Enfuvirtide TORO studies:
48 week results confirm 24 week findings

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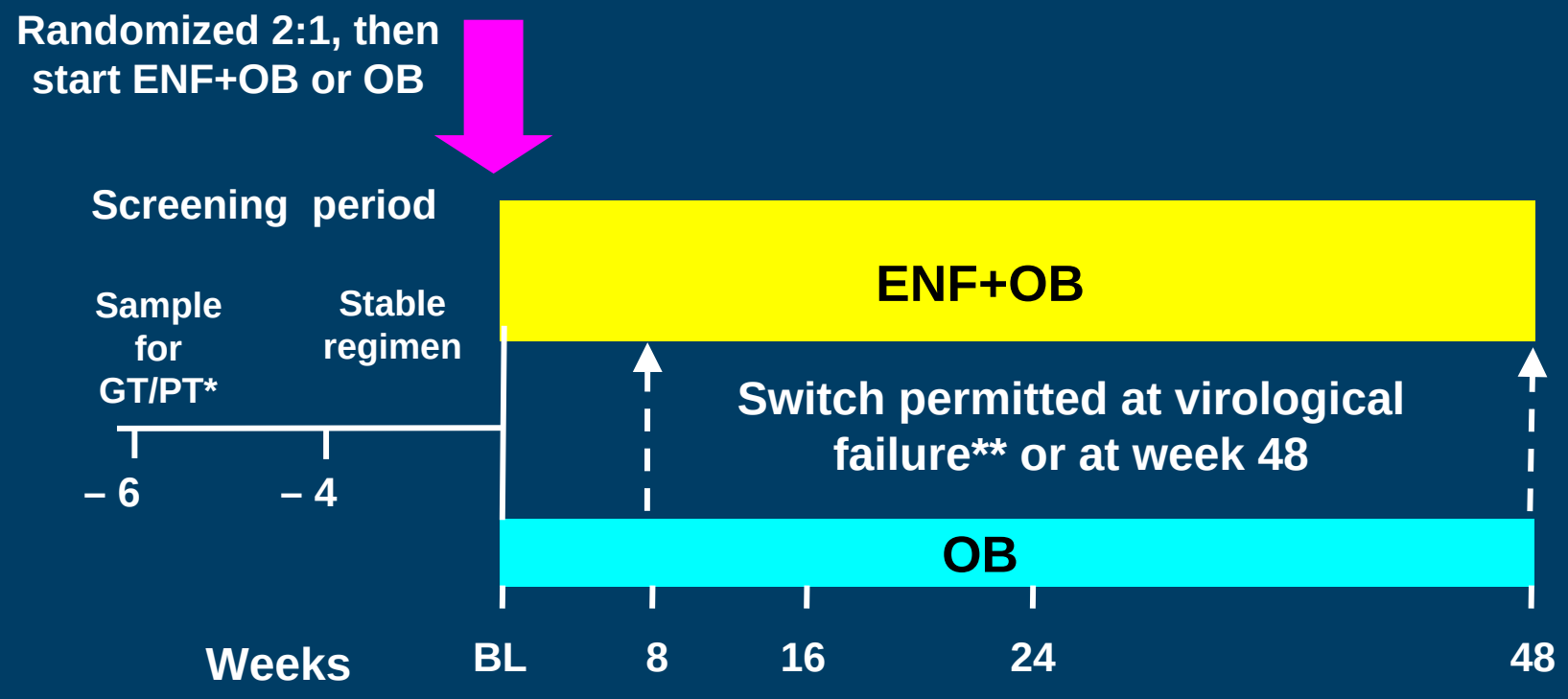
TORO 1 (US, Canada, Mexico, Brazil) & TORO 2 (Europe, Australia)

- **Population**
  - Prior experience to ≥1 NRTI, ≥1 NNRTI, and ≥2 PI (≥1 PI for TORO 2)
  - ≥6 months experience on each class for TORO 1 (≥3 months for TORO 2) or documented viral resistance or class intolerance
  - HIV-1 RNA ≥5000 copies/mL
- **Design**
  - Open label, randomized multi-center, international
- **Treatments (randomized 2:1)**
  - Enfuvirtide (ENF): (90 mg sc bid) + OB
  - Optimized Background (OB): 3–5 ARVs based on history, viral GT/PT
- **Efficacy analyses ENF+OB *vs*. OB**

TORO 1 & TORO 2: Protocol study design



*GT = Genotypic Testing; PT = Phenotypic Testing

**Criteria for virological failure based on 2 consecutive values:

1. <0.5 $\log_{10}$ decrease from baseline starting at week 6 and 8
2. <1.0 $\log_{10}$ decrease from baseline starting at week 14 and 16
3. ≥2 log response and >1 log rebound at any time

