Study Design Issues for registration studies in advanced patients: The Fuzeon (enfuvirtide, ENF, T-20) TORO studies

Miklos Salgo, PhD, MD
Hoffmann-La Roche, Inc.

Salvage Therapy Think Tank
Houston, April 16, 2004

Considerations in developing the ENF Phase III clinical registration plan

- **High unmet medical need for a new class of ARV for use in advanced treatment experienced patients**
- **In Phase II, ENF had been shown to be active in multiple-drug experienced patients**
- **As no new agent should be used in monotherapy, primary objective is to demonstrate additional benefit provided by addition of enfuvirtide to standard of care in these treatment experienced patients**

Background

- **Target population never studied before for a new class of ARV**
- **Limited regulatory guidelines for new agents in advanced patients**
- **Traditional fixed drug regimen control unsuitable for advanced patients**
- **Traditional efficacy endpoints may not be appropriate for advanced patients**
- **Studies had to be open label due to s.c. administration, reconstitution time and signature AE (injection site reactions)**

Major considerations

- **In order to have clinical relevance**
  - Study had to reflect the patient population likely to use the drug in clinical practice
- **In order to be attractive to patients and to accrue in a reasonable period of time**
  - Study had to provide patients with at least the “standard of care” available outside the study
  - Access to ENF for all patients
- **Treatments in the study would have to have acceptable “equipoise” in the view of patients and investigators**

Studies had to be acceptable to 4 major stake holders

- **Patients (and patient advocates and community)**
  - Had to be “patient friendly”
  - Provide potential benefits and clear delineation of potential risks
- **Investigators and HIV experts**
  - Must be safe and acceptable to patients
  - Must be scientifically sound and medically appropriate
- **Regulatory Agencies (U.S. and Europe)**
  - Must unequivocally demonstrate safety and efficacy of the drug
- **Sponsor**
  - Studies must be done efficiently while controlling risks

Feedback on study design from stakeholders

- **Patient Community**
  - U.S. Community Advisory Board
  - EATG
- **Investigators and Advisors**
  - Global and North American Advisory Committees
  - Investigator meetings
- **Regulatory Agencies**
  - FDA End of Phase II meeting, conf. calls
  - National Health Authorities (France, Spain) and Rapporteurs (Sweden, Portugal),
  - CPMP Scientific Advice
- **Internal**
  - Roche/Trimeris Peer Reviews and upper management

Assess the true efficacy and safety of enfuvirtide

- **Need clear demonstration of efficacy that is both clinically meaningful and statistically significant**
- **Proportion of patients below level of detection (%BLQ) commonly used and cited in regulatory guidance documents**
  - Response rate unknown
  - Such categorical responses may miss a true treatment difference at very high or very low responses
- **Need clear comparative safety data**
- **Study group should be representative of those who would use the drug post approval**

Studies had to be “Patient friendly”

- **Individualized “Optimized Background” (OB) or control regimen required**
- **Patients should get at the least the best “standard of care” available outside the study**
- **Use of genotypic and phenotypic viral resistance testing becoming state of the art to optimize changes in therapy and improved response in advanced patients (Viradapt, GREAT and other studies)**
- **Advanced patients have a high medical need for a new class of ARV. Within the confines of a randomized clinical trial those needs have to be addressed**
  - 2:1 randomization
  - “Treatment escape” or switch

Decrease heterogeneity of OB

- **Optimized Background (OB) regimen chosen by physician/patient prior to randomization based on patient's prior history (including prior resistance testing), and BL viral genotype/phenotype**
- **Free choice of OB regimen restricted to 3 to 5 antiretrovirals (exclude patients needing mega-HAART)**
- **Allow use of approved and experimental agents available in that country**
- **Physician and patient must commit to OB regimen prior to the patient's randomization to OB or OB + ENF**
- **Stratify by use vs. non-use of allow experimental agents available in compassionate use/expanded access**

Achieving balance of OB across treatments

- **There will be differences in patterns of OB use by site and country**
- **Stratified prior to randomization by:**
  - screening viral load (<40,000 or ≥40,000 copies/mL)
  - use of any of the allowed experimental antiretrovirals (versus non-use)
- **Study analyses will assess impact of any imbalance across treatments with regards to intensity of the OB regimen (as measured by the Phenotypic Sensitivity Score and other variables)**

Minimizing potential sources of bias

- **Operational (external) biases can be minimized**
  - By allowing the physician and patient free choice of OB, and allowing use of other experimental agents available in expanded access/compassionate use, there should be little incentive to supplement the already optimized regimen
  - Changes to the OB regimen (either treatment) prior to meeting switch criteria limited to those required for toxicity management. Where possible, only substitution of a different antiretroviral from the same class will be permitted

Minimizing potential sources of bias

- **Treatment groups will be handled equally**
  - Rules for changes to OB and switch criteria for virological failure or rebound are identical for both treatments; meeting switch criteria will be considered failure
  - Those on OB will be permitted to add ENF to a revised OB regimen, only after the patient's OB regimen alone has failed
  - Changes in viral load and CD4 cell count AFTER patients on either treatment have met switch (failure) criteria will be a secondary analysis

Adherence *vs.* misrepresentation

- **Any difficulties with adherence were dealt with in a non-judgmental way, relying on positive reinforcement and education to encourage and promote adherence, for the patient's best interest.**
- **In order to discourage and also to monitor potential misrepresentation (which could have introduced a bias), OB confirmatory plasma samples were routinely taken at Week 4 and at VF or at week 24, whichever came first.**

Endpoints and a clinically meaningful response

- **Primary Study Objective:**
  - To demonstrate that ENF added to OB provides an additional drop in viral load of at least 0.5 $\log_{10}$ copies/mL compared to OB regimen alone as measured by the difference in the mean change from baseline in plasma HIV-1 RNA at week 24 between the two arms
- **$\geq$0.5 $\log_{10}$ copies/mL additional suppression seen with OB + ENF compared to OB alone would constitute a clinically meaningful response**

