



Treatment of HIV drug resistance; TMC114 and TMC125

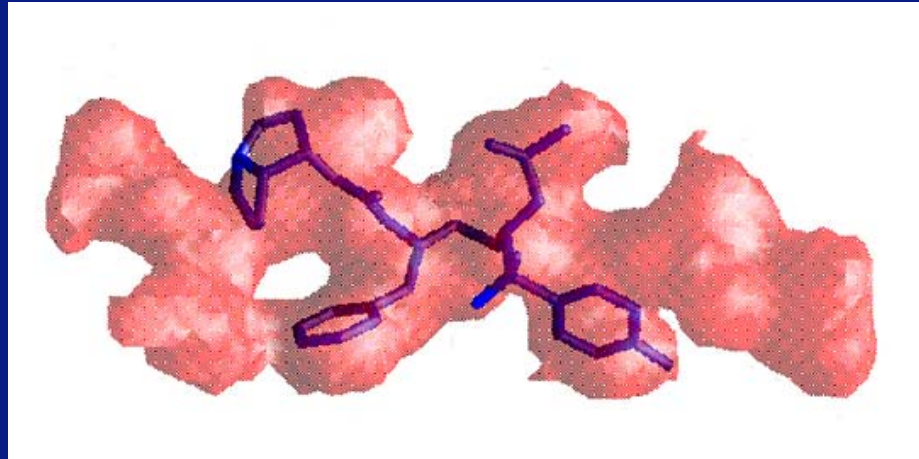
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Treatment of Drug Resistant HIV

TMC114 and TMC125

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TMC114: molecular structure



EC₅₀

Wild-type HIV-1 **1–5 nM¹**

Resistant HIV-1 **<10 nM¹**

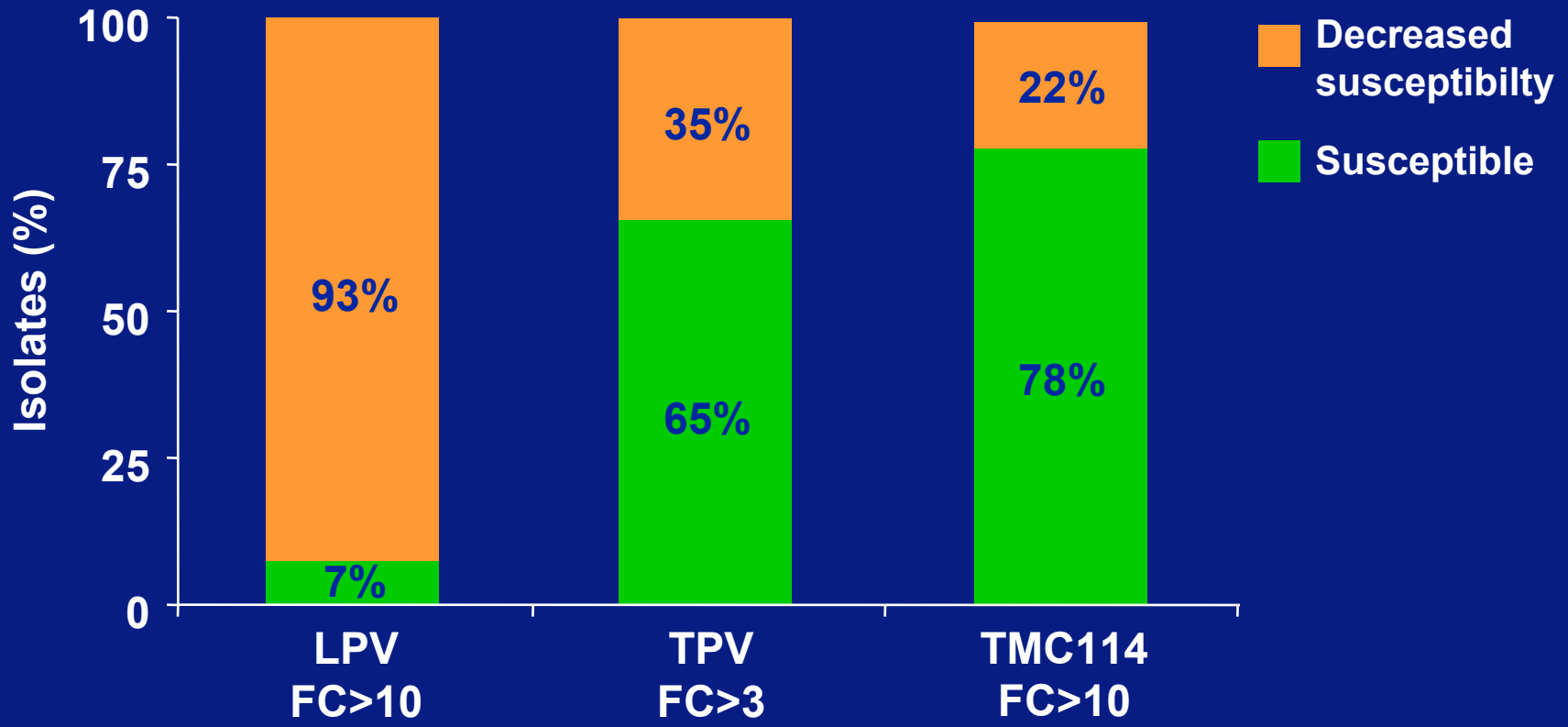
Cytotoxicity (CC₅₀) **>100,000 nM¹**

Selectivity index **>20,000¹**

¹De Meyer S, et al. *Antimicrob Agents Chemother* 2005;49:2314-21.

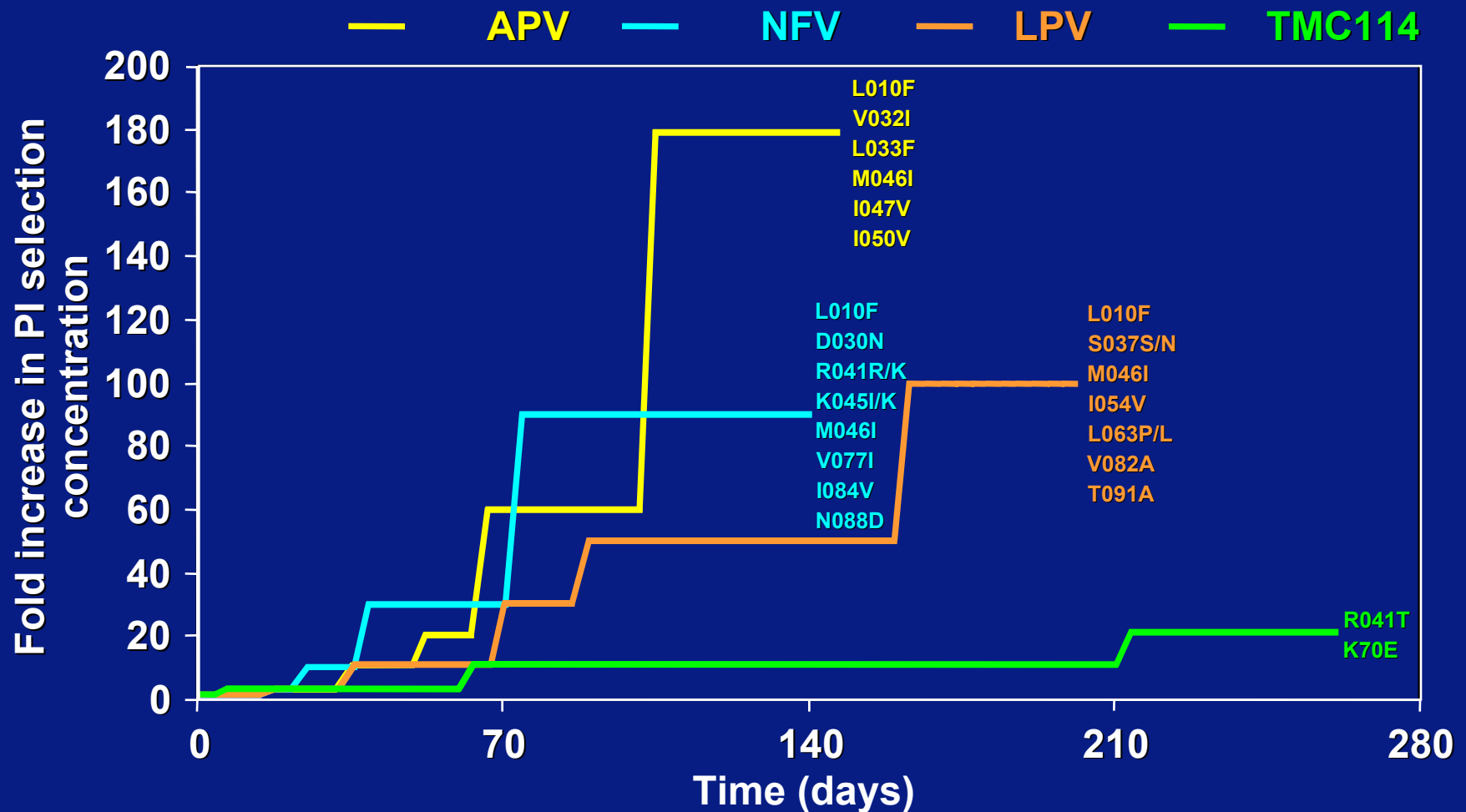
Distribution of antiviral activity of LPV, TPV or TMC114 by clinical cut off

N=2,682 isolates



■ S De Meyer, European Drug Resistance Workshop, Montecarlo, 2006

TMC114: an increased genetic barrier to the development of resistance *in vitro*



POWER 1 & 2: study design

Randomization

- 3-class experience
- ≥ 1 PI mutation
- VL > 1,000 copies/mL
- Investigator selected PI(s) plus OBR (NRTIs \pm ENF)

VF Criteria:

- 1) loss of confirmed virologic response > 1.0 log₁₀ below BL
- 2) never confirmed virologic response > 1.0 log₁₀ below BL

Investigator-selected PI(s) + OBR

TMC114/r
400/100mg qd
+ OBR

TMC114/r
800/100mg qd
+ OBR

TMC114/r
400/100mg bid
+ OBR

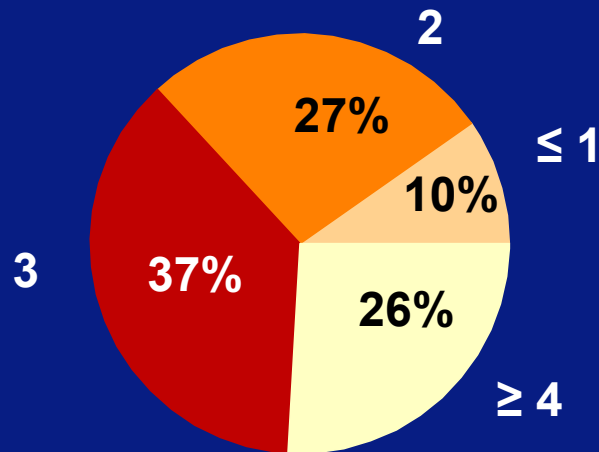
TMC114/r
600/100mg bid
+ OBR

**Screening
6 weeks**

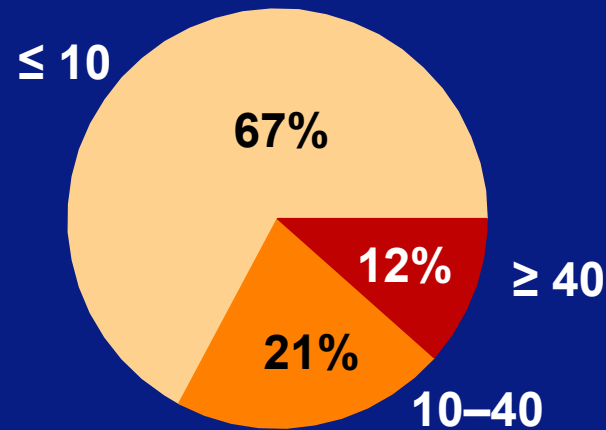
**Dose-finding period
24 weeks**

*Upon protocol-defined VF, patients in the control arm were allowed into a separate rollover study.