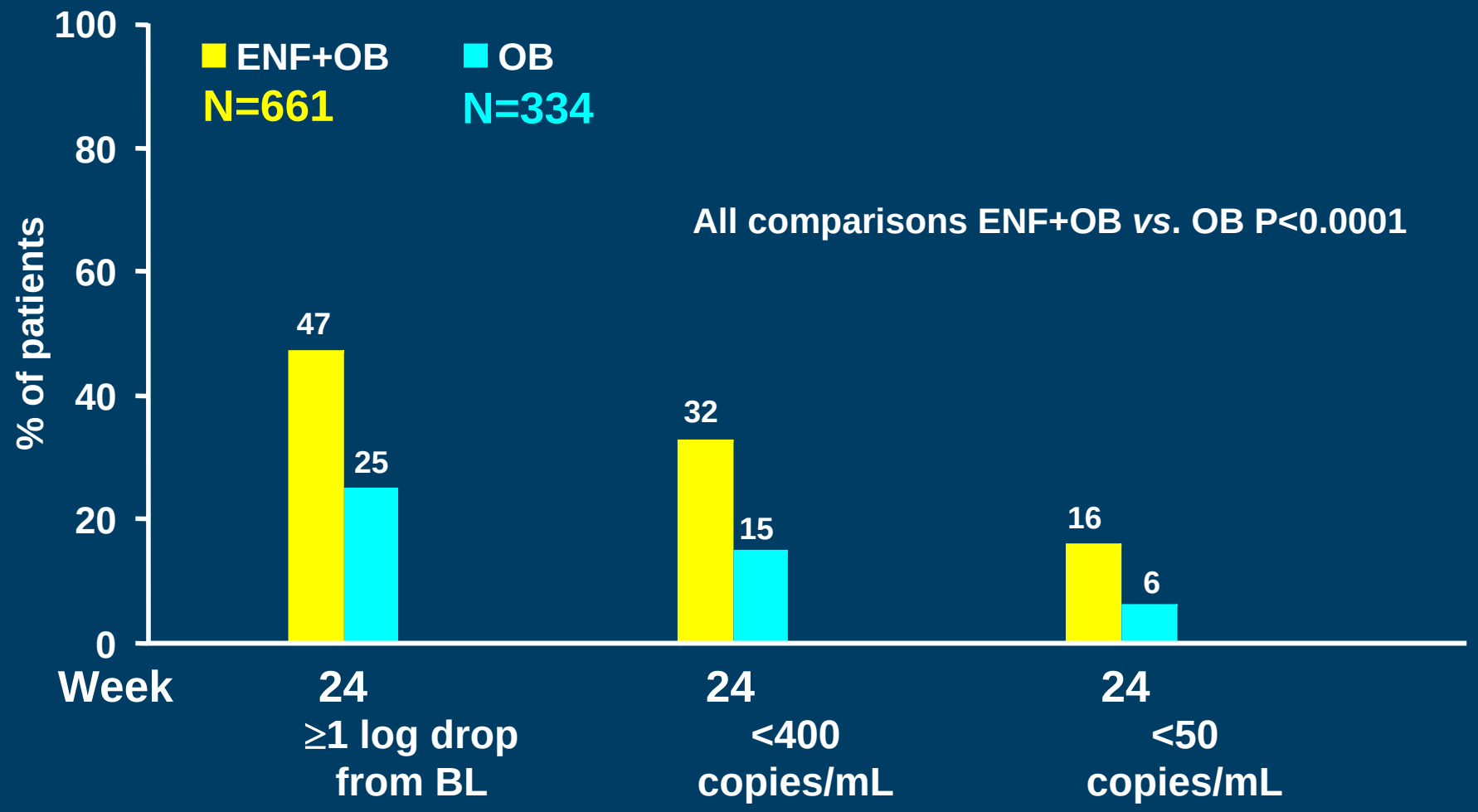
Data following virological failure not included in primary efficacy analyses

TORO 1 & TORO 2: BL characteristics and prior ARV experience

	ENF+OB (N=661)	OB (N=334)
BL RNA (median, $\log_{10}$ copies/mL)	5.2	5.1
BL CD4+ cell count (median, cells/mm^3)	88	97
Number of prior ARVs (median)	12	12
Years since initiating ARVs (median)	7	7
Prior NRTI (median, years)	6.3	6.3
Prior NNRTI (median, years)	1.4	1.5
Prior PI (median, years)	3.8	4.0

The treatment benefit seen at week 24 is maintained at week 48:

Percent responders at week 24 and week 48 (ITT, DC+VF=F)