Pivotal studies: TORO 1 (T20-301: US, Canada, Mexico, Brazil) & TORO 2 (T20-302 : Europe, Australia)

- **Population**
  - Prior experience to ≥1 NRTI, ≥1 NNRTI, and ≥2 PI (≥1 PI for 302)
  - ≥6 mo. experience on each class for 301 (≥3 mo. for 302) or documented viral resistance or class intolerance
  - HIV-1 RNA ≥ 5000 copies/mL on 3 occasions
- **Design**
  - Open Label, Randomized Multi-Center, International
- **Treatments (randomized 2:1)**
  - Optimized Background (OB)
    - 3-5 ARVs based on history, viral GT/PT
  - Enfuvirtide: ENF (90 mg sc bid) + OB

TORO 1 & 2: Primary and secondary objectives at week 24

Primary

- **ENF+OB provides an additional drop in plasma HIV-1 RNA ≥0.5 log_{10} copies/mL *vs.* OB alone at week 24**

Secondary

- **Percentage of patients with ≥1.0 log_{10} drop in HIV-1 RNA, HIV-1 RNA <400 copies/mL and <50 copies/mL**
- **Safety of ENF+OB *vs.* OB alone**
- **PK of ENF**
- **Health-related quality of life (MOS-HIV instrument) of ENF+OB *vs.* OB alone**

TORO 1 & 2: Primary and secondary objectives at week 48

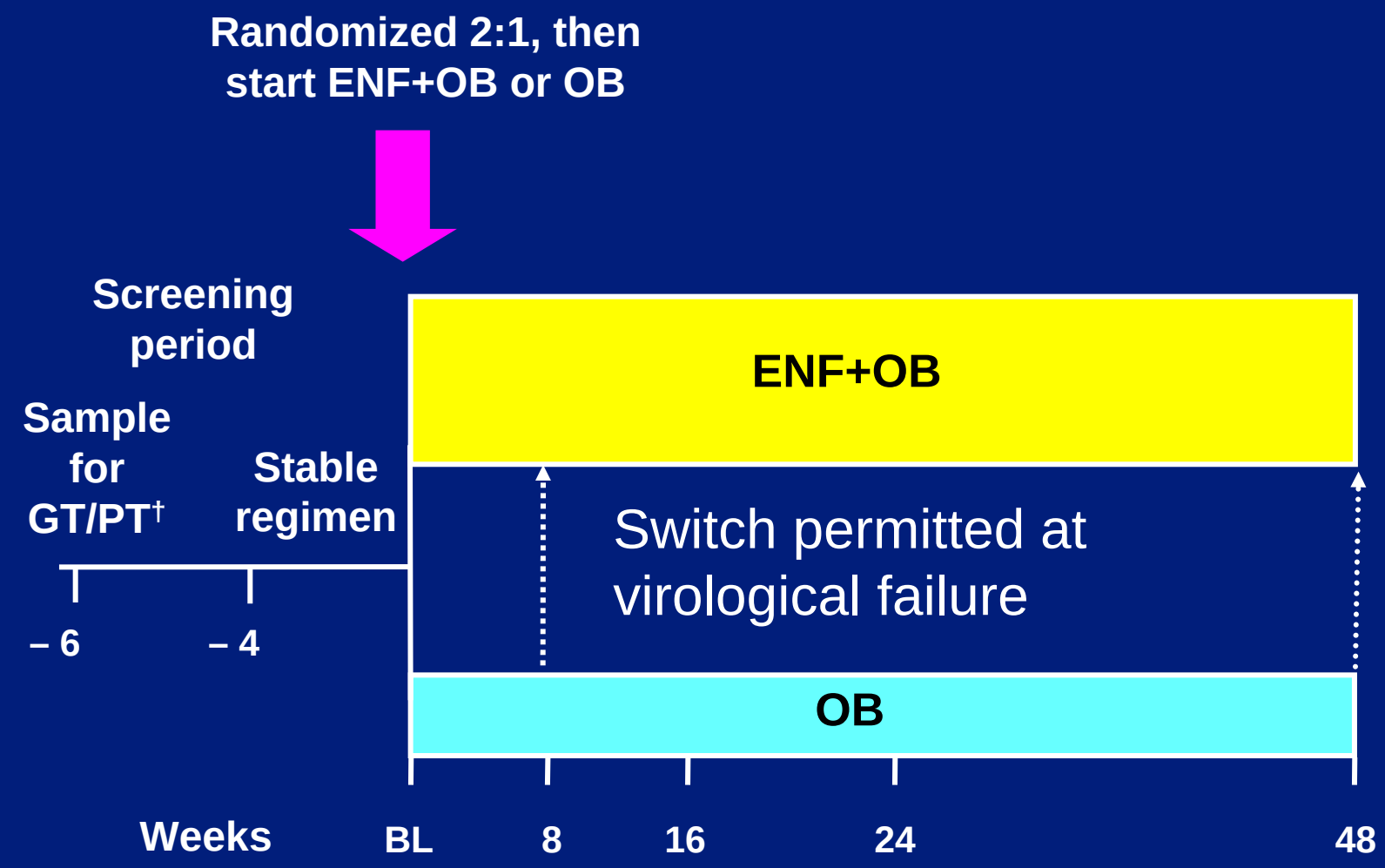
Primary

- **Durability of efficacy of the ENF+OB regimen (percentage of patients who responded at Week 24 and improved or maintained their response at Week 48):**
  - **<50 copies/mL**
  - **50 to 400 copies/mL, or**
  - **>1.0 log10 decrease from Baseline but > 400 copies/mL**

Secondary:

1. **To evaluate the percentage of patients with:**
   - **<50 copies/mL,**
   - **<400 copies/mL, and**
   - **> 1.0 log10 decrease from baseline in plasma HIV-1 RNA,**
2. **To compare the safety of the ENF+OB regimen versus the OB regimen alone at 48 Weeks of treatment.**
3. **To evaluate the pharmacokinetics (PK) of enfuvirtide in triple-class experienced and/or resistant/intolerant patients.**