POWER 1 & 2: resistance characteristics



Primary PI mutation*



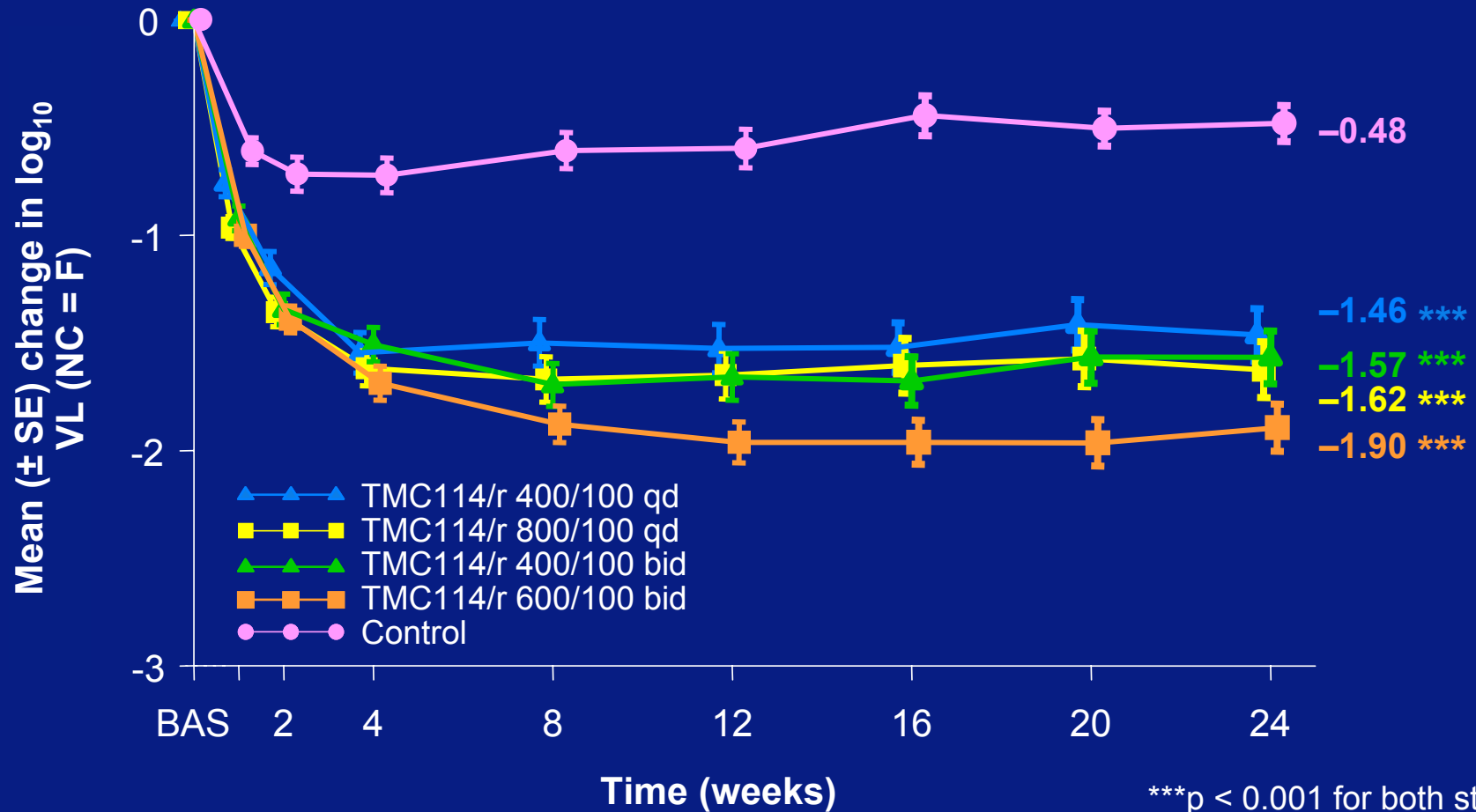
Baseline TMC114 FC

63% had ≥ 3 primary PI mutations

*IAS-USA, October 2005 (Johnson VA, *et al.* 2004;12:119-124.)

Katlama C, *et al.* 3rd IAS, 2005. Abstract WeOaLB0102.
Wilkin T, *et al.* 45th ICAAC, 2005. Abstract 2860.

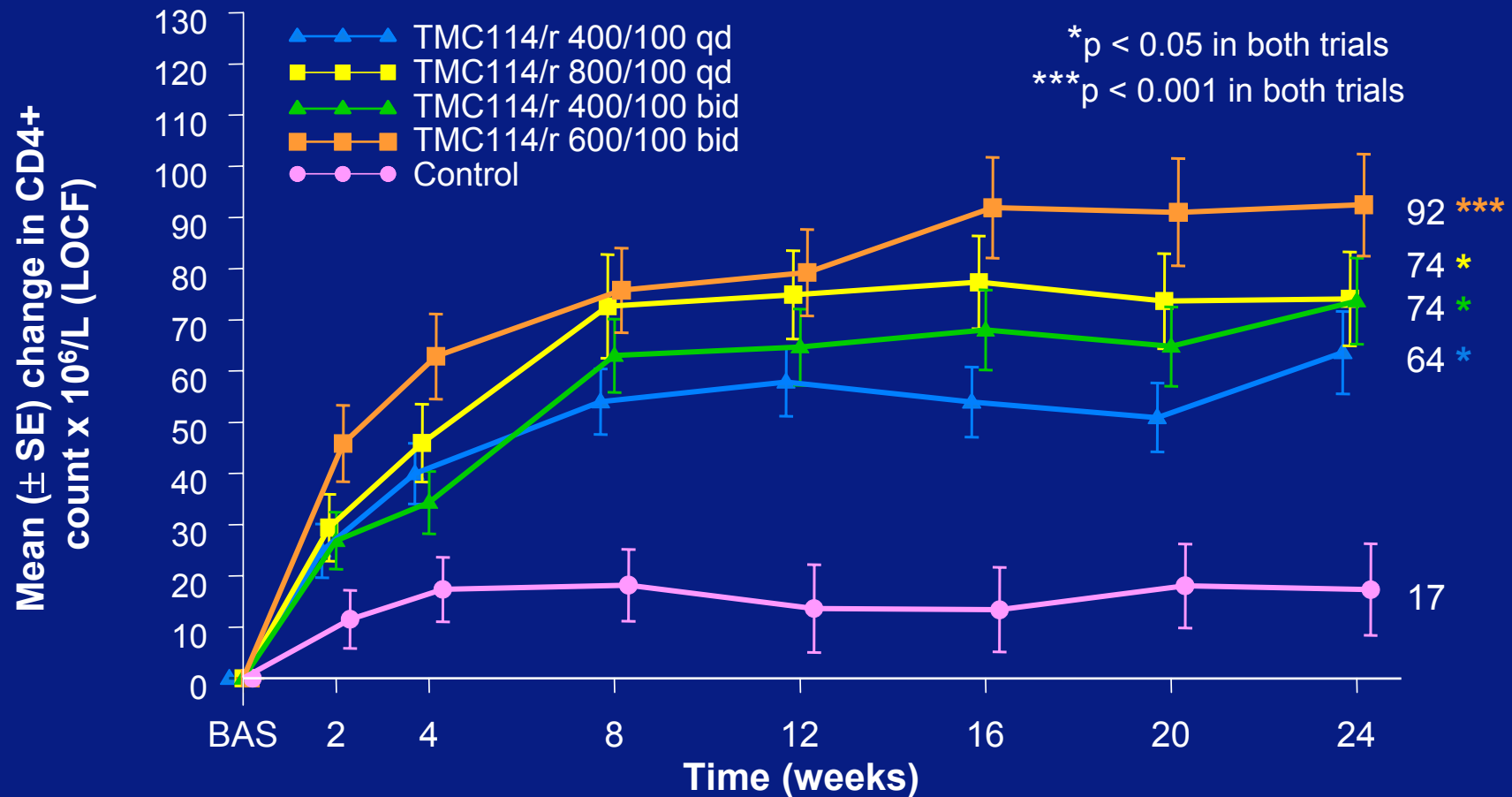
Change from baseline in plasma HIV RNA pooled POWER 1 & 2



ITT non-completers = failure.

