses and Opportunistic Infections (CROI). February 3-6, 2008. Boston, MA, USA.