TORO 1 & TORO 2: Protocol study design



†GT = Genotypic Testing; PT = Phenotypic Testing

TORO 1 & 2: Protocol defined criteria for virological failure (VF)

1. **Failure to achieve ≥0.5 $\log_{10}$ copies/mL suppression by weeks 6 and 8**

2. **Failure to achieve ≥1.0 $\log_{10}$ copies/mL suppression by weeks 14 and 16**

3. **Achieving ≥2 $\log_{10}$ copies/mL suppression**

   followed by

   ≥1 $\log_{10}$ copies/mL rebound

TORO 1 & 2: Unique study design

- **Switch design requires appropriate endpoints and data handling**
  - Efficacy
    - Primary analysis designed to account for switches, drop outs
  - Safety
    - Comparative displays on initially randomized treatment
    - Adjustment for exposure
  - Discontinuations
    - Patients on OB switching to ENF+OB counted separately

TORO 1 & 2: Rationale for selection of primary endpoint and data handling rules

- **High possible range of response due to heterogeneity and use of GT/PT for guidance**
- **Categorical analysis**
  - Percent of patients reach a pre-defined drop (or BLQ): DC or VF = Failure
  - High % of patients (for both arms) might reach >1 log change from BL
  - Few patients might reach <50 or <400 copies/mL
  - may miss true treatment differences (e.g. unable to detect a 15% improvement if OB response is 90%)
- **Continuous variable analysis**
  - Sensitive to treatment difference across entire range of possible response
  - Change from baseline in viral load (log_{10} copies/mL): LOCF
    - Accounts for treatment benefit in VF patients

TORO 1 & 2: Analyses and data handling rules

- **Primary analysis**
  - ITT: all patients randomized, receiving at least one treatment and having at least one follow up value
  - Least Square Means, PSS as covariate
  - Last Observation Carried Forward (LOCF)[1, 2]
- **Secondary categorical analyses**
  - ITT
  - Discontinuations (DC) or virological failures (VF) = failure (F)
  - Sensitivity analyses
- **Safety analyses**
  - Adjust for exposure (patient with event per 100 Pt-Yrs)
  - Combine all patients exposed to ENF [(ENF+OB) + Switch]
  - Risk ratio of exposure adjusted rates
  - Kaplan-Meier plots

[1]Little R and Yao L., Biometrics 52, 1324-33, 1996
[2]Heyting A et al. Statistics in Medicine 11, 2043-61, 1992