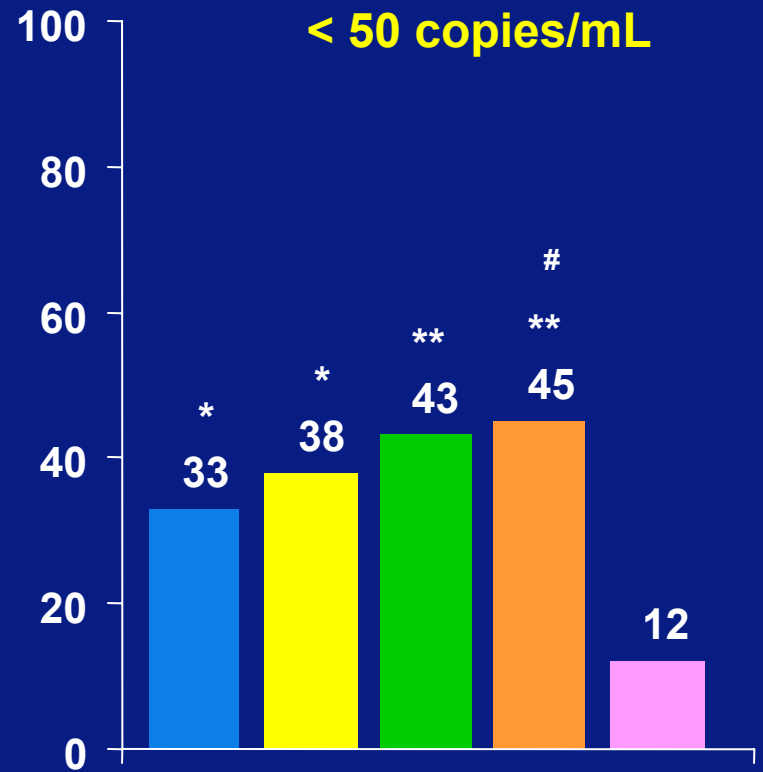
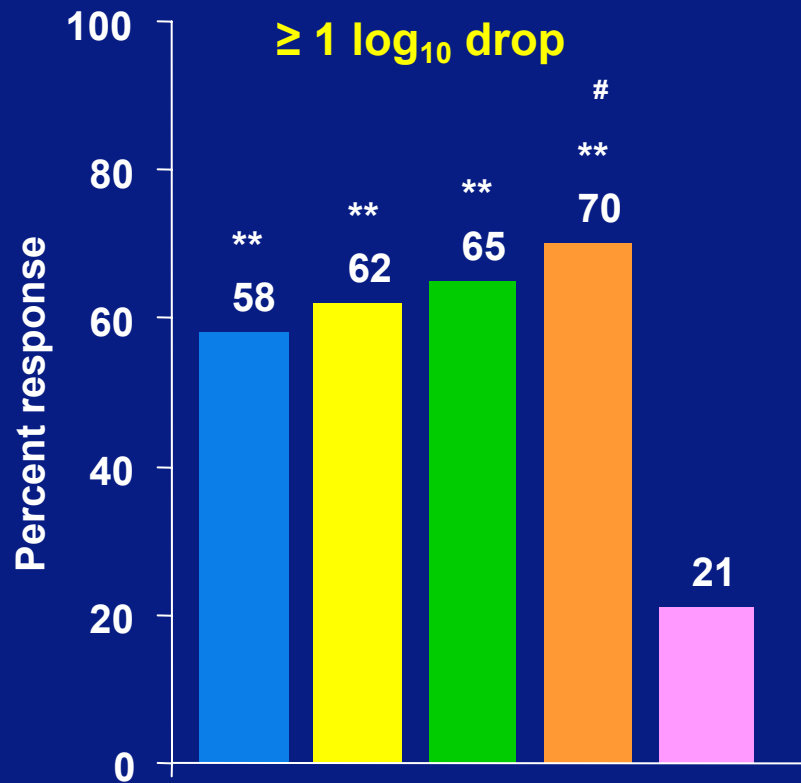
Katlama C, et al. 3rd IAS, 2005. Abstract WeOaLB0102.
Wilkin T, et al. 45th ICAAC, 2005. Abstract 2860.

Change from baseline in CD4+ cell count pooled POWER 1 & 2



Katlama C, et al. 3rd IAS, 2005. Abstract WeOaLB0102.
 Wilkin T, et al. 45th ICAAC, 2005. Abstract 2860.

Virologic response at week 24 pooled POWER 1 & 2



*p < 0.05 in both trials when comparing with control.
 **p < 0.001 in both trials when comparing with control.
 #p < 0.05 in Power 2 when comparing with 400 qd.

■ TMC114/r 400/100 qd ■ TMC114/r 600/100 bid
 ■ TMC114/r 800/100 qd ■ Control
 ■ TMC114/r 400/100 bid

Katlama C, et al. 3rd IAS, 2005. Abstract WeOaLB0102.
 Wilkin T, et al. 45th ICAAC, 2005. Abstract 2860.

ITT TLOVR

POWER 3

- Open label, non randomized analysis
- 327 patients - treatment initiated with TMC114/r
600/100 mg bid
- Patients enrolled in USA, Brazil, and Europe
- Primary Efficacy endpoint - proportion of patients with $\geq 1 \log_{10}$ reduction in HIV RNA by week 24

*VF defined as $<0.5 \log_{10}$ reduction in plasma HIV RNA from baseline at or beyond week 12

POWER 3: major inclusion criteria

- **Similar inclusion criteria to POWER 1 and 2**
- **HIV RNA > 1,000 copies/mL**
- **At least 3 months prior NRTI treatment, and at least one NNRTI used in failing regimen**
- **At least 1 PI treatment received for at least 3 months, with stable PI treatment received for greater than 8 weeks prior screening**
- **At least 1 PI mutation from the IAS-USA 2004 list of primary mutations**
- **No prior treatment with TMC114**
- **Co-infection with hepatitis B or C allowed**

POWER 3: baseline characteristics

All 600 mg bid	POWER 1	POWER 2	POWER 3
n	65	66	327
Disease characteristics			
Mean years of infection	11.1	12.9	12.8
Mean log ₁₀ VL	4.59	4.62	4.62
Median CD4+	176	115	115
Prior PI treatment			
Mean duration (months)	66.7	62.3	69.1
Mean number	3.8	3.8	4.7
Tipranavir (%)	3	5	31
Lopinavir (%)	80	82	88
Prior ENF use, n (%)	11	27	30

POWER 3: baseline resistance characteristics

	POWER 1 600/100 mg bid	POWER 2 600/100 mg bid	POWER 3 600/100 mg bid
n	65	66	327
Number of PR mutations (median)			
Primary PI*	3	3	3
PI resistance-associated*	8	8	9
All PR mutations	18	18	20
Baseline LPV FC			
Median**	>82	>84	>89

* D30N, L33F/I, M46I/L, G48V, I50L/V, V82A/F/L.S/T, 184A/C/V, L90M

**L10F/I/R/V, K20I/L/M/R/T, L24I, D30N, V32I, L33F/I, M36I/L/V, M46I/L, I47A/V, G48V, I50V/L, F53L, I54V/M/L/A/S/T, A71V/T, G73S/A/C/T, V77I, V82A/F/T/S/L, I84V/A/C, N88D/S, L90M

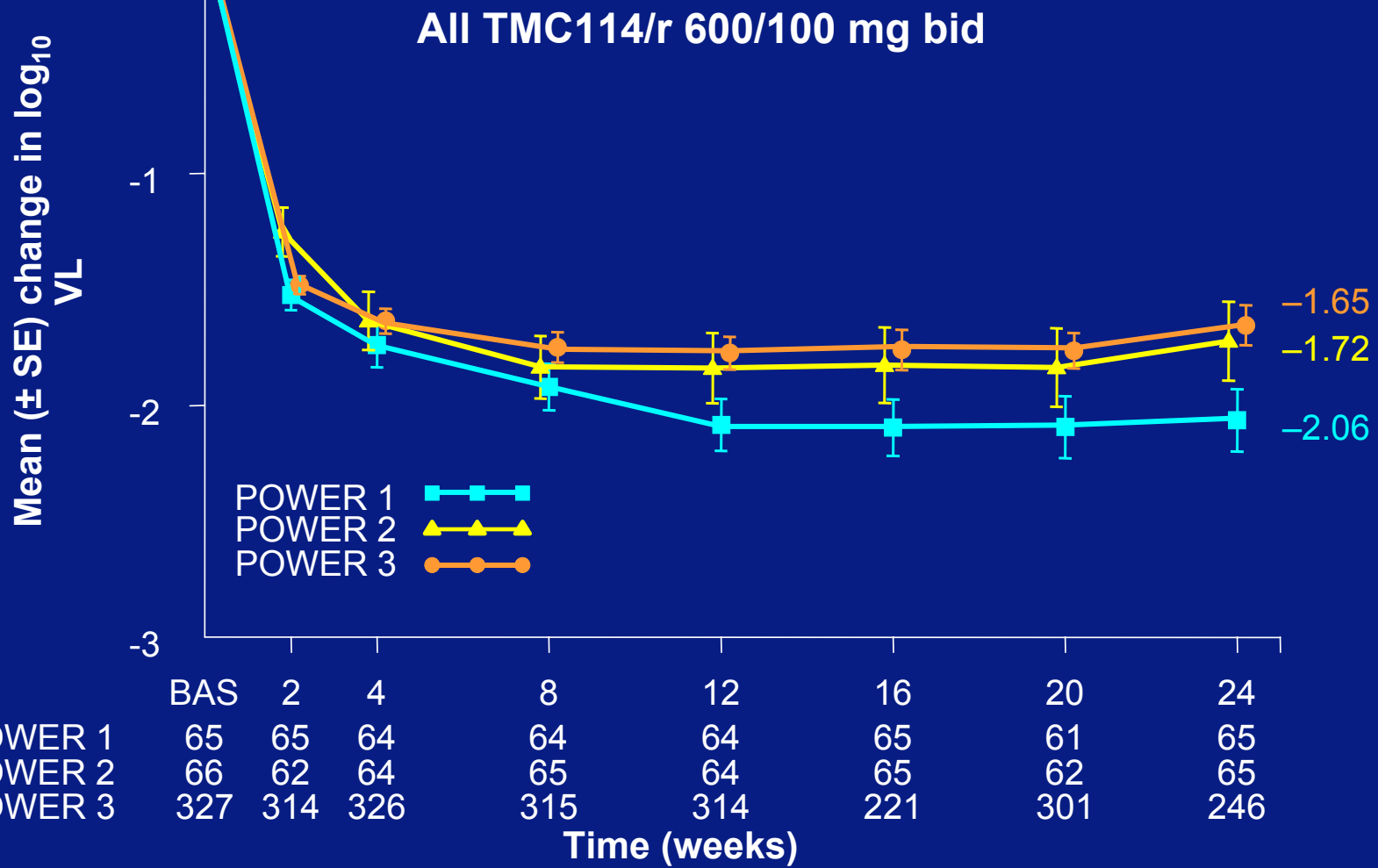
*IAS-USA October 2005

**Actual median FC is right censored

FC, fold change; PR = protease

Molina MC, et al. 12th BHIVA conference. Poster.