2 visits required to confirm viral load response

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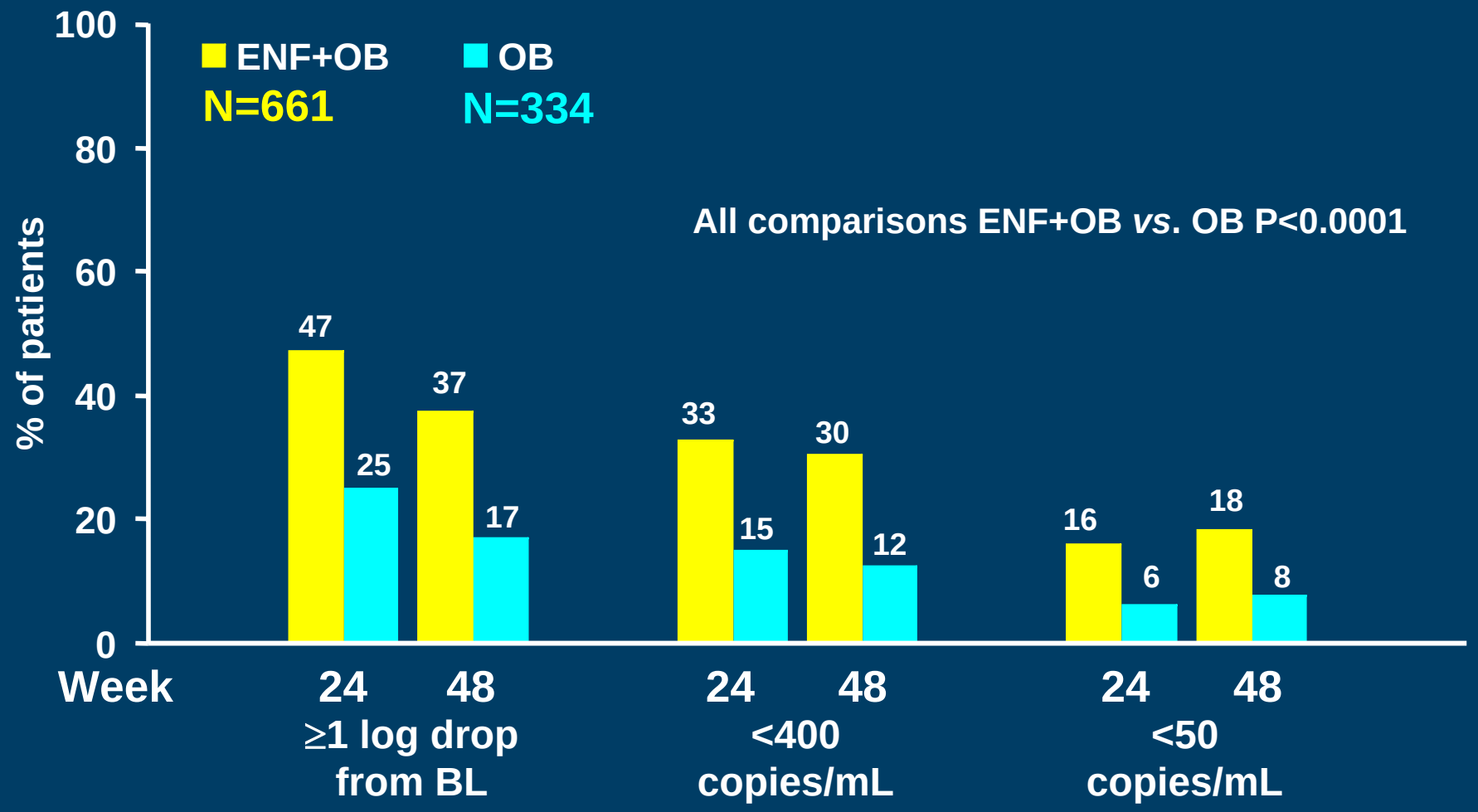
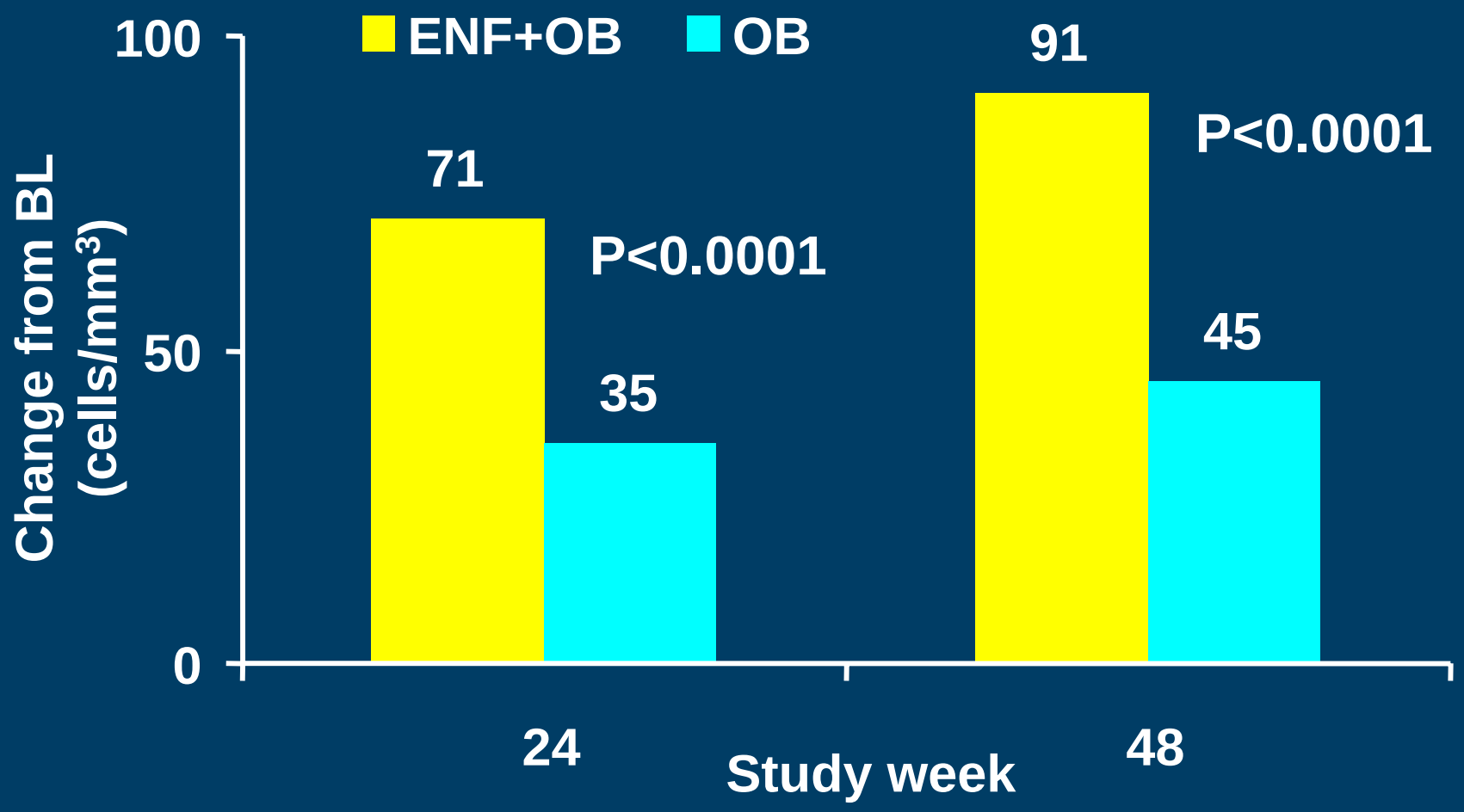
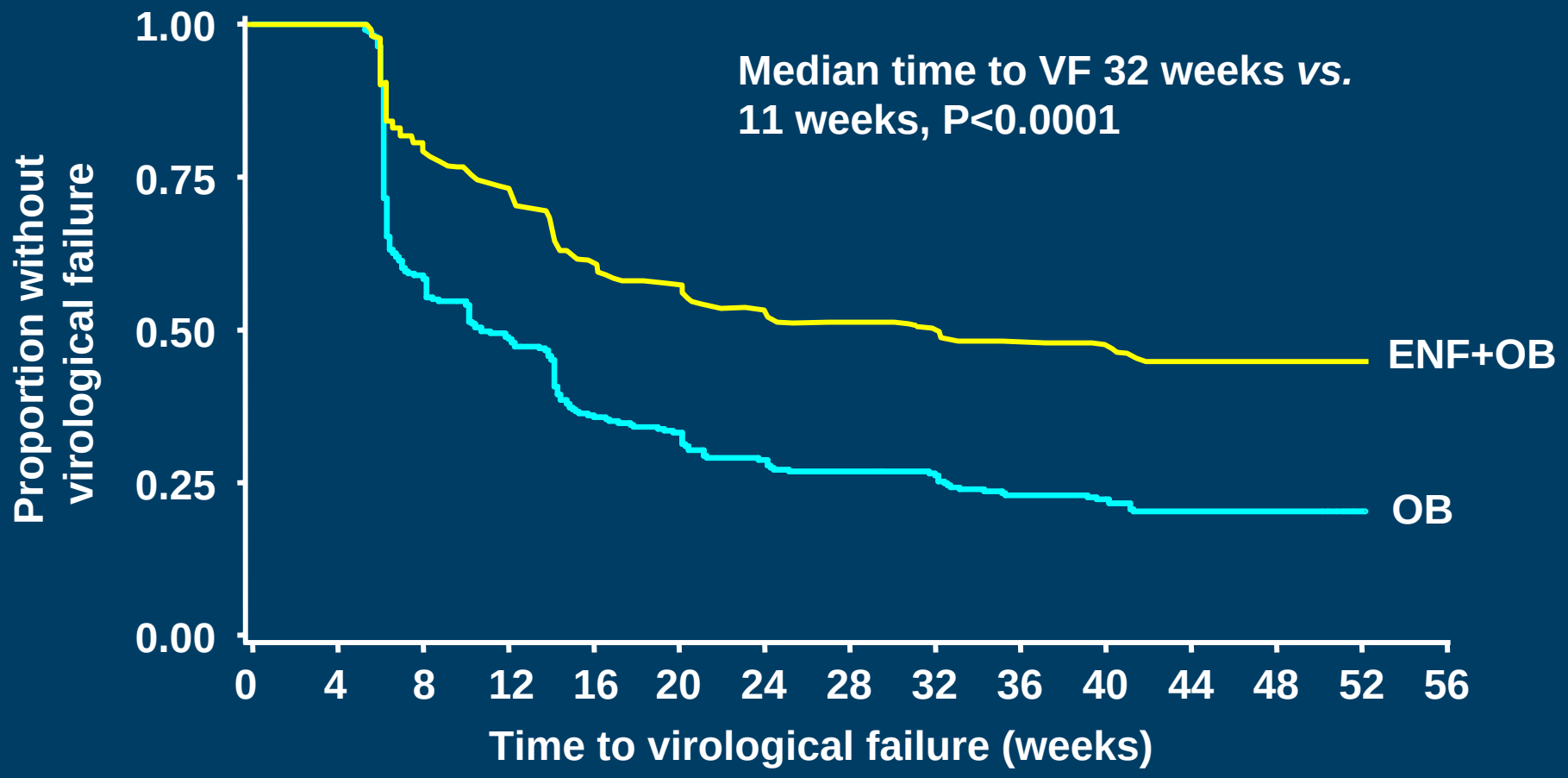