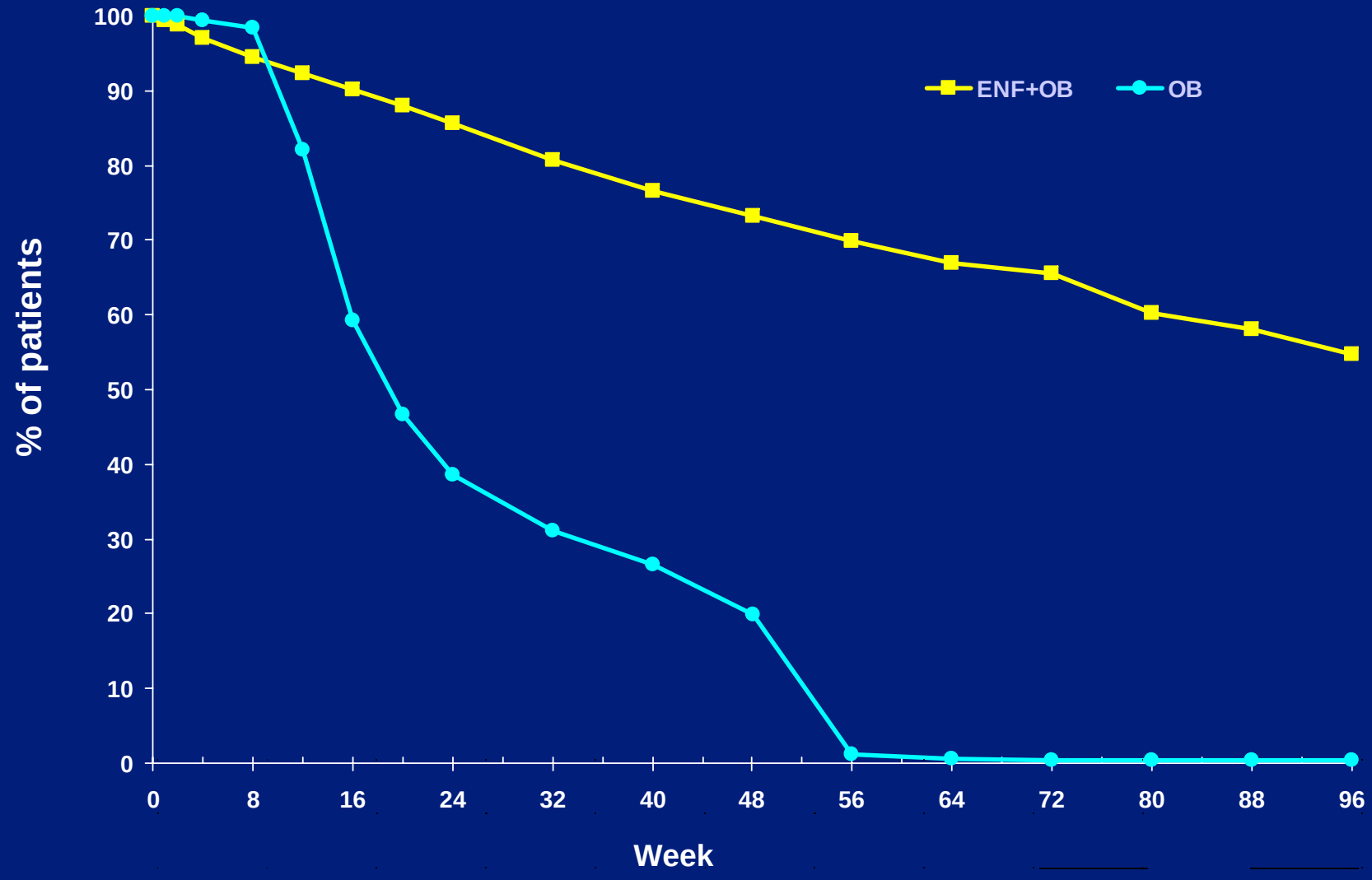
Rationale for pooling TORO 1 and TORO 2

- **Preplanned - included in Analysis Plan**
  - Similar study designs, populations and baseline characteristics
- **More precise estimate of the treatment effect (ENF+OB *vs* OB)**
- **Greater power for subgroup analyses**
- **Safety**

Validation of primary efficacy

- **Primary analysis and LOCF validated by**
  - Cohort analyses, patients completing 8 weeks
  - Sensitivity analyses with more conservative data handling rules including DC or VF = F (no benefit)
- **Secondary analyses**
  - Protocol defined analyses used conservative data handling rules
    - 2 observations required (week 20, 24) to meet responder criteria
    - DC + VF = F
  - FDA algorithm for response (designed to allow cross study comparisons) yielded higher responses and statistically significant treatment differences

Exposure by treatment (ITT: D/C or SW =censored)



Safety assessments: Patient-years of exposure

	ENF+OB N=663	Switch	Combined ENF	OB N=334	Ratio ENF+OB:OB
24 Week Analysis		195 Pts	858 Pts		
	326 Pt-Yrs	44 Pt-Yrs	369 Pt-Yrs	125 Pt-Yrs	2.6:1
48 Week Analysis		222 Pts	885 Pts		
	557 Pt-Yrs	120 Pt-Yrs	677 Pt-Yrs	162 Pt-Yrs	3.4:1
96+ Week Analysis		229 Pts	892 Pts		
	1070 Pt-Yrs	295 Pt-Yrs	1365 Pt-Yrs	164 Pt-Yrs	6.5:1

Potential biases in safety assessment due to switch design

- **Balance for risk factors for AEs achieved with initial stratification and randomization**
- **Switch is early and asymmetric; patients switch from OB to ENF but not *visa versa***
- **Patients meeting VF criteria and switching are the most advanced / not responding to therapy**
- **Balance is lost with switch**
  - VF patients removed from OB arm while VF patients remain on ENF+OB
  - Switch group likely sicker than “non-switch” patients
- **Impact likely to be highest for those AEs where incidence increases with decreased CD4 count**

Lessons Learned
Study Design

- **“Add on” study with “Switch” (treatment escape) design**
- **Allows all patients to receive at least “standard of care”**
- **Switch design allows those randomized to OB alone to receive new ARV**
- **Patients friendly, medically and scientifically sound; statistically robust**
  - Comparator diminshing after week 8, gone after week 48

Lessons Learned
Efficacy

- **Continuous variable (change from BL in viral load) acceptable and useful esp. if response unknown**
  - LOCF data handling rule validated within study but not widely accepted
  - D/C or VF=F or D/C or change treatment=F also useful (latter designed for consistent analyses across studies, but for switch studies does not treat both arms equally)
- **Categorical responses consistent with continuous variable**
- **Analyses**
  - 24 Weeks: Comparative efficacy
  - 48 Weeks: Comparative efficacy and durability of response
  - 96+ Weeks: Long term efficacy, non-comparative

Lessons Learned
Safety

- **Switch design and loss of control arm creates hurdles in safety assessment**
- **Analyses**
  - 24 Weeks: Comparative safety, % of patients
  - 48 Weeks: Comparative safety, rates per 100 Pt-Yrs
  - 96+ Weeks: Rates over time; non-comparative

Conclusion

- **Unique study design**
  - Chosen to be patient friendly
  - Able to assess true efficacy and safety of a new class of ARV in heavily pretreated patients
- **Early switch design requires creative solutions**
  - Selection of efficacy endpoints and data handling rules
  - Sensitivity analyses to validate robustness
  - Recognition and minimization of potential sources of bias
  - Appropriate safety displays

Back Up

TORO 48 Week Results

2nd IAS Conference on HIV Pathogenesis and Treatment, Paris, July 13-16, 2003, LB2