Change from baseline in plasma HIV RNA POWER 3 vs POWER 1 and 2

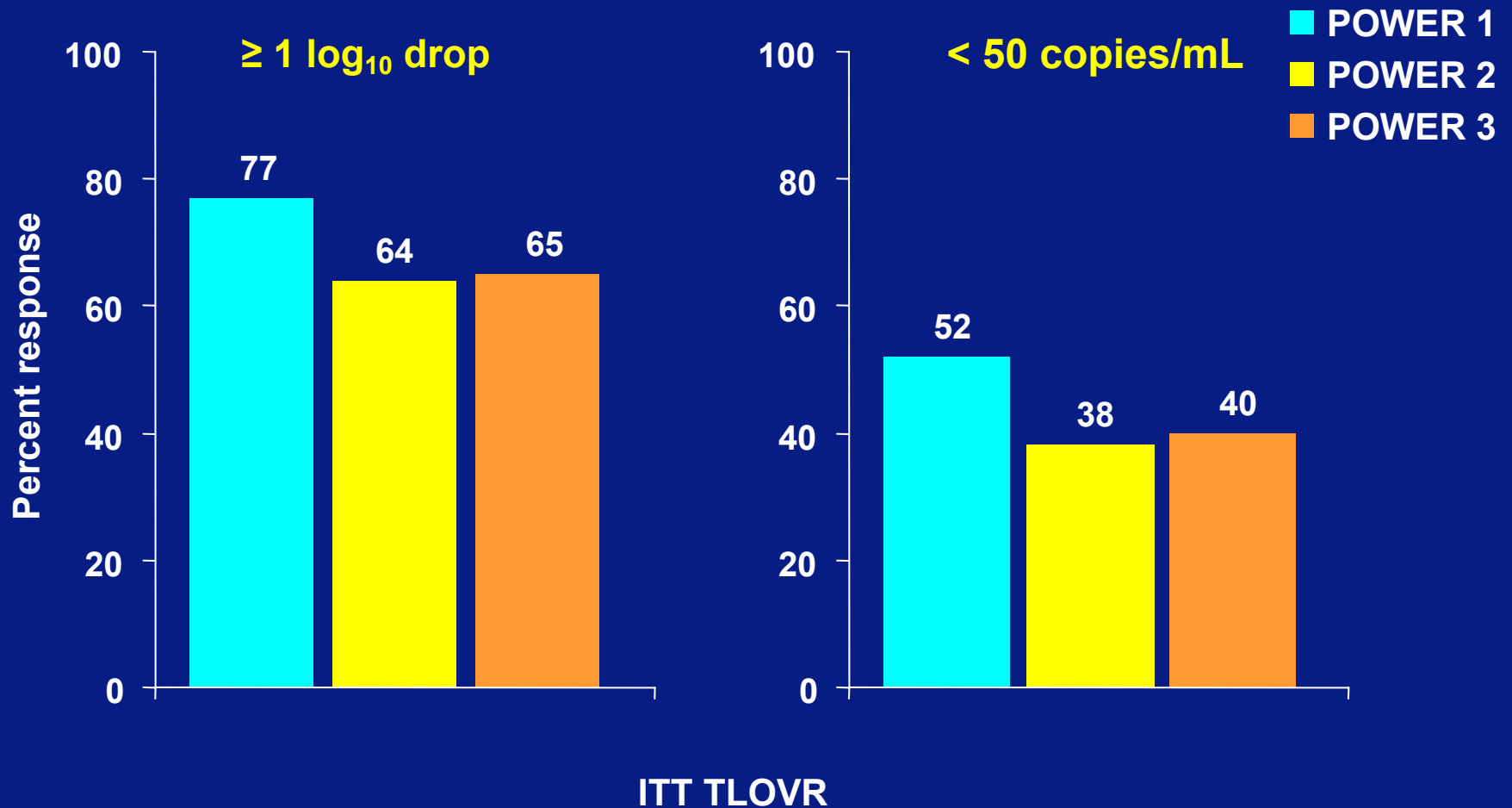


ITT non-completers = failure.

Molina MC, et al. 12th BHIVA conference. Poster.

Virologic response at week 24 POWER 3 vs POWER 1 and 2

All TMC114/r 600/100 mg bid



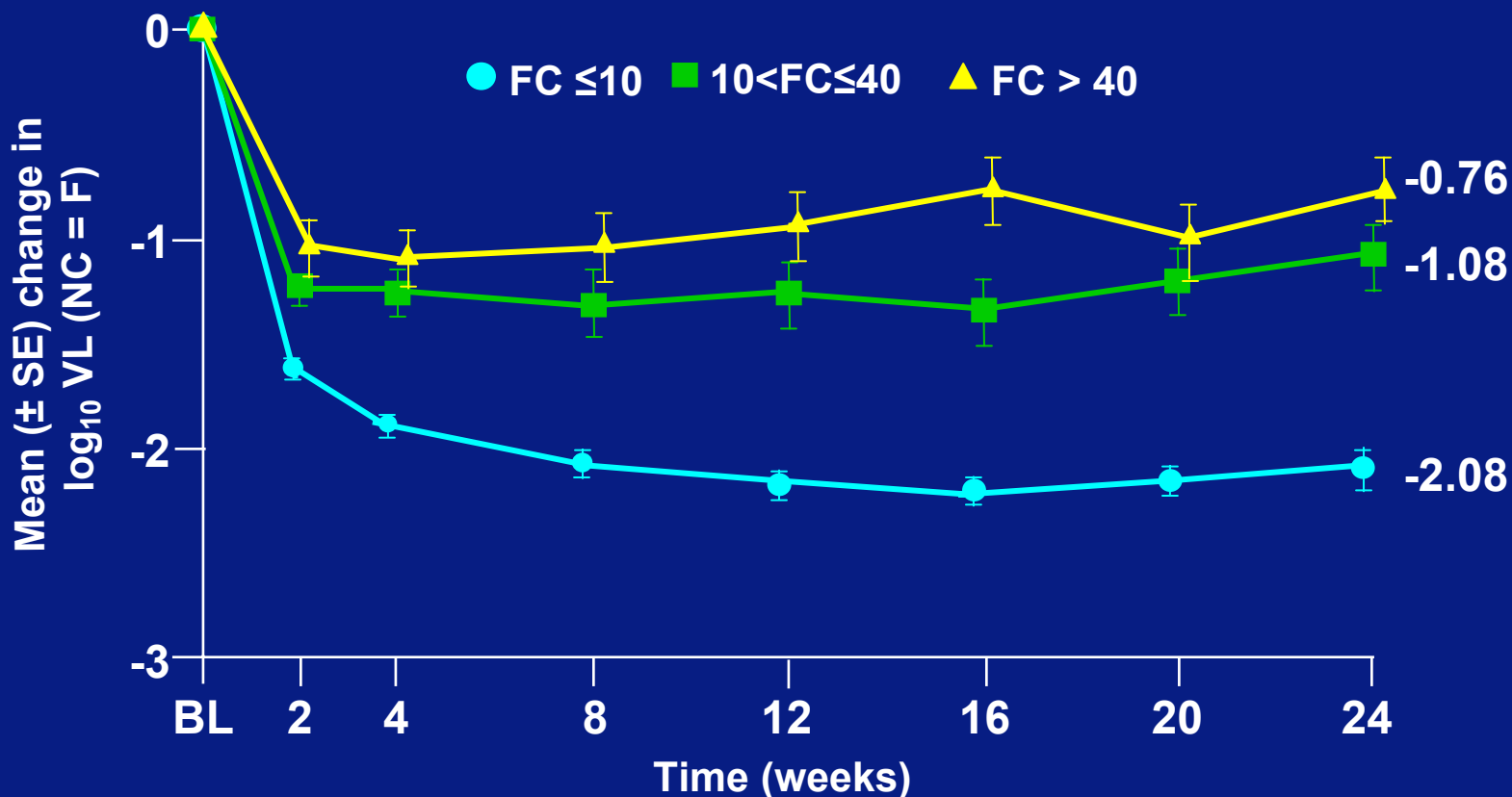
Virologic response at week 24 pooled POWER 1, 2, & 3

Response parameter	TMC114/r 600/100 mg bid (n = 377)	At least one susceptible CPI (n = 34)	No susceptible CPI (n = 86)
$\geq 1 \log_{10}$ copies/mL VL reduction (%)	67	32	16
VL < 50 copies/mL (%)	42	24	7
Mean change in \log_{10} VL from baseline	-1.74	-0.58	-0.43

CPI(s) = control PIs + OBR.

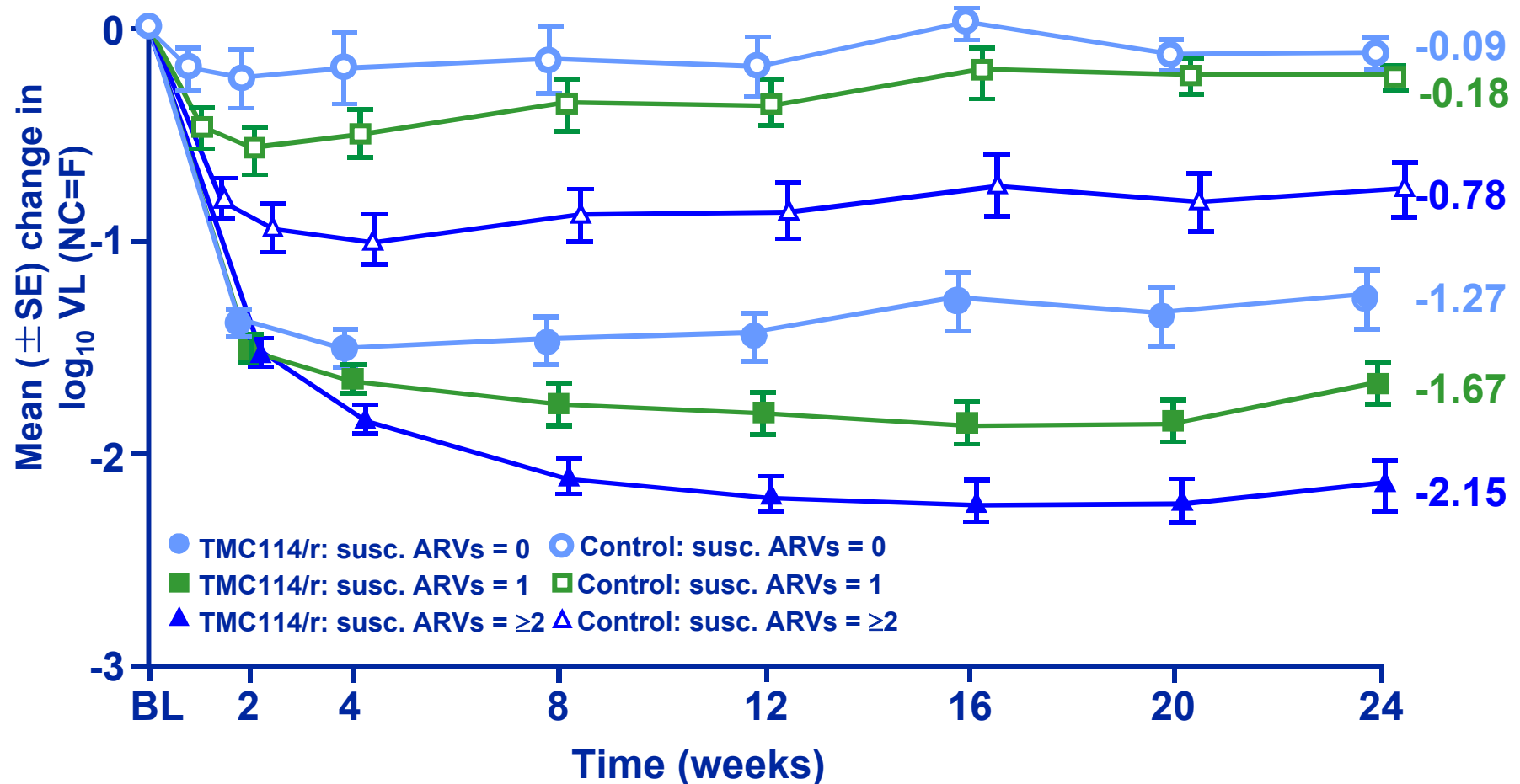
Pozniak A, et al. 12th BHIVA conference. Poster P3.