2 visits required to confirm viral load response

CD4+ cell count adjusted means change from baseline – intent-to-treat population (LOCF) TORO 1 & TORO 2

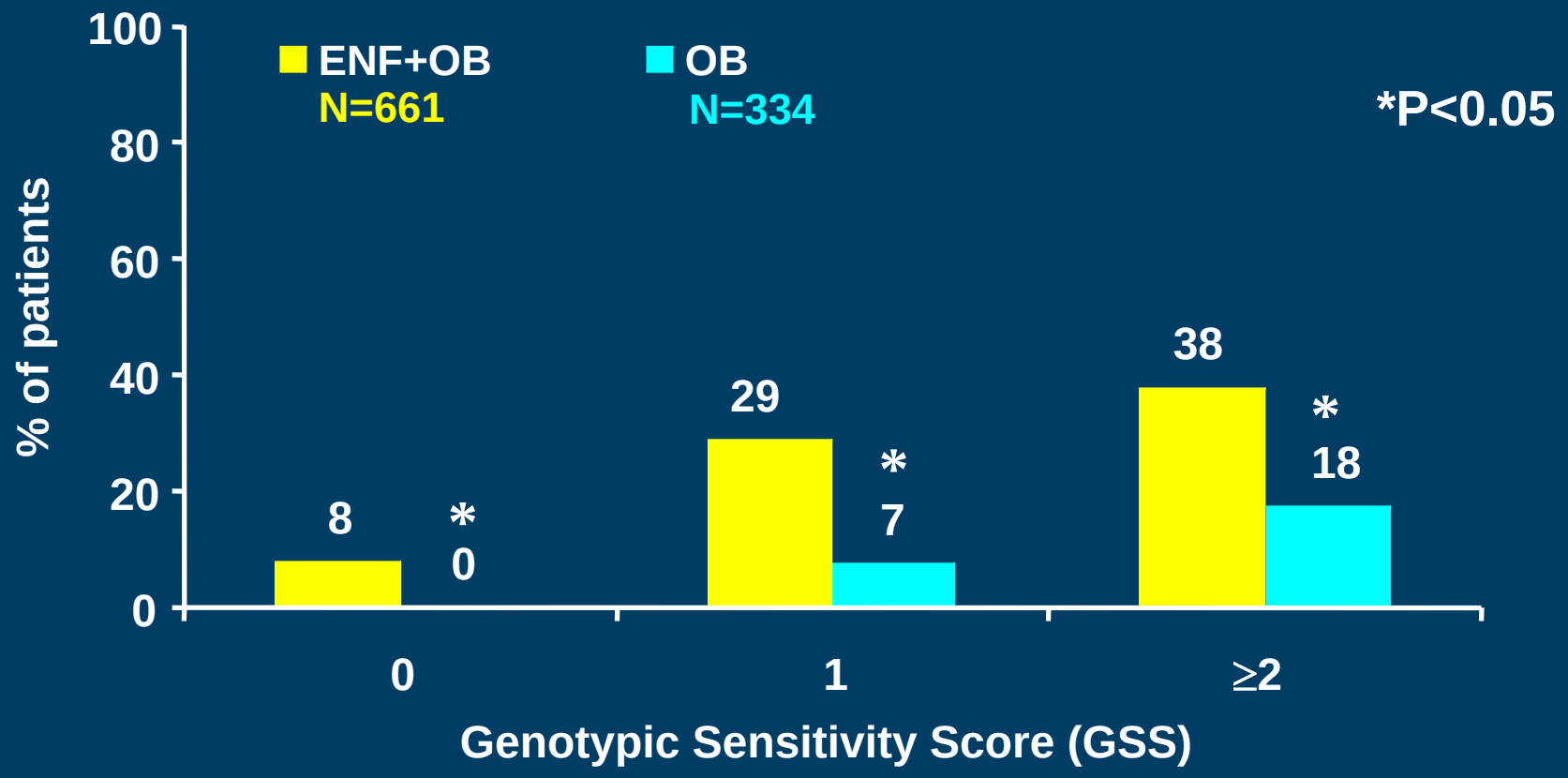


The time to virological failure* was longer on ENF+OB compared to OB