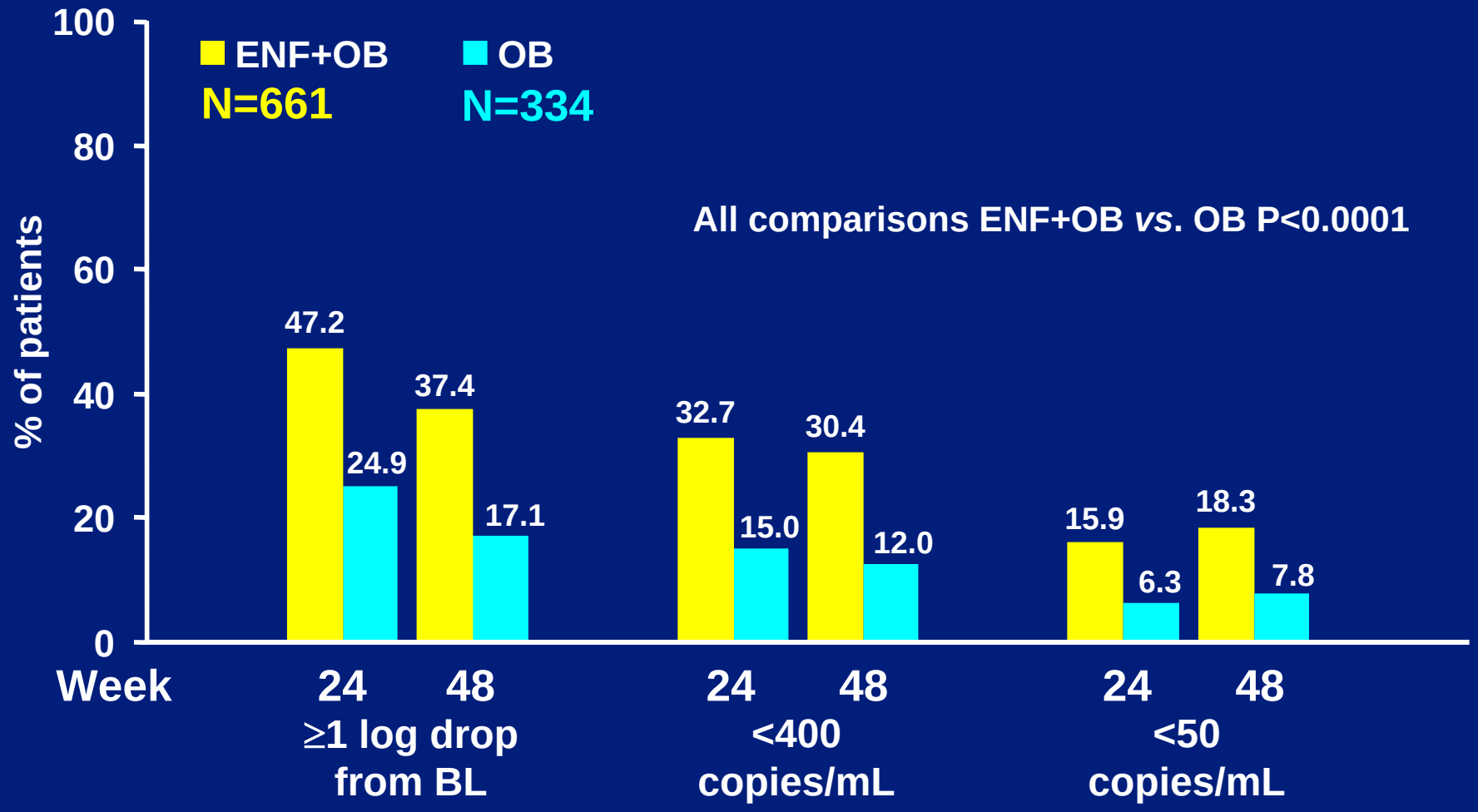
Enfuvirtide TORO studies:
48 week results confirm 24 week findings

Katlama C[1], Arastéh K[2], Clotet B[3], Cooper D[4], Henry K[5], Lalezari J[6], Lazzarin A[7], Montaner J[8], Nelson M[9], O'Hearn M[10], Piliero P[11], Reynes J[12], Trottier B[13], Walmsley S[14], DeMasi R[15], Delehanty J[15], Chung J[16], Salgo M[16]

[1]Pitié-Salpêtrière Hosp., Paris, France; [2]EPIMED, Berlin, Germany; [3]Hosp. Germans Trias i Pujol, Barcelona, Spain; [4]NCHECR, Sydney, Australia; [5]HCMC, MN, US; [6]Quest Clin. Res., CA, US; [7]San Raffaele Sci. Inst., Milan, Italy; [8]Univ. of BC, Vancouver, Canada; [9]C&W Hosp., London, UK; [10]OHSU, OR, US; [11]Albany Med. College, NY, US; [12]CHU Gui de Chauliac, Montpellier, France; [13]Clinique Medicale l'Actuel, Montreal, Canada; [14]Univ. of Toronto, Toronto, Canada; [15]Trimeris, NC, US; [16]Roche, NJ, US

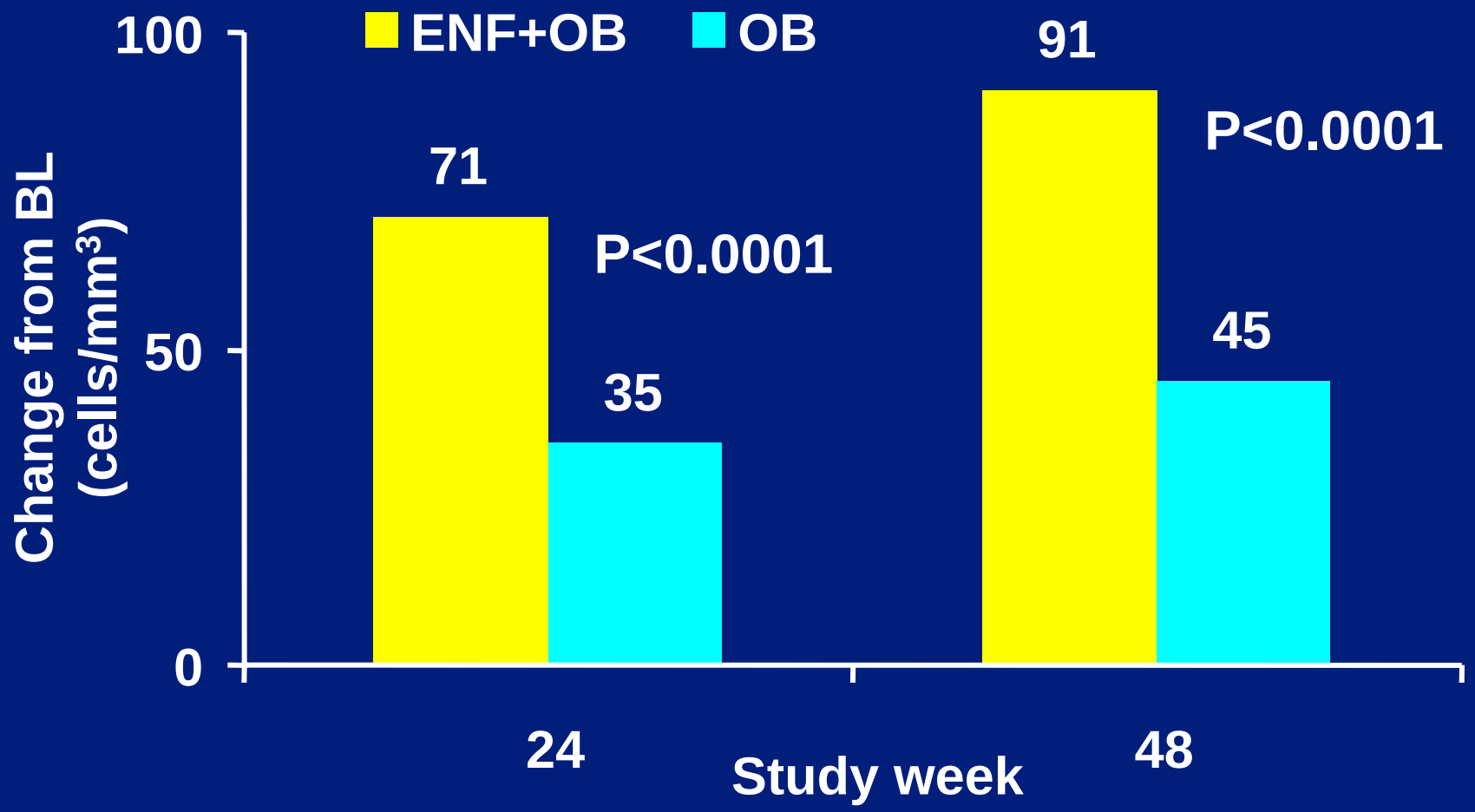
The treatment benefit seen at week 24 is maintained at week 48:

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

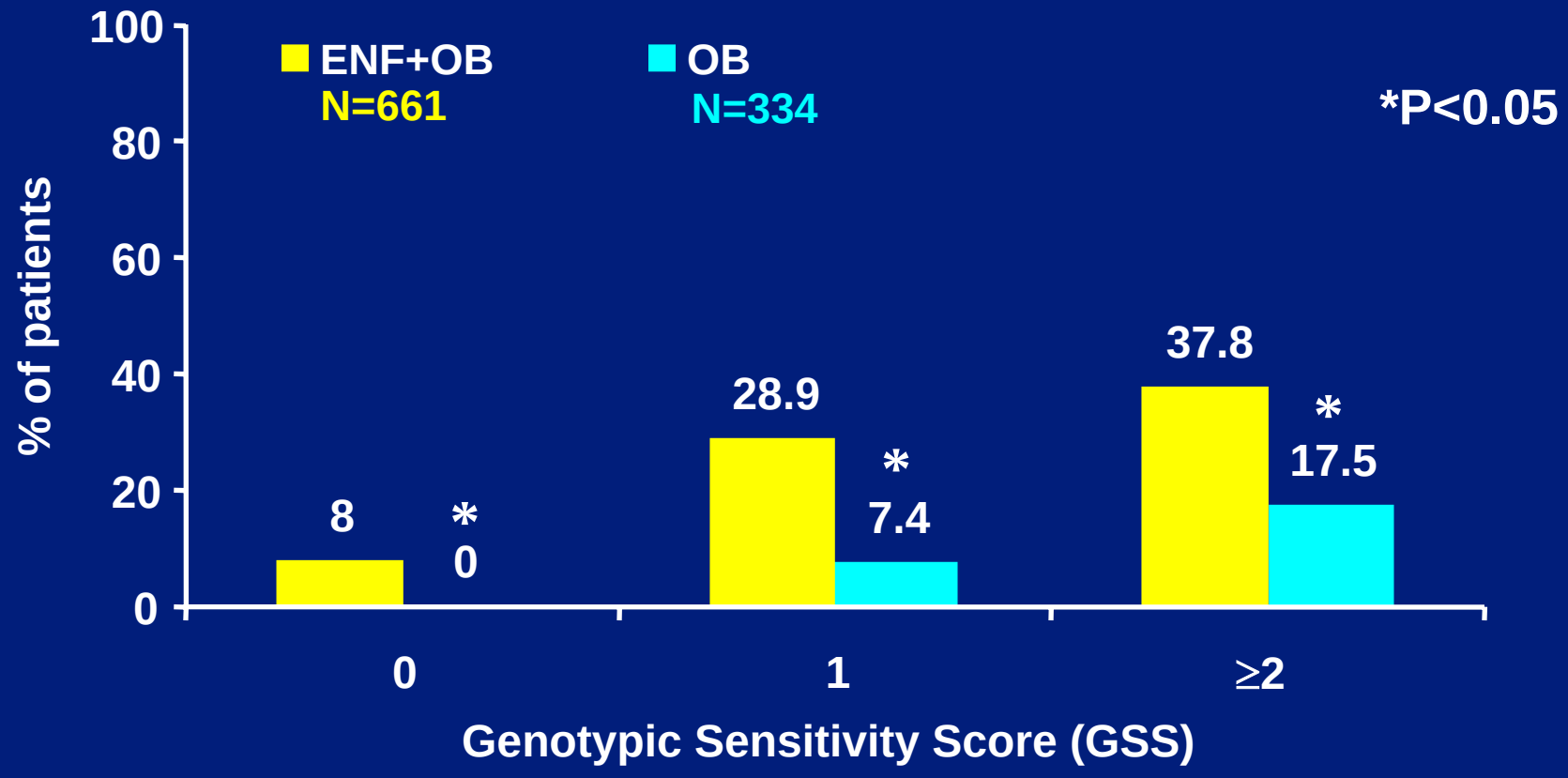


2 visits required to confirm viral load response

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

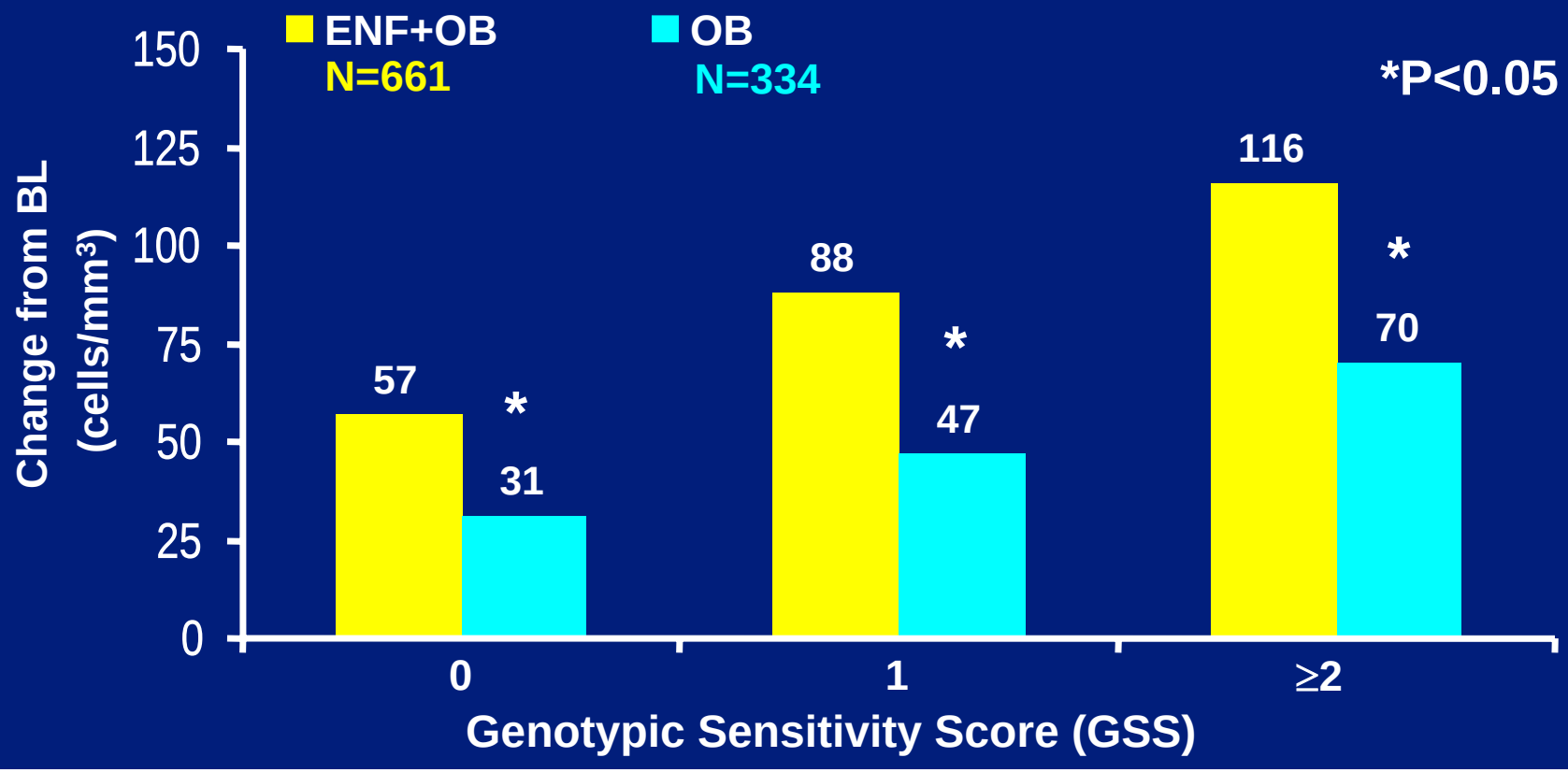