POWER 1, 2, & 3: effect of baseline FC on change in VL at week 24



Reduction in VL from BL was greater for patients with TMC114/r FC ≤ 10 compared with those with higher FC values

POWER 1, 2, and 3: Effect of Susceptible ARVs on the Change in \log_{10} VL from Baseline

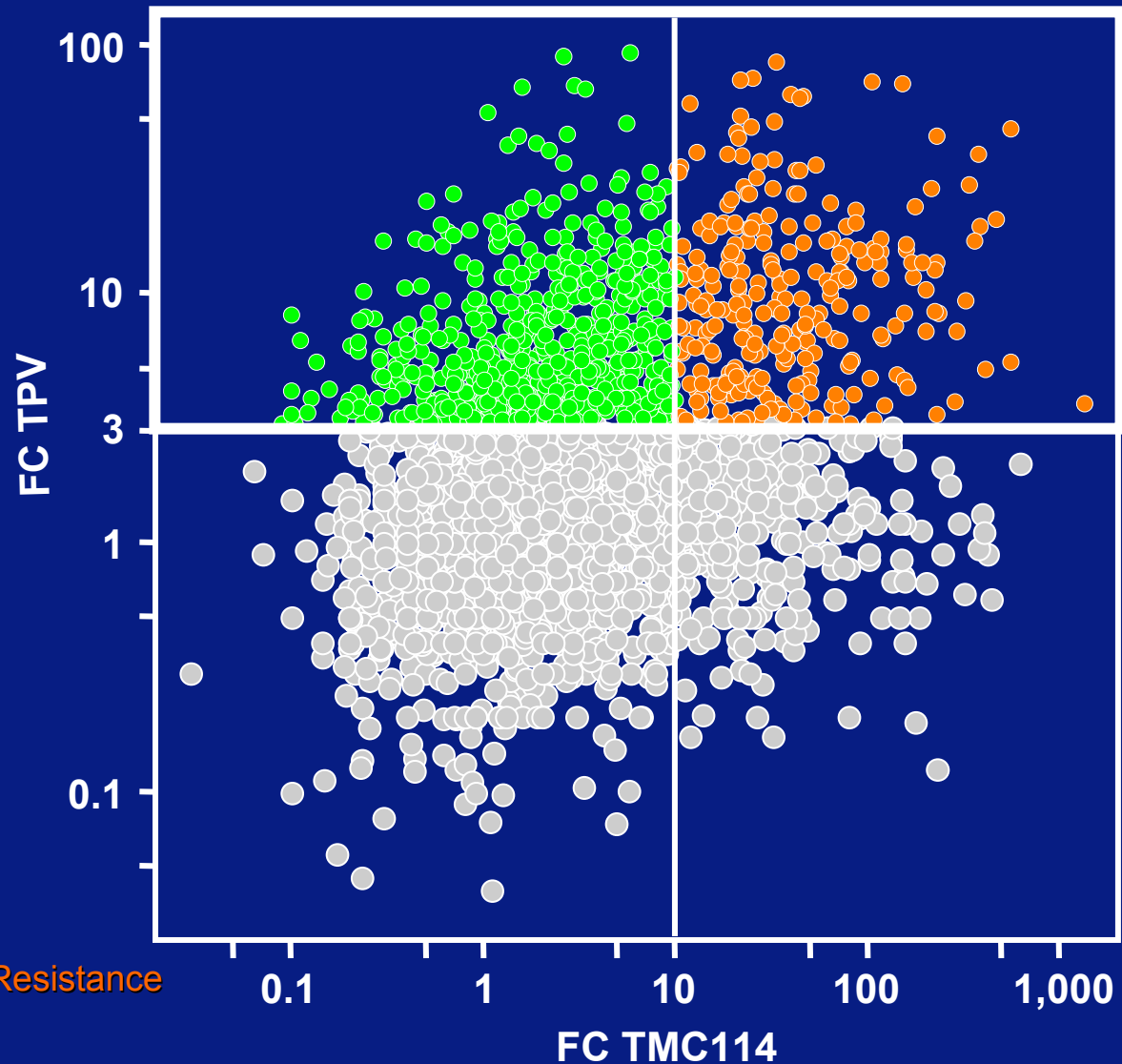


TMC114/r more effective than CPIs even where patients had limited or no susceptibility to ARVs

TMC114 FC versus TPV FC

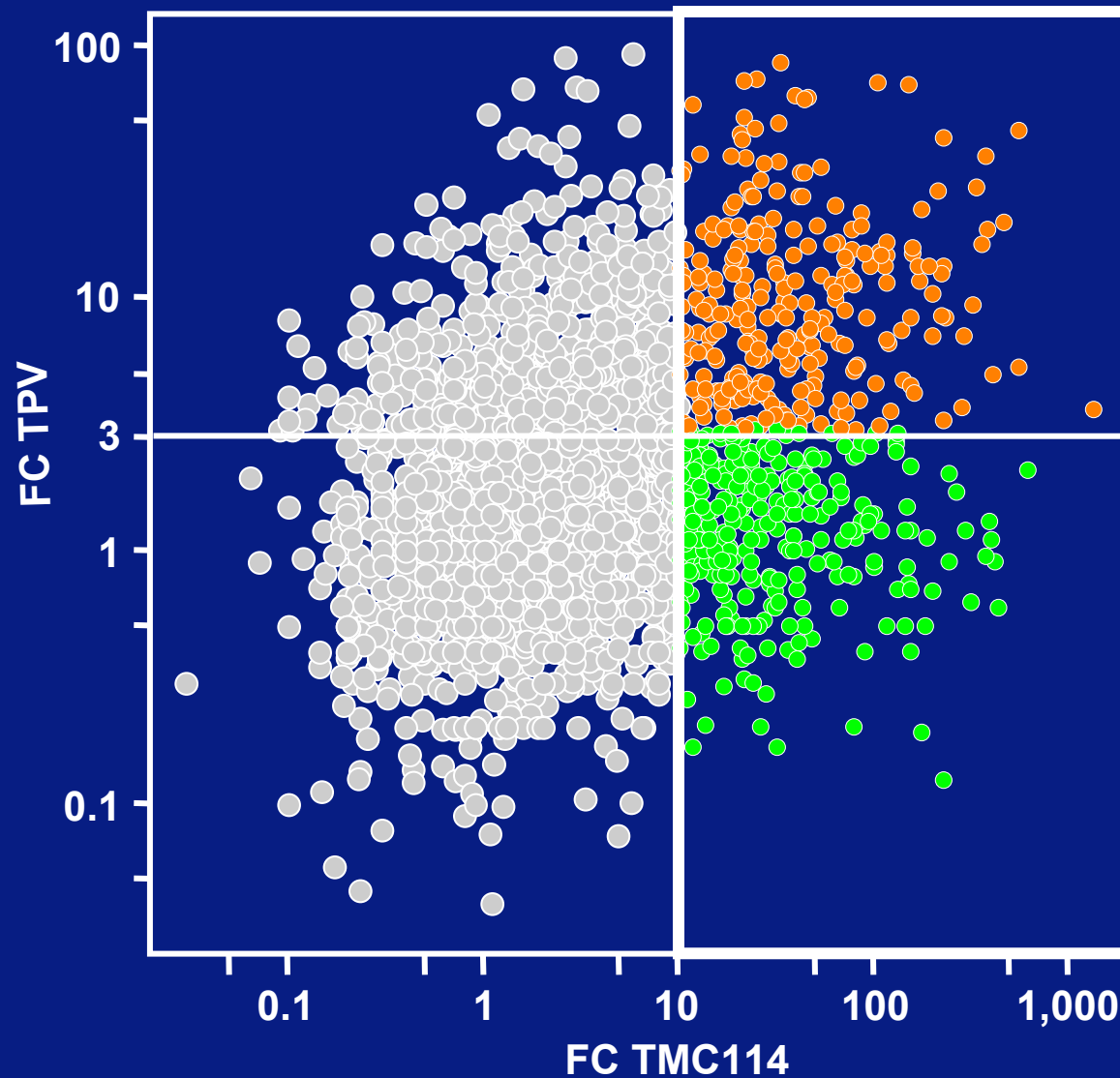
935 isolates with decreased susceptibility to TPV