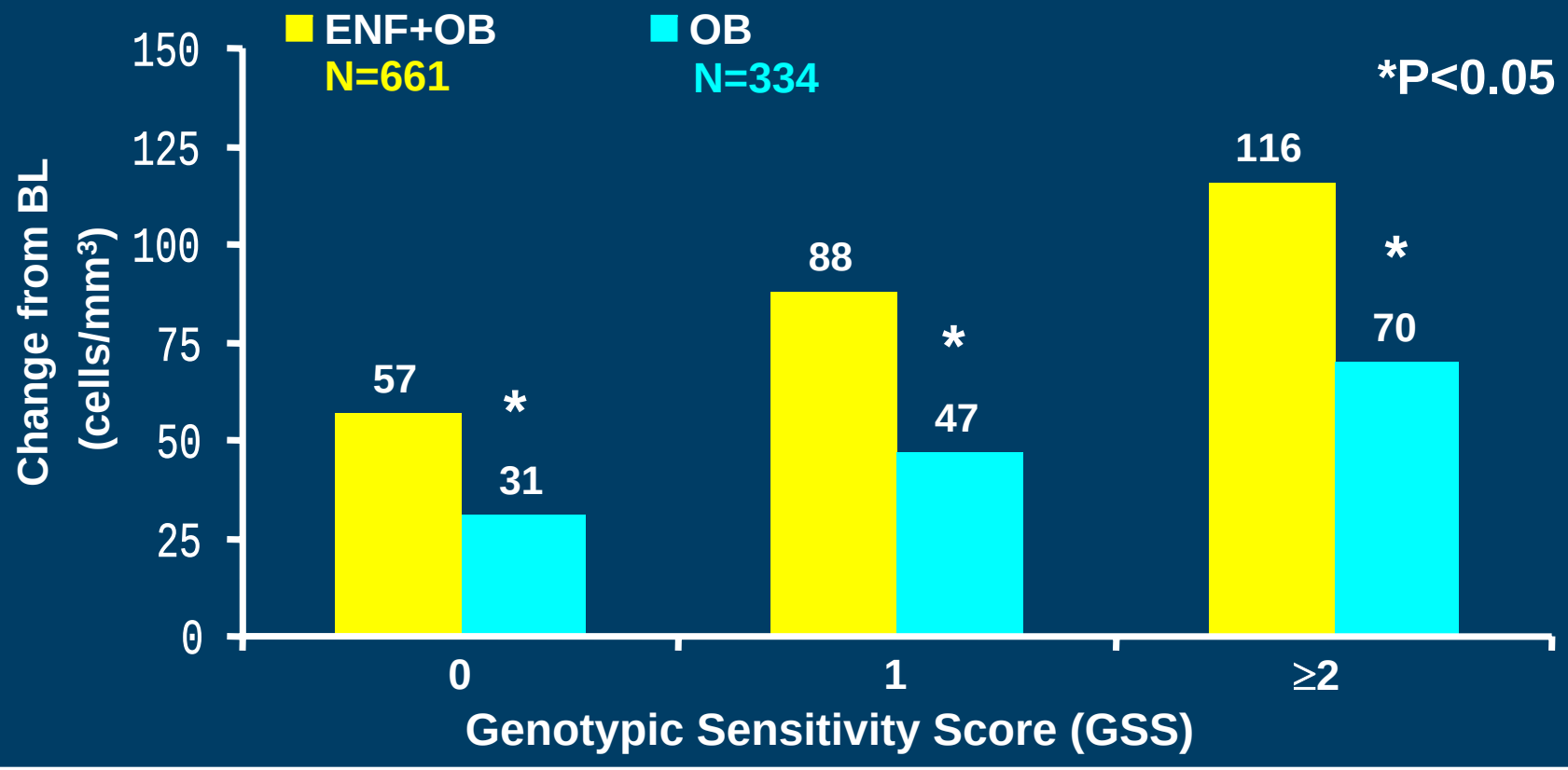
* Protocol defined

Treatment benefit is seen across GSS subgroups for responders with HIV RNA <400 copies/mL, week 48 (ITT, DC+VF=Failure)



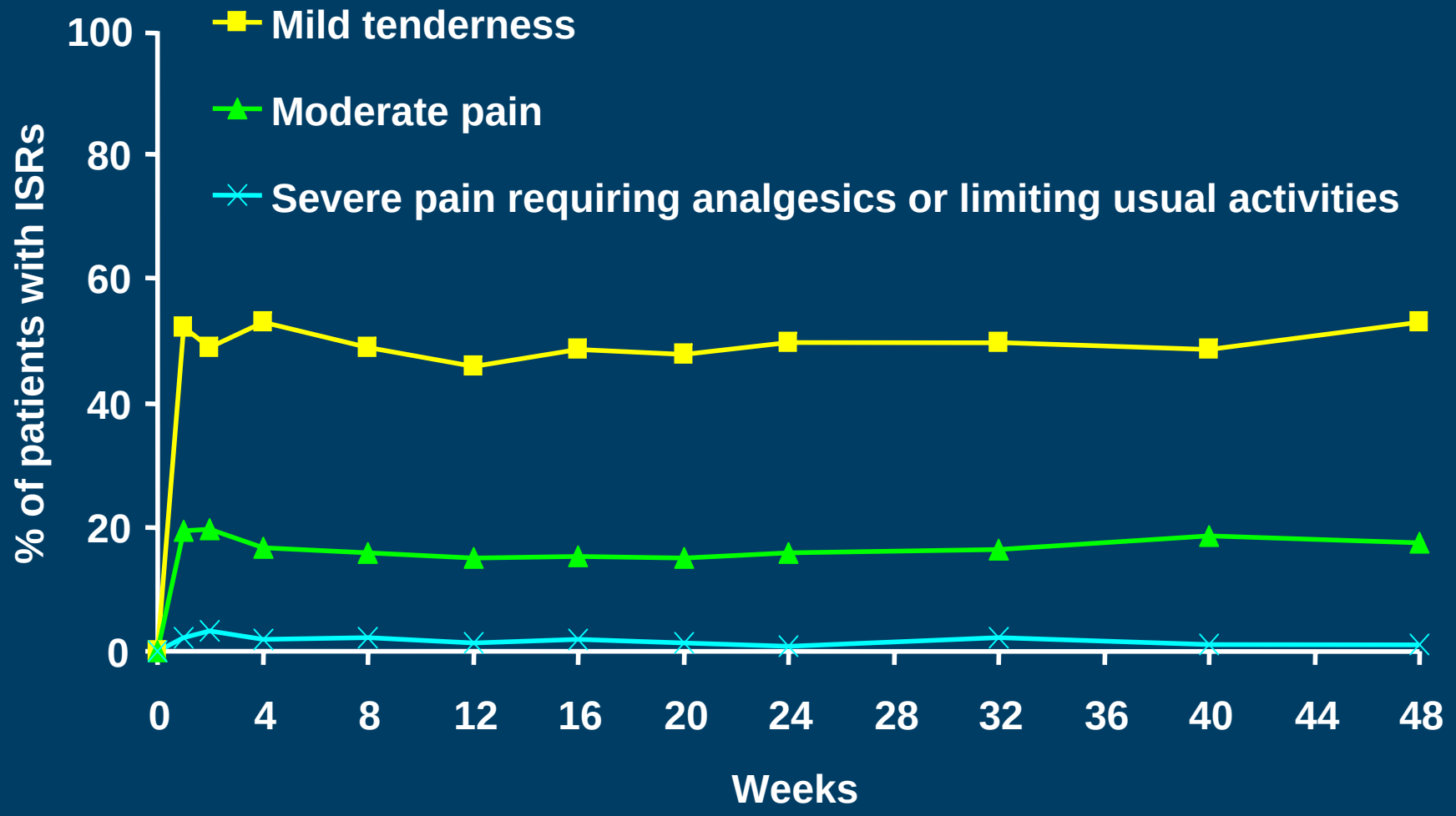
GSS	0	1	≥2
ENF+OB	112	194	344
OB	53	95	183