Treatment benefit is seen across GSS subgroups for responders with HIV RNA <400 copies/mL, week 48 (ITT, DC+VF=Failure)



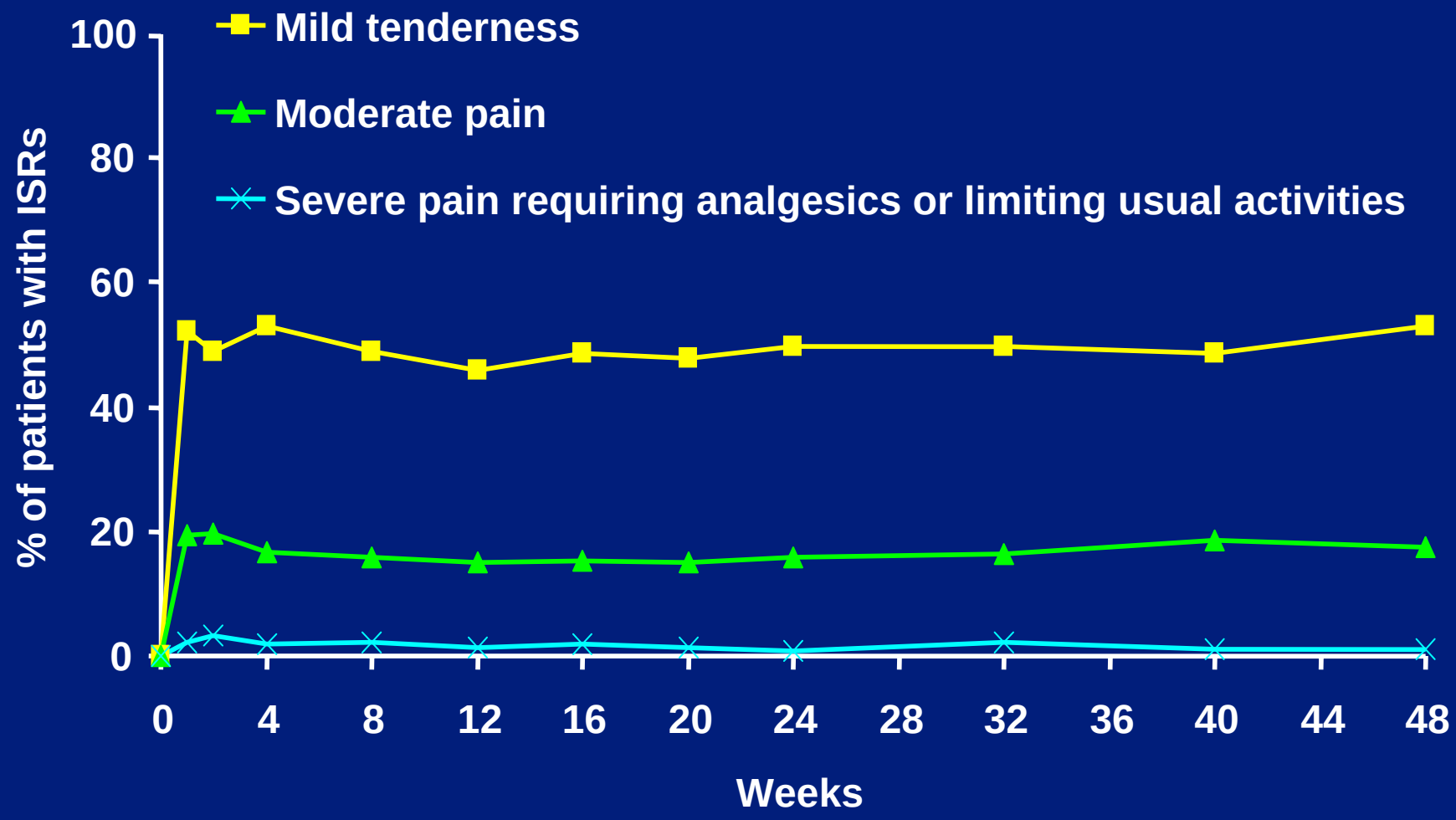
GSS	0	1	≥2
ENF+OB	112	194	344
OB	53	95	183