658 / 935 = 70%
susceptible to
TMC114



■ [S De Meyer](#), European Drug Resistance Workshop, Montecarlo, 2006

TMC114 FC versus TPV FC



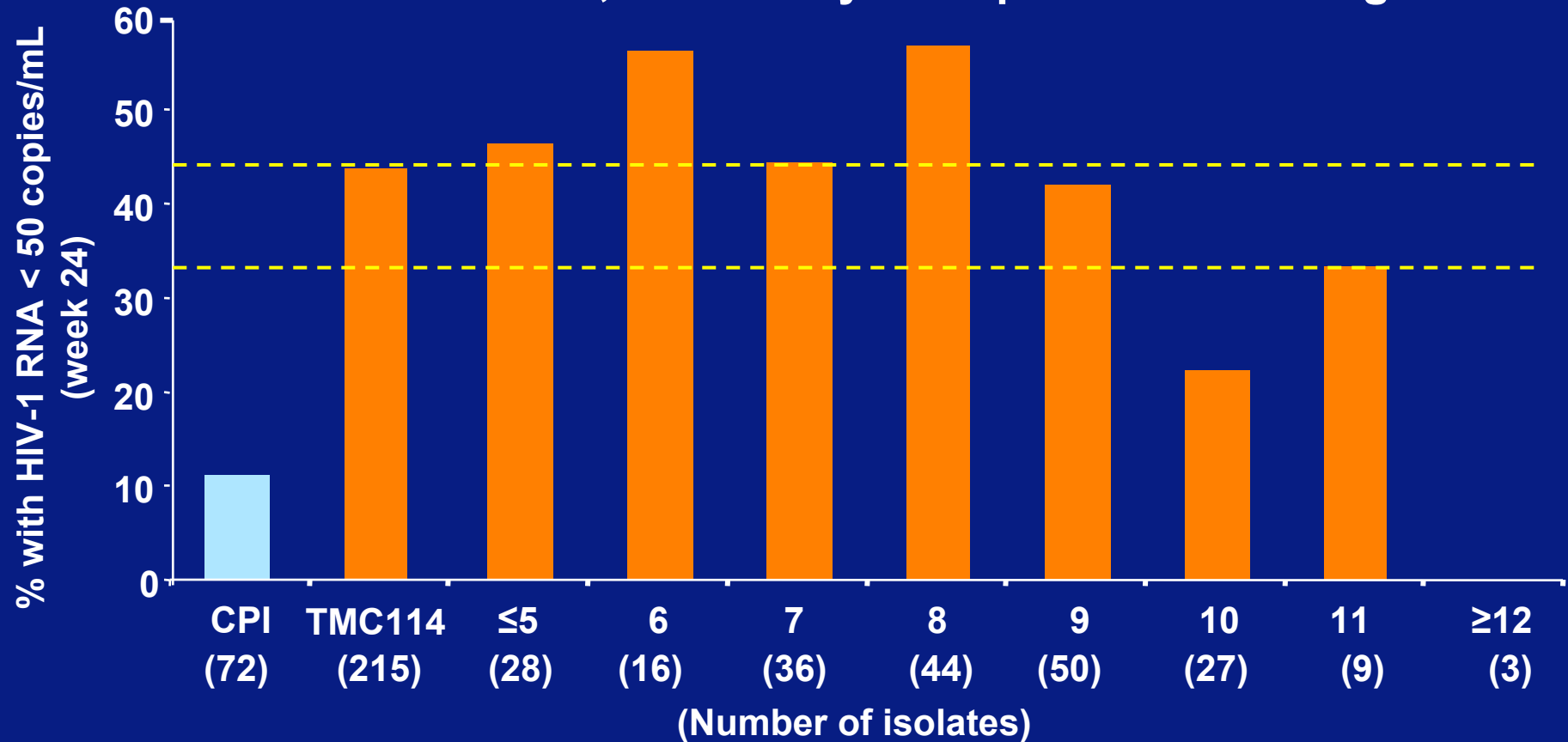
586 isolates with decreased susceptibility to TMC114

309 / 586 = 53% susceptible to TPV

■ S De Meyer, European Drug Resistance Workshop, Montecarlo, 2006

VR <50 copies/mL by number of BL PI resistance-associated mutations*

Pooled POWER 1, 2 & 3 analysis of patients not using ENF

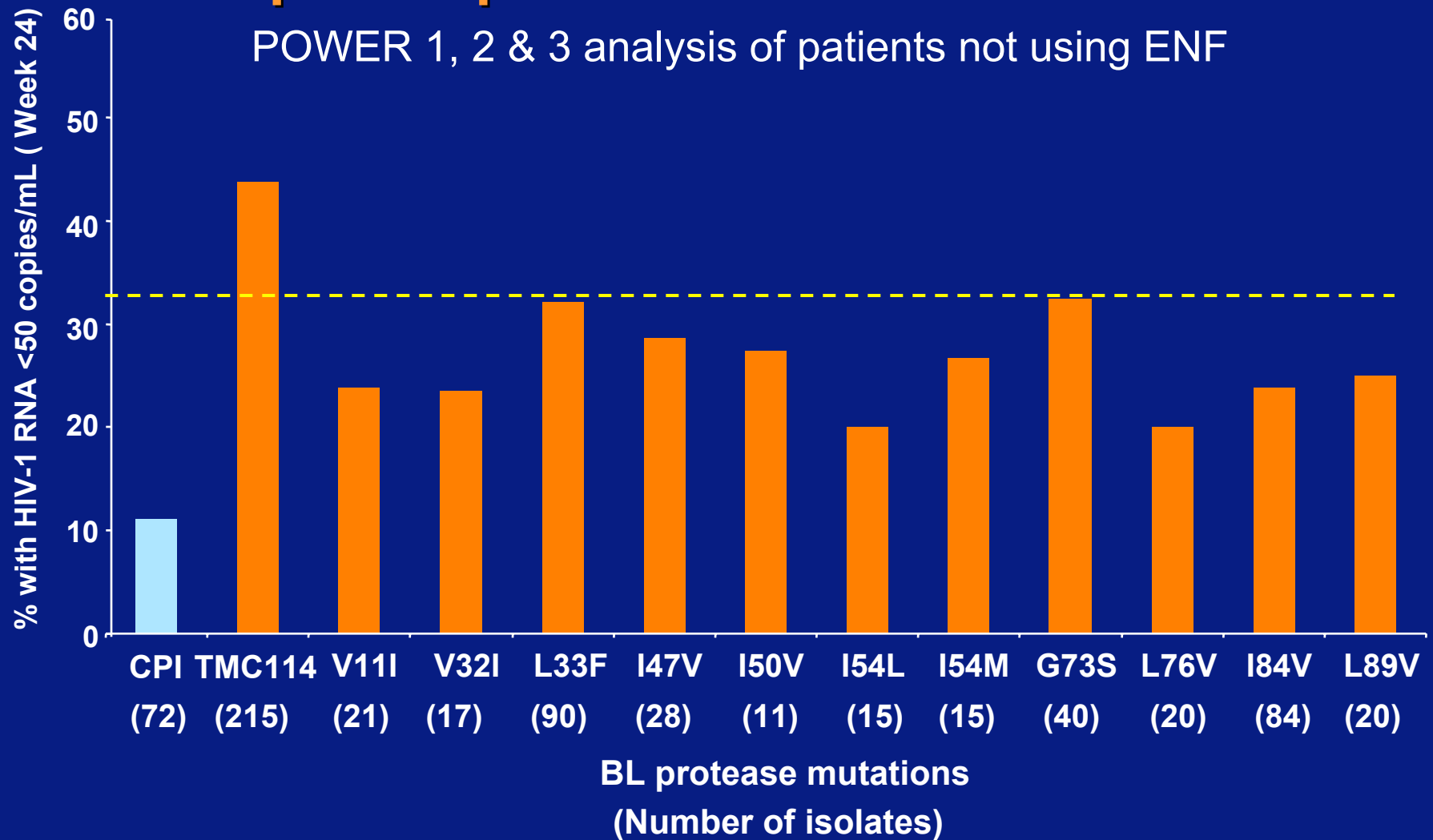


*IAS–USA March 2005

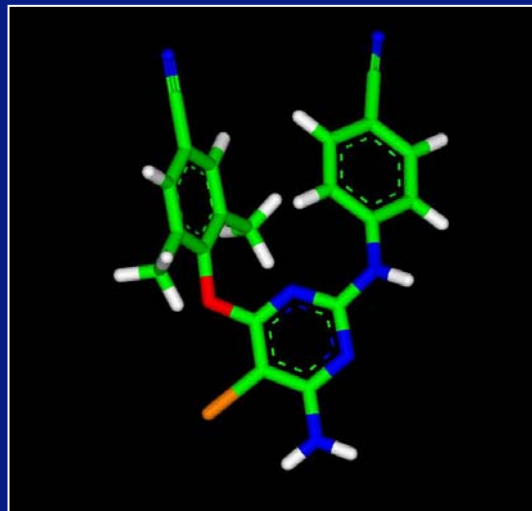
De Meyer S, et al. 13th Conference on Retroviruses and Opportunistic Infections. Oral presentation #157.

Virologic response (<50 copies/mL) by specific protease mutations at BL

POWER 1, 2 & 3 analysis of patients not using ENF



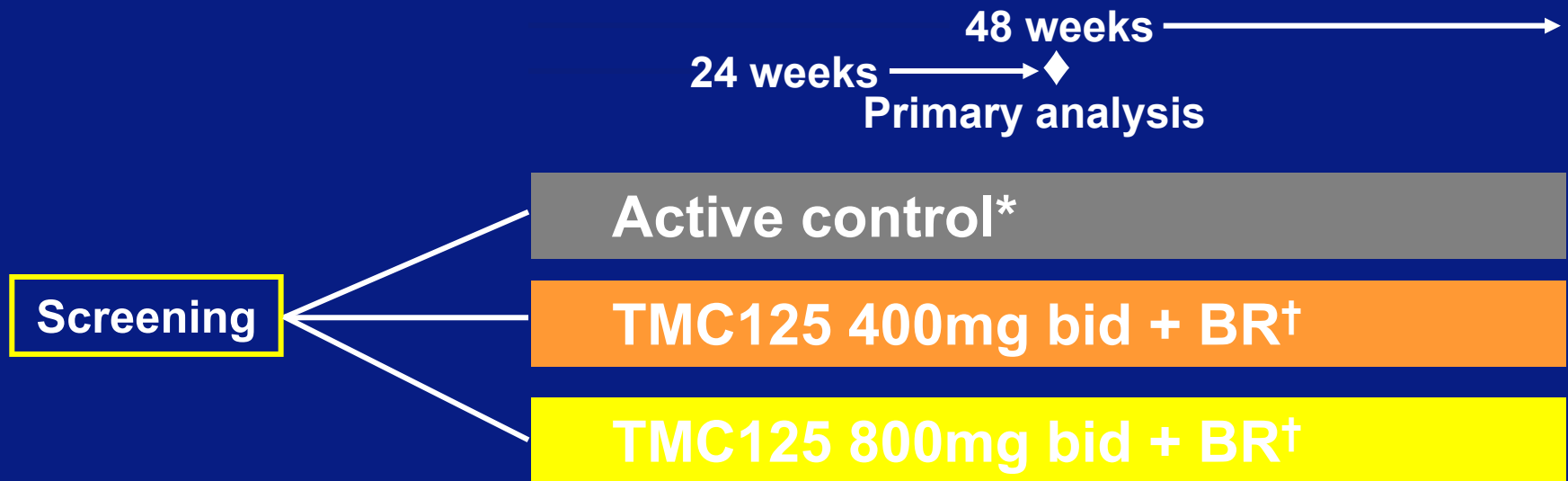
TMC125



TMC125 is equally or more potent (lower EC_{50}) than approved or investigational NNRTIs against wild type HIV-1