CD4+ cell count adjusted mean change from baseline, week 48 (ITT, LOCF) by BL GSS



GSS	0	1	≥2
ENF+OB	110	191	340
OB	52	93	180

Incidence of injection site reactions (ISRs)* by study week and by grade, 48 weeks



* based on pain or discomfort,
% of patients remaining on study

48 Week combined TORO 1 & TORO 2 exposure adjusted AEs (≥5 per 100 patient-years)

	ENF+OB N (Per 100 patient-years)	OB
Total exposure (patient-years)	557.04	162.13
diarrhoea	210 (37.7)	119 (73.4)
nausea	151 (27.1)	81 (50.0)
fatigue	134 (24.1)	61 (37.6)
headache	89 (16.0)	39 (24.1)
insomnia	88 (15.8)	32 (19.7)
peripheral neuropathy	86 (15.4)	22 (13.6)
vomiting	84 (15.1)	43 (26.5)
pyrexia	83 (14.9)	39 (24.1)
depression	80 (14.4)	27 (16.7)
upper respiratory tract infection	80 (14.4)	31 (19.1)
dermatitis	68 (12.2)	38 (23.4)
cough	64 (11.5)	23 (14.2)
weight decreased	62 (11.1)	17 (10.5)
nasopharyngitis	56 (10.1)	19 (11.7)
sinusitis	53 (9.5)	10 (6.2)
oral candidiasis	52 (9.3)	22 (13.6)
dizziness (excluding vertigo)	52 (9.3)	20 (12.3)
bronchitis	50 (9.0)	24 (14.8)

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Total exposure (patient-years)	557.04		162.13	
bronchitis	50	(9.0)	24	(14.8)
appetite decreased	48	(8.6)	8	(4.9)
asthenia	43	(7.7)	14	(8.6)
anxiety	42	(7.5)	11	(6.8)
herpes simplex	41	(7.4)	15	(9.3)
abdominal pain	39	(7.0)	15	(9.3)
myalgia	39	(7.0)	9	(5.6)
pruritus	37	(6.6)	16	(9.9)
skin papilloma	37	(6.6)	5	(3.1)
*pneumonia	37	(6.6)	1	(0.6)
influenza	36	(6.5)	10	(6.2)
lymphadenopathy	33	(5.9)	2	(1.2)
folliculitis	32	(5.7)	13	(8.0)
pain in limb	32	(5.7)	13	(8.0)
dyspepsia	30	(5.4)	17	(10.5)
dry mouth	30	(5.4)	13	(8.0)
constipation	30	(5.4)	9	(5.6)
night sweats	28	(5.0)	12	(7.4)
dry skin	28	(5.0)	7	(4.3)