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)

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)

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

	ENF+OB N	ENF+OB (Per 100 patient-years)	OB N	OB (Per 100 patient-years)
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)

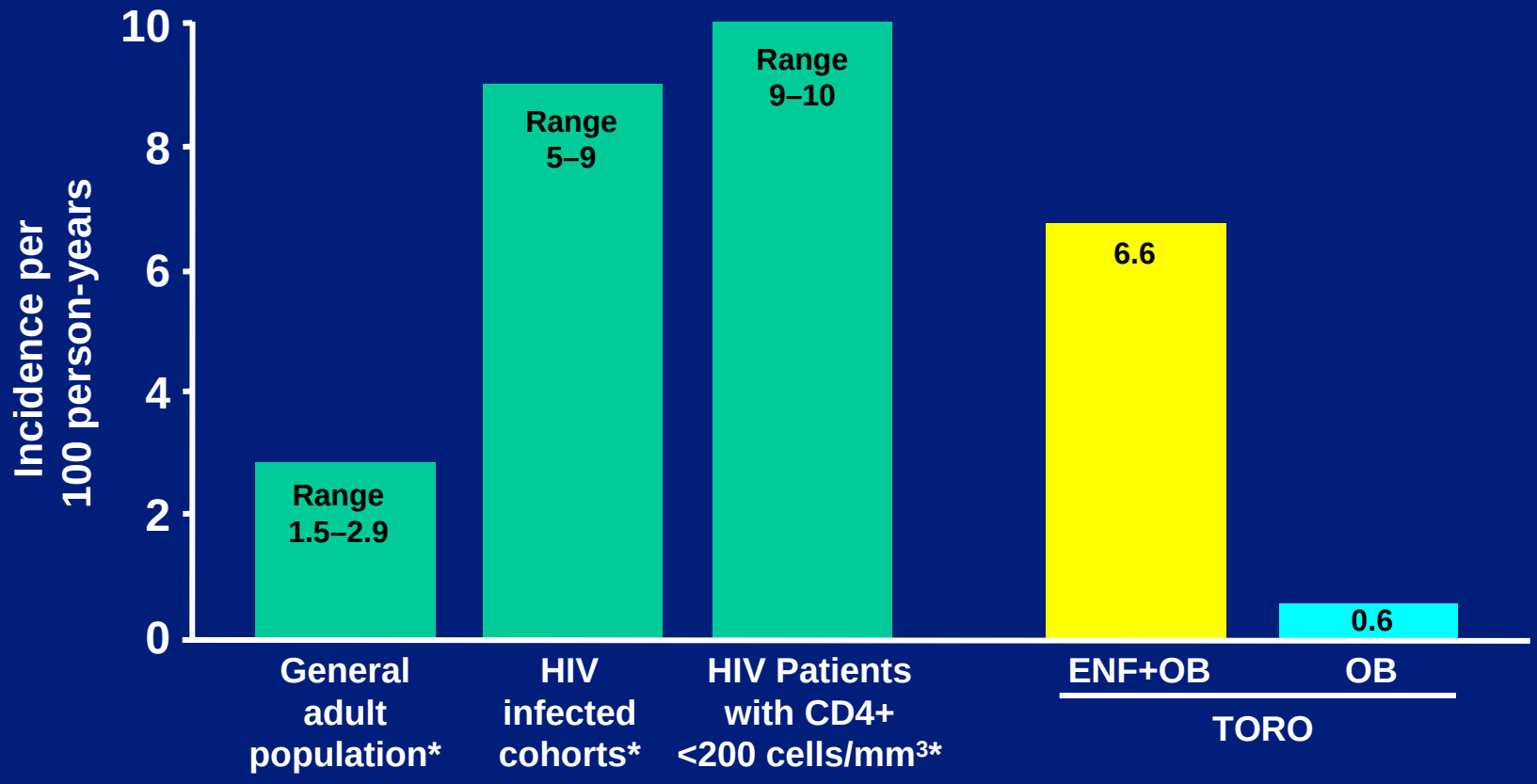
* Collapsed term including all pneumonias

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

	ENF+OB N	ENF+OB (Per 100 patient-years)	OB N	OB (Per 100 patient-years)
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

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