- $EC_{50} = 1.4 \text{ nM}$ (0.6 ng / mL)
- $EC_{90} = 2.9 \text{ nM}$ (1.3 ng / mL)
- $CC_{50} > 100 \text{ } \mu\text{M}$
- Selectivity Index $> 70,000$

TMC125-C223: Study design



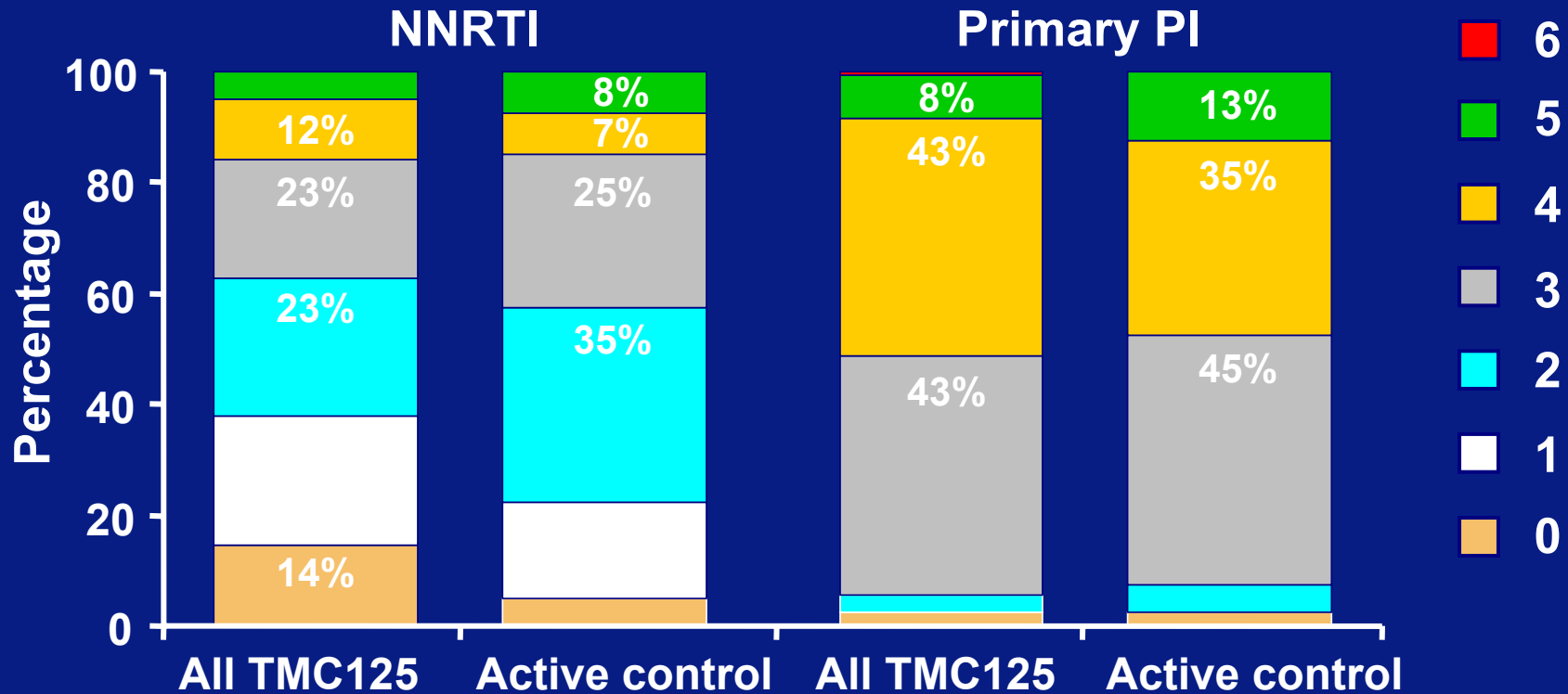
*Active control: best available regimen from licensed agents

†Background regimen (BR): investigator selected NRTIs ± LPV/r ± T-20

- Viral load >1,000 copies/mL
- Documented NNRTI resistance and ≥ 3 primary PI mutations
- Randomised 1:2:2 (Active control vs TMC125 400mg bid vs 800mg bid), partially blinded
- After 48 weeks, patients were enrolled into a long-term follow-up trial

TMC125-C223: Baseline resistance

Number of resistance-associated mutations



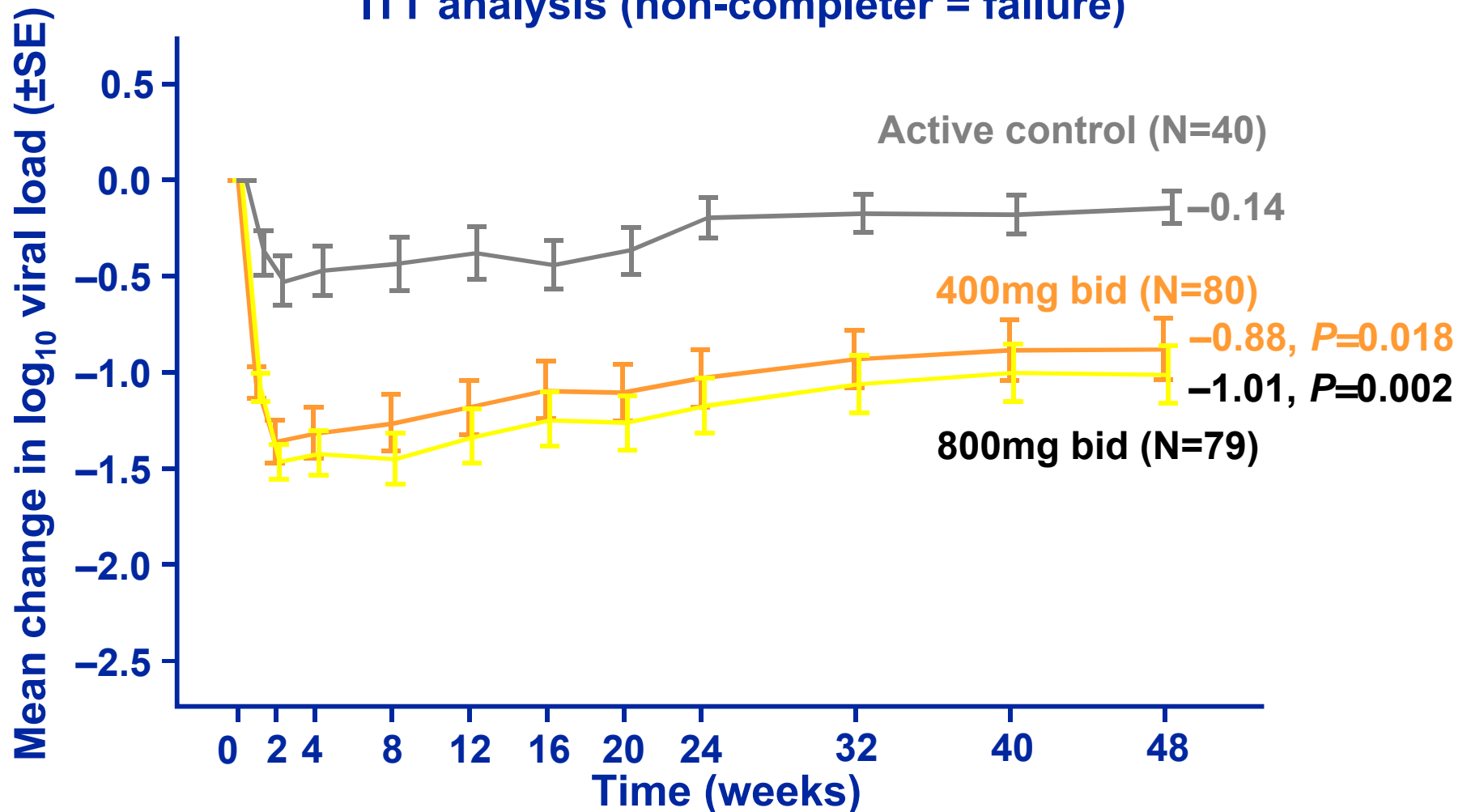
All patients had at least one NNRTI mutation at screening or from prior genotyping