* Collapsed term including all pneumonias

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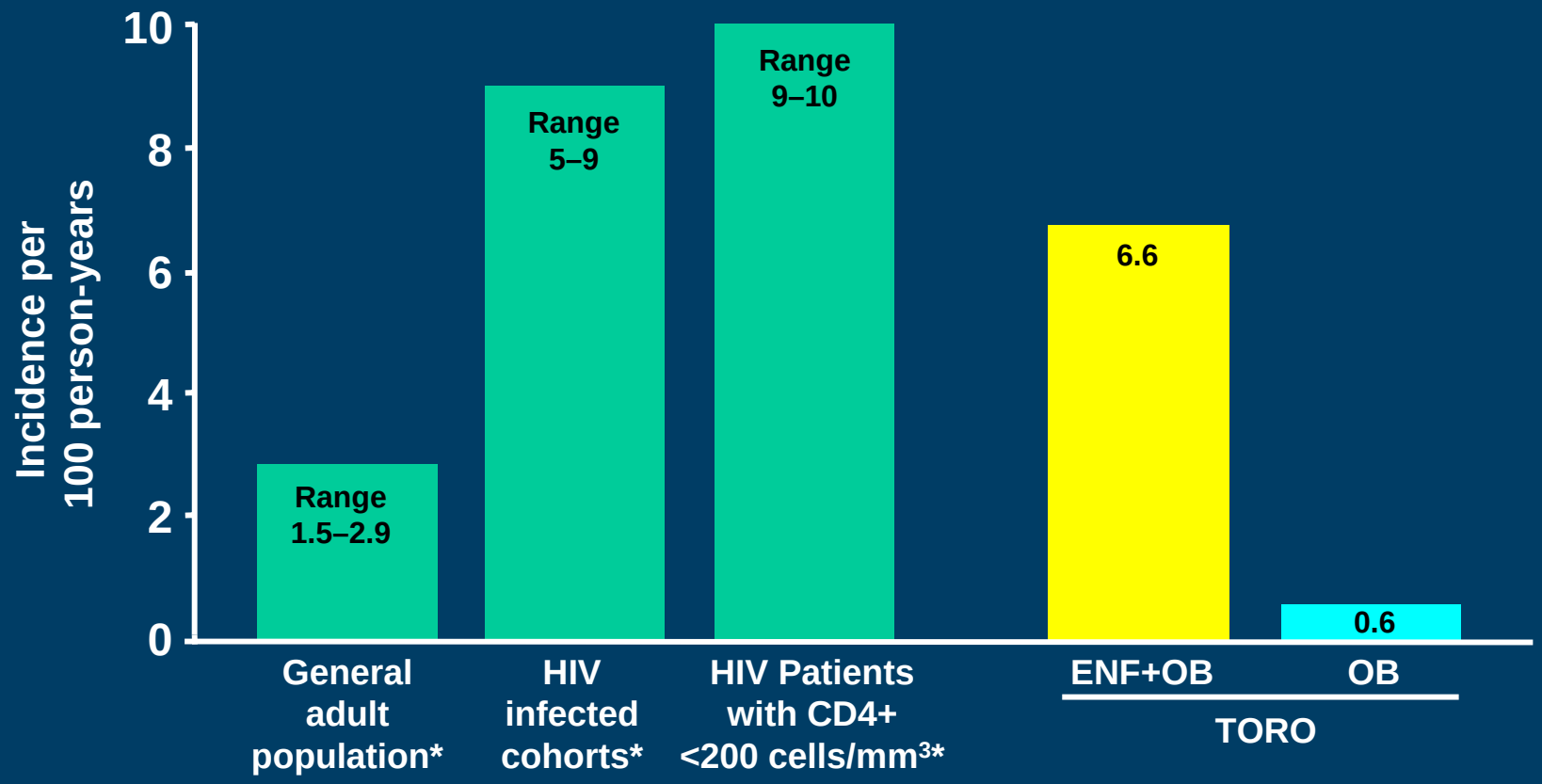
Incidence of bacterial pneumonia in TORO trials and historical controls



*Boschini *et al*. *Clin Inf Dis*, 1996; 23, 107
Hirschtick *et al. NEJM*, 1995; 333, 845
Polsky *et al. Ann Int Med*, 1986; 104, 38
Caiaffa *et al. Am J Resp Crit Care Med*, 1994; 150, 1493
Wallace *et al*. *Am Rev Resp Dis*, 1993; 148, 1523

Safety conclusions, 48 weeks

- **ENF added to a background regimen does not exacerbate most of the known toxicities associated with other ARVs**
- **The most common AE is ISRs, seen in almost all patients**
  - Generally mild to moderate
- **Increased rate of pneumonia observed in ENF+OB arm compared to control arm; drug relationship not established**
- **Hypersensitivity reactions have been attributed to ENF (≤1%) and in some cases have recurred upon re-challenge**

Efficacy conclusions, 48 weeks

- **Percent responders (≥1 log drop from BL, <400 or <50 copies/mL) at week 48 were >2 fold higher on ENF+OB compared to OB alone, all P<0.0001**
- **Change from BL in CD4 count, as well as time to virological failure all significantly improved on ENF+OB compared to OB (all P<0.0001)**
- **Treatment benefit was observed across all subgroups of GSS, including GSS=0**
- **Magnitude of benefit increases with more active ARVs in the OB regimen**
  - Subgroup analyses suggest that use of ENF with at least one active ARV in the OB regimen provides benefit similar or better than that provided with OB alone with ≥2 active ARVs

TORO 1: Acknowledgements

The Authors would like to express their gratitude to all of the patients that participated in the TORO 1 study as well as the numerous Roche and Trimeris study personnel who have worked closely with the following study investigators to bring the TORO 1 study to the 24 week primary analysis.

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TORO 2: Acknowledgements

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