Median fold resistance

- Efavirenz 41.4
- Nevirapine 61.3
- TMC125 1.7

TMC125-C223: Primary endpoint Change in viral load at 48 weeks

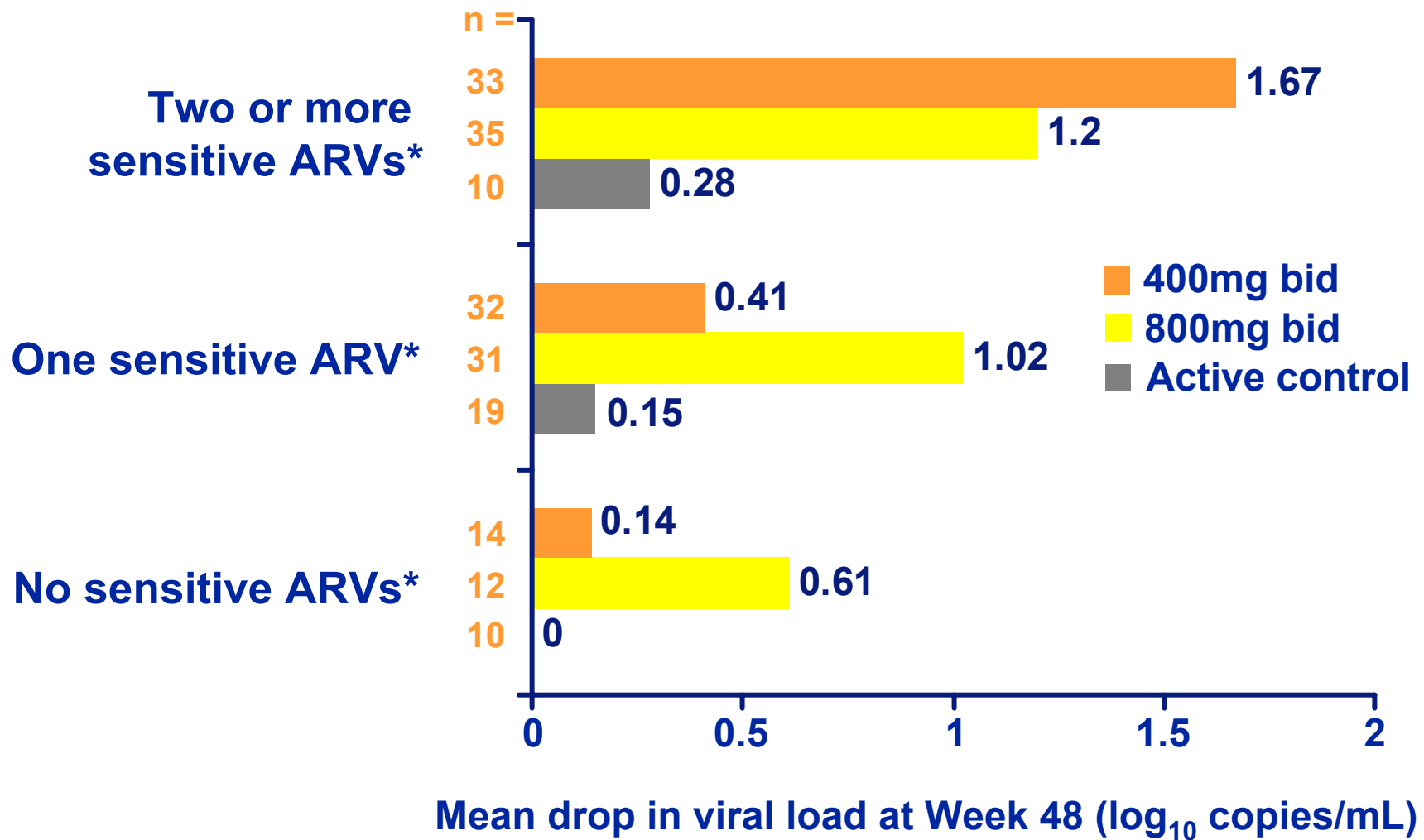
ITT analysis (non-completer = failure)



No statistical difference between the TMC125 groups was observed
EDTA samples and Roche Amplicor® version 1.5 used for HIV RNA analyses

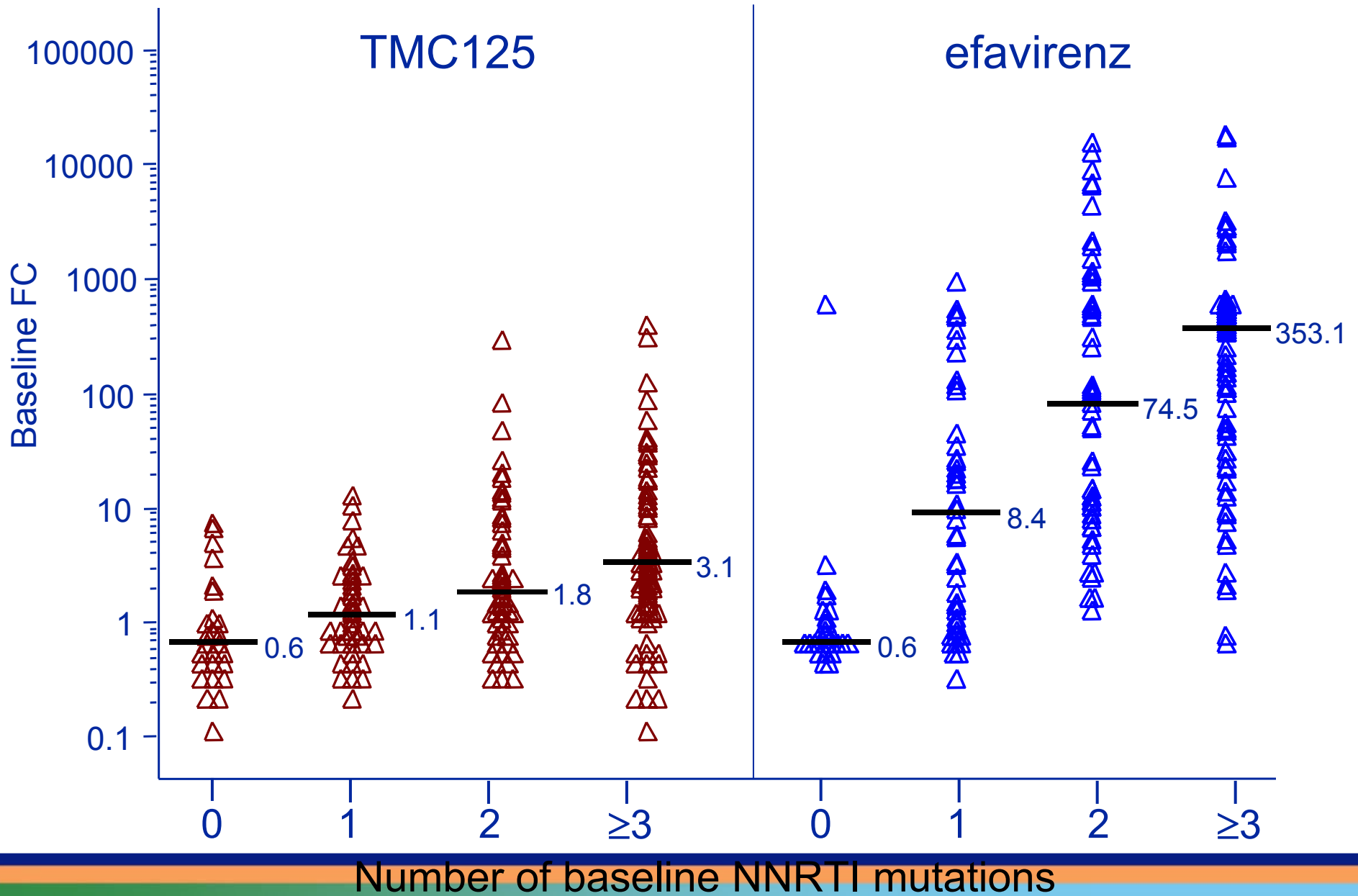
P values versus
active control

TMC125-C223: Impact of sensitive ARVs in the underlying ART*

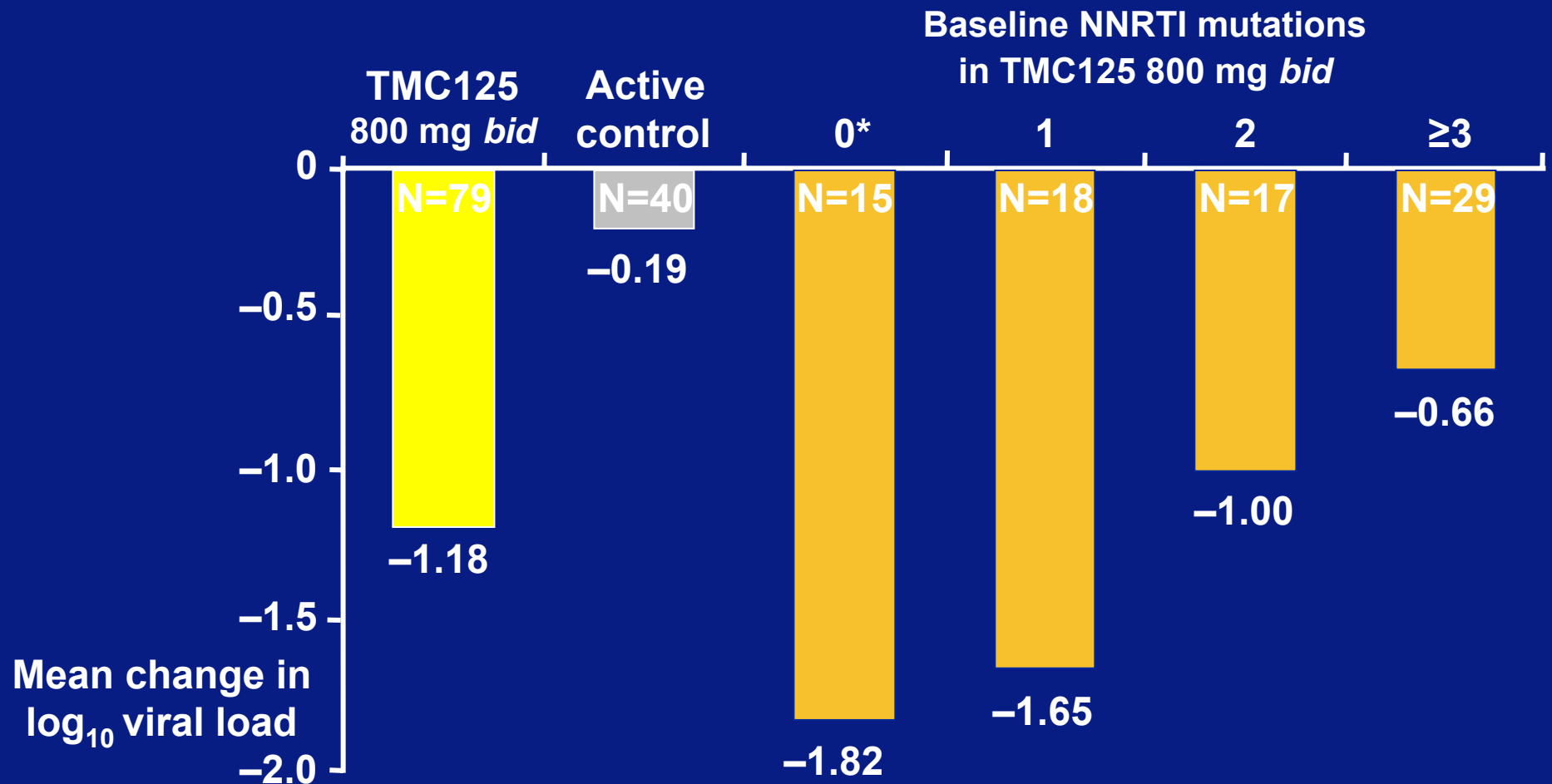


*Excludes TMC125

TMC125-C223: Baseline Resistance - Phenotype



TMC125-C223: Number of NNRTI Mutations and Virologic Response at Week 24



*All subjects had NNRTI mutations from prior genotyping

Conclusions

- **TMC114 and TMC125 have shown potent activity in treatment experienced patients and constitute two important additions to the treatment armamentarium**